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Ozone and Mortality: A Meta-Analysis of Time-Series Studies and Comparison to a Multi-City Study (The National Morbidity, Mortality, and Air Pollution Study)

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ABSTRACT

While many time-series studies of ozone and daily mortality identified positive associations, others yielded null or inconclusive results. We performed a meta-analysis of 144 effect estimates from 39 time-series studies, and estimated pooled effects by lags, age groups, cause-specific mortality, and concentration metrics. We compared results to estimates from the National Morbidity, Mortality, and Air Pollution Study (NMMAPS), a time-series study of 95 large U.S. cities from 1987 to 2000. Both meta-analysis and NMMAPS results provided strong evidence of a short-term association between ozone and mortality, with larger effects for cardiovascular and respiratory mortality, the elderly, and current day ozone exposure as compared to other single day lags. In both analyses, results were not sensitive to adjustment for particulate matter and model specifications. In the meta-analysis we found that a 10 ppb increase in daily ozone is associated with a 0.83 (95% confidence interval: 0.53, 1.12%) increase in total mortality, whereas the corresponding NMMAPS estimate is 0.25% (0.12, 0.39%). Meta-analysis results were consistently larger than those from NMMAPS, indicating publication bias. Additional publication bias is evident regarding the choice of lags in time-series studies, and the larger heterogeneity in posterior city-specific estimates in the meta-analysis, as compared with NMAMPS.

1. INTRODUCTION

Ozone is a common urban air pollutant with well-documented adverse health effects ranging from respiratory symptoms to increased risk for hospital admissions. The U.S. Environmental Protection Agency (U.S. EPA) establishes primary National Ambient Air Quality Standards (NAAQS) for ozone and other criteria pollutants at a level intended to protect human health with an adequate margin of safety. In 1997, the U.S. EPA proposed adding an ozone standard of 80 ppb based on the daily 8-hour maximum concentration (1). The existing daily 1-hour maximum standard of 120 ppb remains in effect for areas in violation. The changes in regulations were in response to demonstrated effects at concentrations below the existing standard and evidence that the 8-hour averaging time better represented the time course of the short-term effects of ozone exposure on the respiratory system. The U.S. EPA is required by the Clean Air Act to

review the NAAQS at least every five years and to revise the standards if needed. At the time of preparation of this report, the EPA has just initiated the process of developing a new Criteria Document for ozone. Presently, over 100 million people in the U.S. live in areas that exceed the 8-hour NAAQS (2).

While many studies have demonstrated the damaging effects of ozone, those on mortality provided a range of results. Several time-series studies identified a positive association of ozone concentration with daily mortality counts (3-13); however, others produced inconclusive evidence including a negative association, no association, or a positive association that was not statistically significant (14-19). The seemingly conflicting results of these studies could result from many factors, including chance or variation across the populations, differing analytic methods, and issues related to data quality and measurement error.

Combining information across single-city results is a reasonable approach for estimating an overall effect and for exploring sources of heterogeneity. There are two main approaches for combining information. The first is a quantitative meta-analysis of published studies' results. The second is a multi-city study in which a uniform analytical framework is applied to time-series data for single cities, and then the city-specific estimates are pooled to generate an overall estimate. These two approaches can help resolve controversies from seemingly divergent individual study estimates, increase statistical power, and improve the generalizability of results.

Several previous meta-analyses examined the relationship between ozone and mortality, each finding a statistically significant relationship. Recently reported meta-analyses of ozone and mortality include a study by Thurston and Ito (20), which combined results of 16 studies and explored differences in approaches to the modeling of weather; the analysis of Levy et al. (21), which used four U.S. studies based in Cook County, Illinois and Philadelphia; the work of Stieb et al. (22, 23), who extracted results from 109 single- and multi-city studies for random effects pooling; and a World Health Organization report that investigated ozone and mortality in Europe (24). In previously conducted multi-city time-series studies of ozone and mortality, some found a statistically significant association: studies of 15 European cities (25); six French cities (26); and 80 U.S. cities in one of the National Morbidity and Mortality Air Pollution Study

(NMMAPS) analyses (27). A positive, but not statistically significant relationship was identified by Saez et al. (28) for seven Spanish cities, and analysis of data from seven major cities of Korea found a negative, non-statistically significant association (29). Zmirou et al. (30) identified a relationship between ozone and cardiovascular and respiratory mortality for four cities in western Europe.

NMMAPS initially involved mortality data for 90 large U.S. cities from 1987 to 1994 (27, 31-36). Our recent analysis of the extended and updated NMMAPS data base for the period 1987 to 2000 included 95 cities in the U.S. and used a uniform statistical framework within each city to estimate a national-average association between short-term changes in ozone and mortality (37). This work investigated multiple model structures, different lag times including a week long distributed lag and various single-day lags, concentration metrics, and potential confounding by particulate matter (PM) and temperature. Total, cardiovascular, and respiratory mortality and several age categories were considered. City-specific estimates were combined using a Bayesian hierarchical approach to calculate the overall effect of ozone on mortality.

The advantages of either of these approaches over a single city estimate are the gains in statistical power, the generation of an overall estimate, and the exploration of heterogeneity. However, in the meta-analytic approach, the independently conducted single-city studies generally differ in their statistical model, approaches to addressing confounding by weather and long-term trends, and adjustment for additional pollutants. Meta-analyses are also subject to publication bias; a positive association may be more likely to be submitted or accepted for publication; thus, results of meta-analyses may be biased towards an over-estimation of the true effect, but the degree of publication bias is difficult to quantify.

Comparison of results from the meta-analysis and multi-site studies provides the opportunity to: 1) identify a lower and upper bound for the pooled effect; 2) quantify publication bias; and 3) explore sources of heterogeneity of effects across studies. In this paper, we conduct a meta-analysis of 144 estimates from 39 time-series studies of ozone and mortality published from 1990 to June 2004. By combining information across the time-series studies, we estimate pooled effects by several lags, age groups, cause-specific

mortality, location, and concentration metrics. To assess publication bias, we compare the pooled estimates from the meta-analysis to results from NMMAPS.

2. MATERIALS AND METHODS

In this section we describe the meta-analysis protocol and the statistical methods used for pooling the results across studies.

2.1 Selection of studies and estimates for meta-analysis

The time-series studies included in the meta-analysis were systematically selected based on the following criteria:

- Studies provided numerical estimates of the relationship between short-term changes in ozone and mortality as well as an indication of the uncertainty of the central estimate (e.g., 95 percent confidence interval, or t-value).
- Only published, peer-reviewed studies were considered.
- Results based on NMMAPS research were excluded from the meta-analysis.
- Studies were published and indexed from 1990 to June 21, 2004.
- Publication was in English.
- Estimates were provided for total, cardiovascular, and/or respiratory mortality.

Studies were not excluded on the basis of other criteria, such as adjustment by co-pollutants, as these factors were recorded to be explored in later analysis. Studies that met the above criteria were identified using *pubmed* (www.pubmed.com), a service of the National Library of Medicine that includes over 14 million citations. Searches for *pubmed* included the words "mortality" or "time-series" in the title and/or abstract in addition to the terms "ozone" or "O_3" in the title and/or abstract. Additional potential references were provided by the U.S. EPA Office of Air Quality Planning and Standards and the Health Effects Institute (HEI) peer-reviewed report of re-analysis of PM and time-series studies (27). If a study was updated, such as through newly available statistical techniques or an updated dataset, the most recent results were chosen. For instance, reanalysis of time-series studies in response to issues identified with default

implementation of generalized additive models (*gam*) in S-Plus software (38) were used rather than those from the original study, when available.

The authors, and other faculty, postdoctoral researchers, and doctoral candidates at the Johns Hopkins Bloomberg School of Public Health coded the characteristics and results of each selected time-series study. Coding for each time-series study was double-checked. Investigators of the original studies were contacted regarding any questions (e.g., what lag was used).

Only one estimate from each study was included in each meta-analysis result, except where a single study provided results from multiple cities, in which case each city-specific result could be included. Meta-analysis results were not generated if an insufficient number of single estimates (less than four) were available within a particular stratum of results. Estimates of short-term lags were classified as single day lags of 0 (same day), 1, or 2 days or a two-day average of lags 0 and 1 or lags 1 and 2. When estimates for multiple lags were provided for a single study, the estimate for lag 0 was used, as this lag was most commonly given. This approach minimizes the bias of choosing the lag with the largest effect, although some studies only presented results for a single lag. If estimates were given for lags 1 and 2, but not for lag 0, the estimate for lag 1 was included. Only estimates based on the whole year's data were used, except in analyses specifically investigating the warmer time periods, typically the summer. Results are for all ages and without PM adjustment unless otherwise specified.

The selected time-series studies presented results in several forms, such as a log-relative rate, the percent increase in mortality, or the regression coefficient, each corresponding to a specified increase in ozone concentrations. The uncertainty of the central estimate was provided as a 95 percent confidence interval, standard error, t-statistic, or ratio of some measure of the central estimate to the standard error. These data were converted to the corresponding log-relative rate ($\hat{\beta}^s$) its standard error ($\sqrt{v^s}$), so that multiple studies could be combined in the meta-analysis.

Studies provided results for several concentration metrics. Results for the daily average, daily 8-hour maximum, and daily 1-hour maximum were considered. Daily 1-hour and 8-hour maximums calculated for specified time periods that included the daytime but not the whole 24-hour period (e.g., 1-hour maximum from 10am to 8pm)

were included, as the peak ozone levels do not occur at night. Concentration metrics for a specific time period of the day (e.g., noon to 8pm) were not considered as these can differ from the peak average on that day. Results from studies using the 1-hour and 8-hour maximum values were converted to the daily average, except in analysis that specifically addressed comparison across concentration metrics. If information to construct a conversion ratio was provided by the study, this ratio was used. Otherwise, the daily 1-hour and 8-hour maximums were converted to the daily average at a ratio of 2.5 and 1.33, respectively. These relationships have been used elsewhere (20).

2.2 Statistical methods for meta-analysis

We combined information across locations and estimated the pooled effect using a two-stage Bayesian hierarchical model (39-42). At the first stage, we assumed that the estimated effect $\hat{\beta}^s$ is normally distributed with mean equal to the true effect β^s, and variance equal to the statistical variance of $\hat{\beta}^s$, here denoted by v^s. At the second stage, we assumed that the true β^s is normally distributed with mean μ and between-study variance τ^2. The goal of our Bayesian meta-analysis was to estimate the marginal posterior distribution of the pooled effect μ by taking into account the within-city variance (v^s), which measures the statistical uncertainty in the estimation of β^s, and the between-study variance (τ^2), which measures the heterogeneity across cities of the true β^s. In summary, our model specification can be described as:

$$\begin{aligned} &\hat{\beta}^s \mid \beta^s, v^s \sim N(\beta^s, v^s), s = 1,..., S \\ &\beta^s \mid \mu, \tau^2 \sim N(\mu, \tau^2) \end{aligned} \quad (1)$$

We fit model (1) by use of Monte Carlo Markov Chain Methods (43) implemented by the software Winbugs (44). A priori, we assume that μ has a normal distribution with zero mean and very large variance (flat prior) and that $1/\tau^2$ has a *Gamma* distribution with shape and scale parameters equal to 0.001 and 0.001.

We investigate the sensitivity of the posterior distribution of μ to the specification of the prior distribution for the heterogeneity variance τ^2. In addition, to make the posterior inference on μ more robust to outliers, at the second stage we calculate the overall effect estimates assuming that: a) the true β^s is distributed as a mixture of two normal distributions $\beta^s \mid \mu, \tau^2 \sim (1-p)N(\lambda_1, \tau^2) + pN(\lambda_2, \tau^2)$ where $\mu = (1-p)\lambda_1 + p\lambda_2$; and that b) the true β^s is distributed as a student-t distribution with 3 degrees of freedom $\beta^s \mid \mu, \tau^2 \sim t_3(\mu, \tau^2)$.

2.3 Multi-city study

In recent NMMAPS analyses (37) we estimated the national-average short-term effect of ozone on mortality by combining information across 95 large U.S. cities from 1987 to 2000. The study explored multiple lag structures and model specifications. A generalized linear model with natural cubic splines was used with adjustment for time-varying confounders (weather, seasonality, and long-term trends). A Bayesian hierarchical model was used to combine the city-specific estimates into an overall effect, as shown in Equation 1. The statistical models used have been made available at: *http://www.ihapss.jhsph.edu/software/NMMAPS/NMMAPS.htm*. Full details are reported elsewhere (37).

3. RESULTS

A total of 144 estimates from 39 studies were included in the meta-analysis (3-5, 7, 9, 11-15, 18, 19, 26, 28, 45-69). We considered the following:

- Mortality outcome: total, cardiovascular, or respiratory
- Location: U.S. or elsewhere
- Potential confounding by PM: no adjustment for PM or adjustment by either PM_{10} or $PM_{2.5}$ (PM with an aerodynamic diameter no more than 10 or 2.5 microns, respectively)
- Cycle of analysis: yearly data or warm periods (e.g., summer)
- Lag: 0, 1, or 2 days; average of days 0 and 1; or average of days 1 and 2
- Age: all ages or the elderly ($\geq$ 64 or $\geq$ 65)

- Concentration metric: daily average, daily 1-hour maximum, or daily 8-hour maximum

These same issues were also considered in pooled estimates for NMMAPS.

We performed a chi-square test for heterogeneity on several subsets of studies, including the U.S. for total mortality and both the U.S. and non-U.S. combined for total mortality. Rejecting the hypothesis of non-heterogeneity, we fit the two-stage Bayesian hierarchical model in Equation (1) and approximated the posterior distribution of the pooled effect μ. Table 1 shows posterior mean and 95 percent posterior intervals of μ under alternative distributional assumptions for the second stage and under alternative prior specifications. The two numbers in parentheses denote the number of estimates and the number of studies, respectively. Note that a single study can contribute multiple estimates if it considers more than one city.

TABLE 1. Sensitivity analysis results of the pooled log-relative rates with respect to the specification of the Bayesian hierarchical model for pooling

	U.S. only (11,9)*		U.S. and non-U.S. (41,32)*	
	Posterior mean†	95% posterior interval	Posterior mean†	95% posterior interval
II Stage: $\beta^s \mid \mu, \tau^2 \sim N(\mu, \tau^2)$				
$1/\tau^2 \sim Gamma(0.01,0.01)$	0.84	0.47, 1.21	0.83	0.53, 1.12
$1/\tau^2 \sim Gamma(0.001,0.001)$	0.84	0.48, 1.20	0.83	0.53, 1.12
$1/\tau^2 \sim Gamma(0.0001,0.0001)$	0.84	0.49, 1.19	0.83	0.53, 1.12
II Stage: $\beta^s \mid \mu, \tau^2 \sim (1-p)N(\lambda_1, \tau^2) + pN(\lambda_2, \tau^2)$ $1/\tau^2 \sim Gamma(0.001,0.001)$	0.83	0.42, 1.24	0.92	0.57, 1.26
II Stage: $\beta^s \mid \mu, \tau^2 \sim t_3(\mu, \tau^2)$ $1/\tau^2 \sim Gamma(0.001,0.001)$	0.84	0.48, 1.20	0.71	0.46, 0.97

* The numbers in parentheses are the number of city-specific estimates and number of studies.
†Percent increase in mortality per 10 ppb increase in ozone.

The pooled estimates are robust to all of these model specifications. Therefore as a baseline model we assume at the second stage that $\beta^s \mid \mu, \tau^2 \sim N(\mu, \tau^2)$ with $1/\tau^2 \sim$

Gamma (0.001,0.001). We also explored the findings with respect to a problem with the default implementation of generalized additive models (*gam*) in the commonly used statistical software package, S-Plus (38, 70). The pooled estimate for studies without *gam* problems, such as those that used other modeling techniques or used gam exact (38) was larger.

Table 2 shows the posterior means and 95 percent posterior regions of the pooled effects for total, cardiovascular, and respiratory causes separately for U.S. cities only and for the U.S. and other locations combined. These pooled effects included time-series studies for short-term lags (defined as lags of 0, 1, or 2 days; or average of either days 0 and 1 or days 1 and 2).

TABLE 2. Posterior means and 95% posterior intervals of the pooled log-relative rates for cause-specific mortality

	U.S. only		U.S. and non-U.S.	
	Posterior mean*	95% posterior interval	Posterior mean*	95% posterior interval
Total	0.84 (11,9)	0.48, 1.20	0.83 (41,32)	0.53, 1.12
CVD	0.85 (5,4)	-0.66, 2.39	1.07 (25,18)	0.68, 1.46
Respiratory	0.65 (4,4)	-1.84, 3.21	0.43 (23,17)	-0.47, 1.34

*Percent increase in mortality per 10 ppb increase in ozone. The numbers in parentheses are the number of city-specific estimates and number of studies.

Overall we found that a 10 ppb increase in ozone in the few previous days is associated with a 0.83 percent increase in total mortality (95 percent posterior interval 0.53 to 1.12). Pooled effects where similar for studies within the U.S. and when studies outside the US were included. When studies from all locations were considered, we found that the pooled effect for CVD mortality is larger than for total mortality. Pooled effects for respiratory mortality were not statistically significant and were lower than the pooled effects for CVD or total mortality.

The pooled estimate for total mortality in the U.S. was based on 11 estimates from nine studies in the following nine communities: St. Louis; Kingston/Harriman, Tennessee; Santa Clara; Buffalo; Chicago; Philadelphia; Los Angeles; Detroit; and the Coachella Valley, California. Eight of these areas (all but the Coachella Valley) were included in NMMAPS ozone analysis.

We made two comparisons between the pooled effects obtained from the meta-analysis and from NMMAPS. First, we compared the pooled effects by including all the cities (nine from the meta-analysis and 95 from NMMAPS). Second we restrict the comparison to the eight cities that were included both in the meta-analysis and in NMMAPS.

Figure 1 compares the marginal posterior distributions of the overall effect under the meta-analysis (based on 11 estimates from the 9 cities) and in NMMAPS (95 U.S. cities, all lag 0). When we combined information across the 95 cities, the national average effect of same day ozone on mortality from NMMAPS was a 0.25 percent (95 percent confidence interval: 0.12, 0.39) increase in mortality for a 10 ppb increase in the same day's ozone concentration. Figure 2 compares the marginal posterior distributions of the overall effect under the meta-analysis and in NMMAPS for the 8 cities common to both the approaches. (8 U.S. cities, all lag 0). When we combined information across the 8 cities, the NMMAPS pooled effect of same day ozone concentration was 0.48 percent (0.03, 0.92 percent) as compared to the meta-analysis estimate of 0.83 percent (0.38, 1.29 percent). In both cases (using the 8 cities or using all the estimates), the estimated pooled effects from NMMAPS were lower than estimates from the meta-analysis. This pattern is indicative of possible publication bias, although it could be related to model structure.

Figure 1. Posterior distributions of pooled log-relative rates of all-cause mortality associated with 10 ppb increase in ozone in NMMAPS (95 cities) and for the meta-analysis of the U.S. (11 estimates)

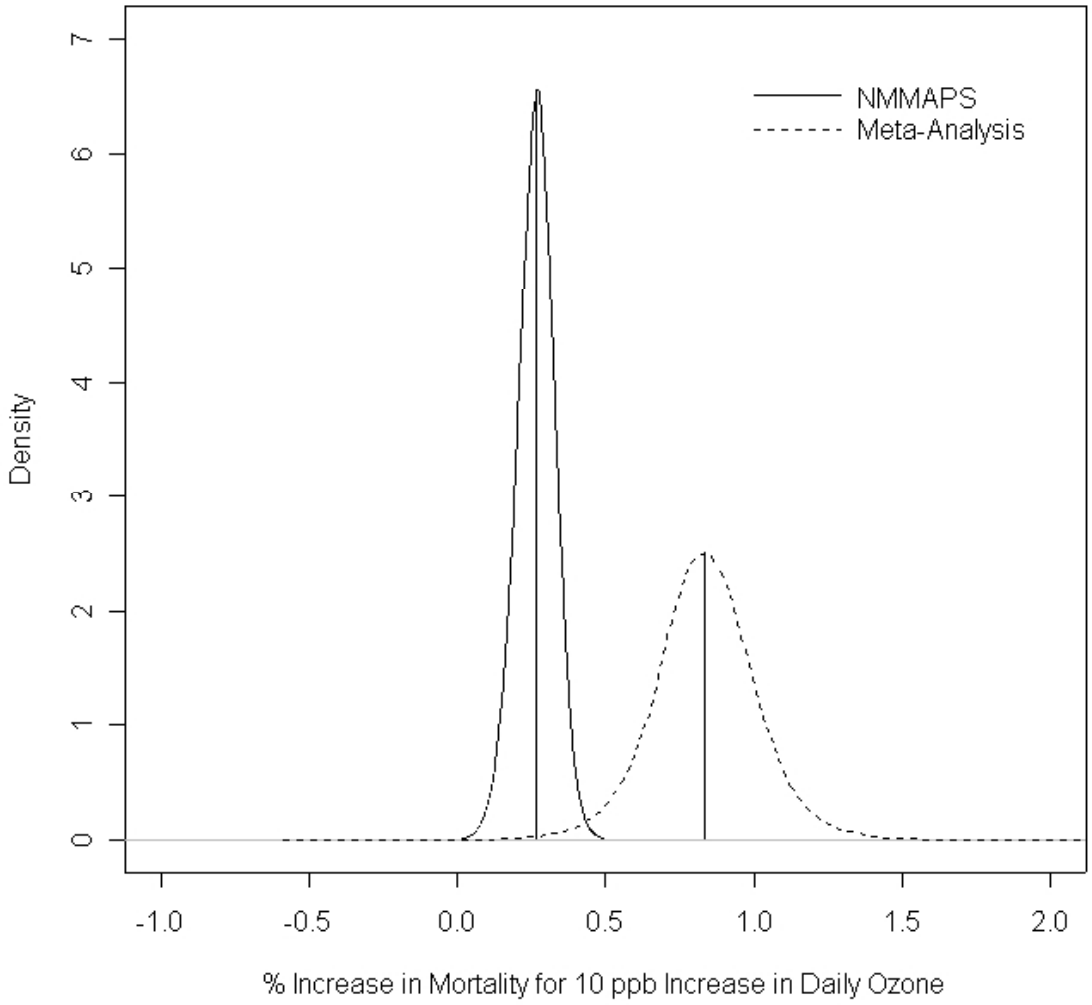
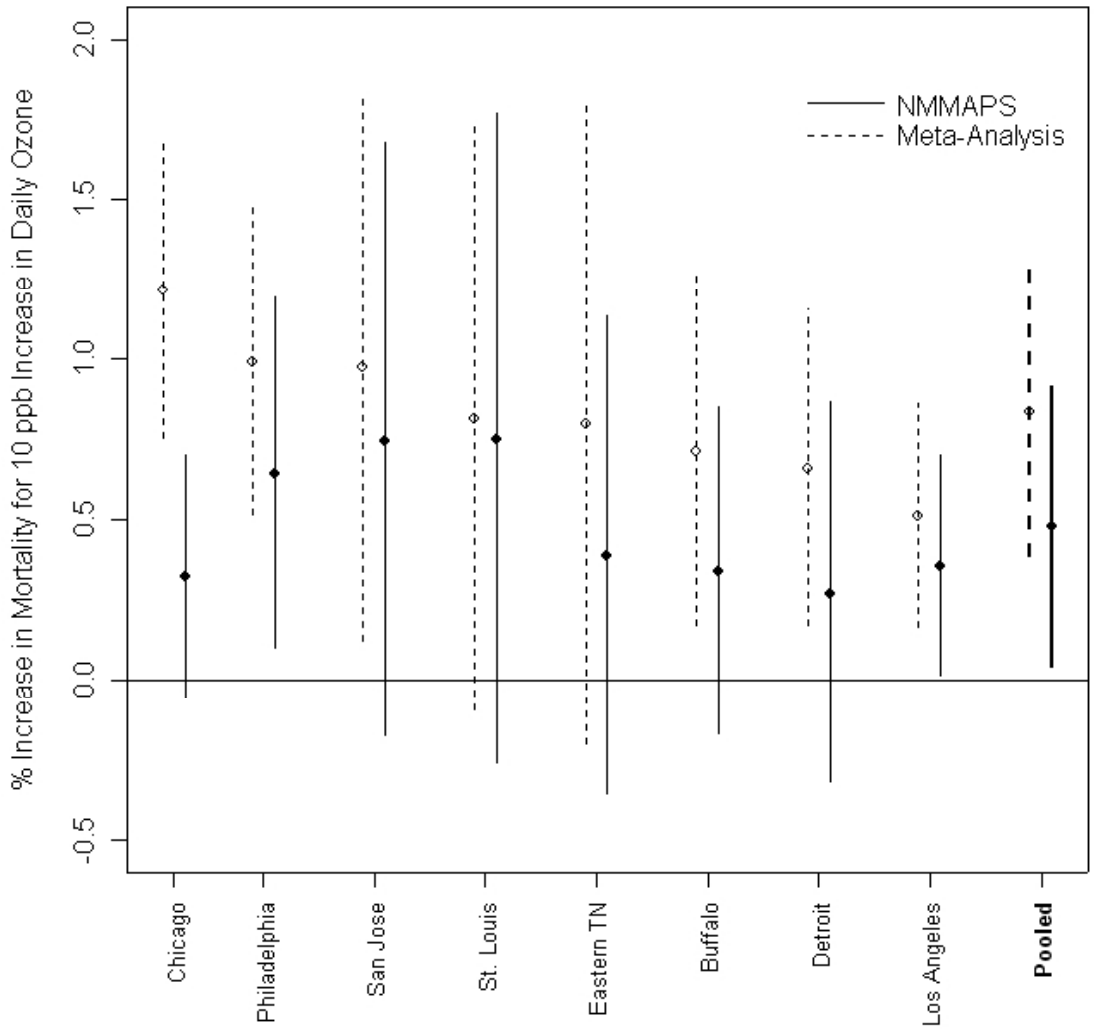


Figure 2. City-specific posterior means and 95% posterior intervals of the log-relative rate of mortality associated with 10 ppb increase in ozone for the 8 cities included in NMMAPS and in the meta-analysis

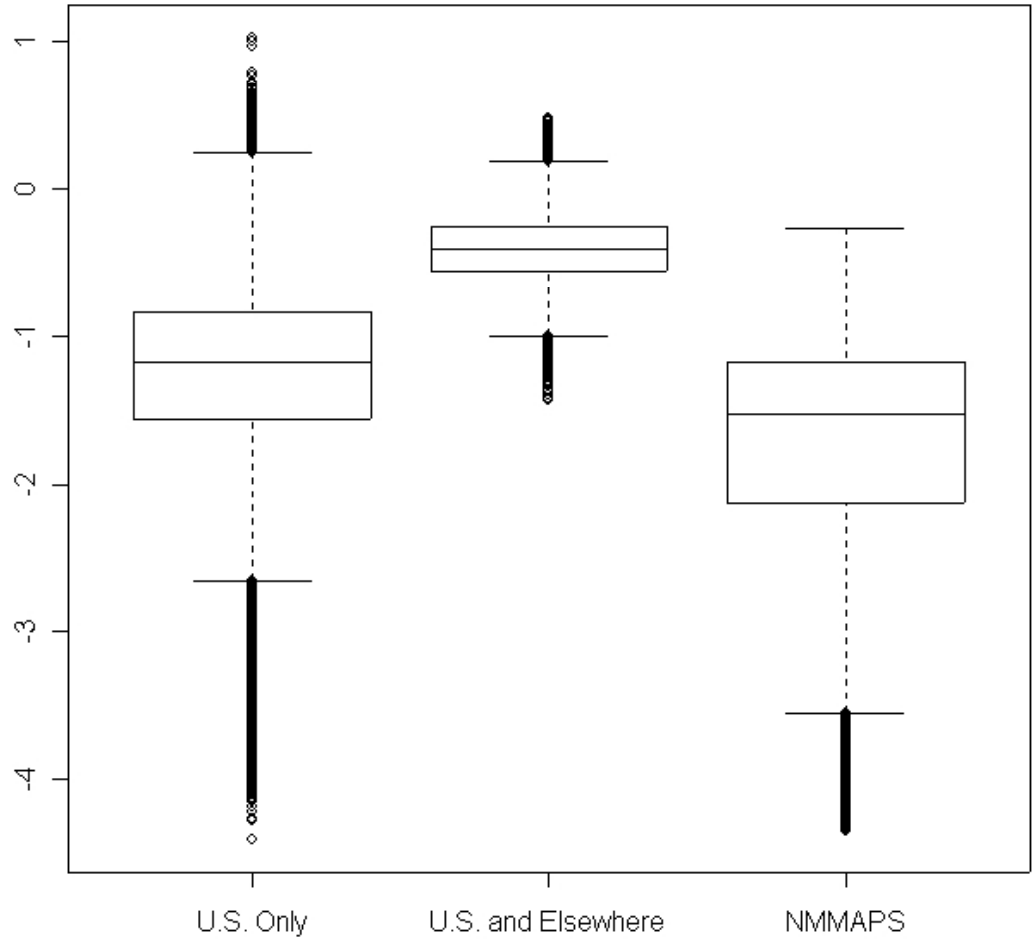


The pooled effect from the meta-analysis for cardiovascular and respiratory mortality combined was slightly higher than the overall effect for total mortality. This pattern was also observed in the NMMAPS analyses.

Figure 3 shows the posterior distribution of the heterogeneity parameter τ for total mortality and for the U.S. and non-U.S. studies combined. The city-specific effects

included in the meta-analysis were more heterogeneous than estimates from NMMAPS. In the meta-analysis there were several sources of heterogeneity in addition to potential differences between cities. These included differences in the specification of the statistical models, in the data quality, the potential for publication bias and other factors.

Figure 3. Marginal posterior distribution of the log of heterogeneity parameter (τ) for: 1) meta-analysis of 11 U.S estimates; 2) meta-analysis of 41 U.S. and not U.S. estimates; and 3) for 95 NMMAPS cities in [37]



In Table 3 we summarize the pooled estimates from the meta-analysis with and without adjustment for PM (either PM_{10} or $PM_{2.5}$). In the time-series studies, the adjustment for PM was made by including the daily level of PM as a covariate in the

Poisson regression model. Pooled effects were robust to the PM adjustment. These results are consistent with recent the NMMAPS analyses (37).

TABLE 3. Posterior means and 95% posterior intervals of the pooled log-relative rates with and without adjustment for PM

	U.S. only		U.S. and non-U.S.	
	Posterior mean*	95% posterior interval	Posterior mean*	95% posterior interval
No PM adjustment	0.84 (11,9)	0.48, 1.19	0.83 (41,32)	0.53, 1.12
Adjustment by PM	0.74 (5,5)	0.06, 1.43	0.94 (11,11)	-0.07, 1.96

*Percent increase in mortality per 10 ppb increase in ozone. The numbers in parentheses are the number of city-specific estimates and number of studies.

Table 4 shows posterior means and 95 percent posterior regions of the pooled effect for total mortality for lags 0, 1, and 2 from both the meta-analysis (using studies from the U.S. and elsewhere) and NMMAPS. For both the meta-analysis and in NMMAPS, the pooled effects were largest at lag 0 and smallest at lag 2. Also, the pooled estimates from the meta-analysis were consistently higher than those from NMMAPS, again providing evidence of publication bias.

TABLE 4. Posterior means and 95% posterior intervals of the pooled log-relative rates for total mortality at various single-day lags

	Meta-Analysis		NMMAPS	
	Posterior mean*	95% posterior interval	Posterior mean*	95% posterior interval
No lag (same day)	0.81 (20,17)	0.47, 1.15	0.25	0.12, 0.39
Lag 1 day	0.56 (19,17)	0.05, 1.07	0.18	0.06, 0.30
Lag 2 days	0.24 (10,9)	-0.06, 0.55	0.14	0.03, 0.26

*Percent increase in mortality per 10 ppb increase in ozone. The numbers in parentheses are the number of city-specific estimates and number of studies.

To further explore publication bias with respect to choice of lag, we calculated a pooled estimate for a variety of single day lag times, and compared the estimates for studies that provided results for only a single lag to those that provided multiple lags. Table 5 compares pooled estimates obtained by combining studies that provided a single lag estimate (0 or 1), versus pooled estimates obtained by combining studies that reported estimates for multiple lags including lags 0 or 1. The pooled effects from the studies that

provided a single lag estimates were larger than those obtained from the studies that provided multiple estimates. This indicates that the lag with the highest effect is more likely to have been reported.

TABLE 5. Posterior means and 95% posterior intervals of the pooled log-relative rates by reported lags

	Studies provided only a single lag		Studies provided estimates for multiple lags	
	Posterior mean*	95% posterior interval	Posterior mean*	95% posterior interval
No lag (same day)	1.05 (11,9)	0.42, 1.69	0.66 (9,8)	0.27, 1.04
Lag 1 day	0.80 (9,8)	-0.75, 2.38	0.39 (10,9)	0.01, 0.77

*Percent increase in mortality per 10 ppb increase in ozone. The numbers in parentheses are the number of city-specific estimates and number of studies.

Effect estimates are larger for the elderly (i.e., those 64 years and older or those 65 and older). For this age category, a 10 ppb increase in daily ozone is associated with a 1.27 percent (0.65, 1.89 percent) increase in total daily mortality, including ten estimates from nine studies from both in and outside of the U.S. This is higher than the estimate for all ages, at 0.83 percent (0.53, 1.12 percent). This effect modification by age is consistent with the NMMAPS analyses, which also found larger effects for the elderly (37).

Table 6 shows that the pooled effects obtained from studies that used the whole year's data and the pooled effects from studies that analyzed only data in the warmer time periods for total mortality and for CVD mortality. Some time-series studies of ozone and mortality explored the relationship during a particular time of year, such as May to October or the summer, as warmer time periods reflect the peak ozone season, as the chemical reactions that form ozone are temperature dependent (71). In the NMMAPS analysis, no appreciable difference was observed between the ozone and mortality relationship for the whole year and the association during May to October.

TABLE 6. Posterior means and 95% posterior intervals of the pooled log-relative rates for the warm time
periods and for the whole years

	Yearly Data		Warmer Time Periods	
	Posterior mean*	95% posterior interval	Posterior mean*	95% posterior interval
Total Mortality U.S.	0.84 (11,9)	0.48, 1.19	1.34 (4,3)	-0.45, 3.17
Total Mortality U.S. and non-U.S.	0.83 (41,32)	0.53, 1.12	1.50 (11,10)	0.72, 2.29
CVD Mortality U.S. and non-U.S	1.07 (25,18)	0.68, 1.46	2.45 (5,4)	0.88, 4.10

*Percent increase in mortality per 10 ppb increase in ozone

4. DISCUSSION

Both the meta-analysis and NMMAPS results provide strong evidence of an association between short-term exposure to ozone and mortality. Results from these two approaches have a consistent pattern of findings: larger effects for cardiovascular mortality (for the meta-analysis) and cardiovascular/respiratory mortality (for NMMAPS) than for total mortality; larger effects at lag 0 as compared with lags 1 or 2; and a lack of confounding by PM.

We found several results that indicate publication bias in the reporting of time-series studies of ozone and mortality. The effect estimates for meta-analysis were much larger than those for the NMMAPS multi-city analysis. Larger pooled effects were shown for combining estimates of studies that reported a single lag (either 0 or 1) as compared with those that reported multiple lags, signifying that the lag with the largest effect was more likely to be reported. A comparison of 21 time-series studies on PM_{10} and mortality and the NMMAPS analysis of 88 cities also provided evidence for publication bias (72). A recent meta-analysis of time-series and panel studies of ozone, particulate matter, and mortality also found evidence of publication bias (24). Therefore, although meta-analyses are very useful for combining information from different studies and investigating differences such as in location and study design, they are likely to over-estimate the true relationship between ozone and mortality.

Results from the new meta-analysis are consistent with other meta-analyses of ozone time-series studies, as shown in Table 7. Our meta-analysis indicates that short-term changes in ozone affects mortality, with an estimated 0.83 percent increase in total mortality (0.53, 1.12 percent) for a 10 ppb increase in the daily average ozone level. This corresponds to approximately a 0.33 percent increase in mortality (0.21, 0.45 percent) for a 10 ppb increase in the daily 1-hour maximum. To compare this estimate to other meta-analyses, all the estimates need to be based on the same measure of ozone concentration, such as the daily average. While the relationship between different ozone metrics varies by location, we used ratios of 2.5 and 1.33 to convert results using the daily 1-hour maximum and 8-hour maximum, respectively, to the daily average, as has been performed in other work, so that results are roughly comparable (Thurston and Ito 2001, Levy et al. 2001). For example, a 10 ppb increase in the daily average ozone concentration corresponds to approximately a 25 ppb increase in the daily 1-hour maximum concentration.

TABLE 7. Comparison of pooled estimates from other meta-analyses of ozone and mortality

Meta-Analysis Study	% Increase*	95% CI
Thurston and Ito (2001)	0.89	0.56,1.22
Thurston and Ito (2001) †	1.37	0.78,1.96
Stieb et al. (2003)	1.12	0.32,1.92
Levy et al. (2001)	0.98	0.59,1.38
Anderson et al. (2004)	0.78	0.39,1.18
Present meta-analysis	0.83	0.53,1.12

*Percent increase in mortality per 10 ppb increase in ozone
†Included only studies that considered a nonlinear relationship between temperature and mortality.

The 1997 modification to the existing NAAQS was based largely in evidence of adverse respiratory effects that could be produced in laboratory experiments at ozone concentrations that were prevalent in many metropolitan areas of the United States. At that time, limited single-city time-series analyses indicated that ozone might also increase mortality on a short-term basis. The continued accumulation of results over the subsequent years shows consistent evidence of an effect of ozone on daily mortality counts (Table 7). As for the effect of particulate matter on mortality, a variety of

mechanisms may be relevant, reflecting ozone's potential to cause airways and pulmonary inflammation.

While the meta-analysis results provide strong evidence for an effect of ozone on mortality, the comparison to results from NMMAPS provides a clear indication of publication bias in reports of single-cities studies. Such publication bias may have multiple explanations, from the choice of analytic strategies and pathways taken in model development to the tendency of investigators to submit findings that are "positive" and for journals to preferentially publish reports of statistically significant associations. Quantitative analyses of the public health impact of ozone based on single-city results or meta-analyses of such results would tend to over-estimate the detrimental effect of ozone and the benefits of control. We recommend caution against using the results of single cities studies, whether individually or pooled, for impact assessment. Multi-city approaches, like NMMAPS, offer a now-feasible alternative that is less subject to publication bias.

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