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Meta-analysis of the association between short-term exposure to ambient ozone and respiratory hospital admissions

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Abstract
Ozone is associated with health impacts including respiratory outcomes; however, results differ across studies. Meta-analysis is an increasingly important approach to synthesizing evidence across studies. We conducted meta-analysis of short-term ozone exposure and respiratory hospitalizations to evaluate variation across studies and explore some of the challenges in meta-analysis. We identified 136 estimates from 96 studies and investigated how estimates differed by age, ozone metric, season, lag, region, disease category, and hospitalization type. Overall results indicate associations between ozone and various kinds of respiratory hospitalizations; however, study characteristics affected risk estimates. Estimates were similar, but higher, for the elderly compared to all ages and for previous day exposure compared to same day exposure. Comparison across studies was hindered by variation in definitions of disease categories, as some (e.g., asthma) were identified through $\geqslant$3 different sets of ICD codes. Although not all analyses exhibited evidence of publication bias, adjustment for publication bias generally lowered overall estimates. Emergency hospitalizations for total respiratory disease increased by 4.47% (95% interval: 2.48, 6.50%) per 10 ppb 24 h ozone among the elderly without adjustment for publication bias and 2.97% (1.05, 4.94%) with adjustment. Comparison of multi-city study results and meta-analysis based on single-city studies further suggested publication bias.

Keywords: ozone, hospital admissions, human health, air pollution, meta-analysis

S Online supplementary data available from stacks.iop.org/ERL/6/024006/mmedia

1. Introduction

Ozone is a highly reactive air pollutant that can irritate airways and interfere with host defense mechanisms [1] and is associated with the risk of respiratory symptoms (e.g., coughing, wheezing), mortality, and hospital admissions [2, 3]. Time-series and case-crossover studies have examined the risk of respiratory hospitalizations or emergency room/department visits (emergency visits) as a function of short-term exposure to ambient ozone.

Many single-city studies observed associations between ozone and hospital admission for respiratory diseases [4–7], including total respiratory diseases or general respiratory illness [8–23] and cause-specific respiratory diseases such as pneumonia [10, 24–26], chronic obstructive pulmonary disease (COPD) [10–25, 27–32], and asthma [31, 33–50]. Other studies reported no association or inconsistent results for total or general respiratory illnesses [51–59] or specific respiratory diseases [58, 60–70]. Some studies found mixed results for different age groups or seasons [71–73]. Other potential confounders include co-pollutants, such as particulate matter (PM), with results differing by study [30, 32, 37, 75, 77].

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Larger studies investigated multiple locations, reporting several individual-city estimates and/or a combined estimate across several locations. Many multi-city studies, such as the 'Air Pollution and Health: A European Approach' (APHEA) project, found significant associations between ozone and hospital admissions for certain disease categories (e.g., total respiratory diseases, COPD), age group (e.g., the elderly), or season (e.g., warm season) [78–83].

Although several studies identified links between ozone and risk of respiratory hospital admissions, several key questions remain, such as why study results differ, which would inform understanding of the overall scientific evidence for health risk and guide future research. Study and population characteristics such as location or age may impact effect estimates and thus hinder comparability across studies. For example, ozone was associated with increased respiratory hospitalizations among older people in Rotterdam but not Amsterdam [84], and was associated with increased COPD and pneumonia admissions in Minneapolis–St Paul, US, but significant associations were not observed in Birmingham, US [85]. Other study characteristics that may influence results include season, which can affect levels of ozone and other confounders, such as weather. Ozone levels are generally higher in summer due to photochemical formation [86]. Season can modify exposure patterns such as the use of open windows versus air conditioning, and these factors can differ by location. For instance, in analyses of 8 h maximum ozone and total respiratory hospitalization of persons >64 years in London and Hong Kong, both cities had associations for all year and for the warm season; however, in cool seasons, only Hong Kong had an association [77].

We investigated how various study characteristics impact results by using meta-analysis to integrate findings from previous studies with consideration of their uncertainty. Similar methods have been applied elsewhere, such as in the study of short-term ozone exposure and mortality [87–89]. The goals of this project are to: assess the overall state of scientific evidence on ozone and respiratory hospital admissions; explore variation in effect estimates, such as by study location or age; and investigate some of the challenges inherent in meta-analysis such as publication bias, which is caused by the tendency for authors to submit or journals to publish statistically significant results as opposed to null or uncertain results.

2. Methods

We identified previously conducted studies by searching PubMed for the following in the title and/or abstract: (1) 'ozone' or 'O_3', and (2) 'hospital admission*', 'hospitalization*', 'emergency room', 'emergency department', or 'emergency visits', where '$*$' reflects truncation indicating acceptance of any value. We selected studies meeting the criteria that they: (1) investigated the association between short-term ozone exposure (a single day or a few days) and hospital admissions or emergency visits for respiratory diseases through time-series or case-crossover approaches; (2) provided quantitative results with quantitative measures of the estimate's uncertainty; (3) included a non-linear function for temperature in the regression model, except for season-specific results (e.g., warm season); and (4) were peer-reviewed and published in English from 1990 to 2008. Some early time-series analysis used linear regression models [12, 33, 51, 90–95] and were excluded due to the non-normally distributed health data [96]. We excluded a study that applied logarithmic transformation to ozone exposures [97].

We recorded study characteristics including time frame and location of the study, disease categories (e.g., pneumonia, asthma), disease diagnosis codes (e.g., the International Classification of Disease ICD-9 codes), type of hospital visit (e.g., general hospital admissions, emergency visits), effect estimates with uncertainties in various formats (e.g., percentage change in risk of hospitalization and 95% confidence interval), ozone units (e.g., ppb, μg m^{-3}), ozone temporal metric (e.g., 24 h mean), age of subjects (e.g., elderly), lag (e.g., same day as lag0, previous day as lag1, average of same and previous days as lag0–1), season of analysis (e.g., summer), and co-pollutants included in models. Many studies reported multiple estimates as they explored several disease categories, age groups, seasons, or other factors. For studies presenting results from several cities, the meta-analysis included one result per city per study. For multi-city studies that only reported a combined estimate across cities, we analyzed these results separately and did not include them in the meta-analysis, in order to compare single-city and multi-city results.

We used the standard chi-squared test, χ^2, to examine the homogeneity among effect estimates. Under homogeneity, the fixed-effect model was used to combine estimates; otherwise, the random-effect model was used [98]. We used statistical software R (version 2.9.2). We required at least four estimates to calculate an overall estimate in the meta-analysis. Results are presented as the percentage change in risk of hospital visit per 10 ppb increase in 24 h ozone. We also present key results based on the daily 8 h maximum ozone metric. Stratification was used to explore whether meta-analysis estimates differ by use of ozone metric, age, lag for exposure, season, or region.

Studies used different metrics and units for ozone concentrations. We converted all results in μg m^{-3} to ppb for comparison using standard pressure and temperature. We converted results in all other metrics (i.e., 8 h maximum, 8 h mean, 1 h maximum) to the 24 h mean, with an assumption of a proportional relationship between different metrics. The 8 h mean, corresponding to the 8 h average of a specific time period when ozone concentrations are anticipated to be high (e.g., 9 am–5 pm [11]), was assumed to approximate the 8 h maximum. We considered multiple conversion ratios of 1 h maximum:8 h maximum:24 h mean ozone as: (1) 2:1.5:1 as previously applied by the US Environmental Protection Agency (EPA) [99], (2) 1.76:1.53:1 from a national study of 78 US communities [100], and (3) a specific ratio for each community. The actual relationship among ozone metrics differs by community, ozone level, and season [100]. For the third approach, we used community-specific ratios based on data from a previously conducted study of 78 US communities [100] and a database of air pollution

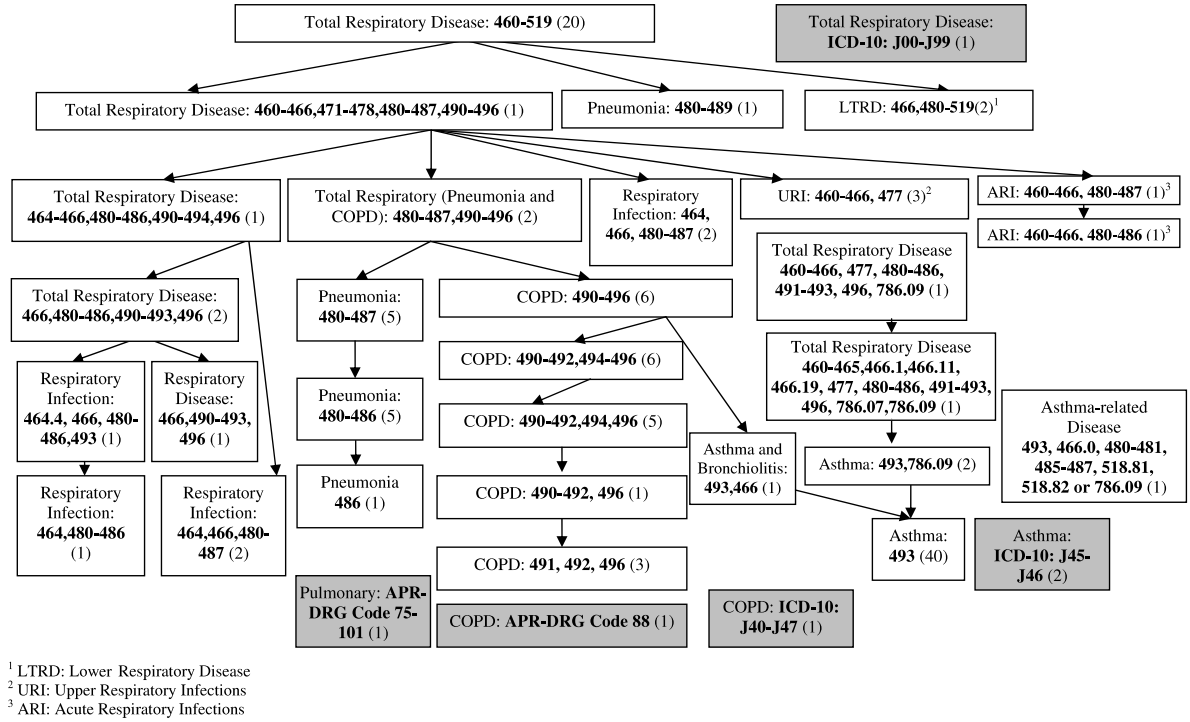

Figure 1. Disease categories and diagnosis codes in selected studies. Note: the diagnosis codes in bold are ICD-9 unless specified. Numbers in parentheses indicate how many studies reported estimates for each specified disease category. The white-background boxes show the studies using ICD-9 codes to define disease categories. The gray-background boxes show the studies using other diagnosis codes (e.g. ICD-10 codes, APR-DRG codes). One study can be included in multiple boxes; estimates are provided for multiple disease categories.

concentrations for European communities [101]. For cities not in these databases, a ratio of 1.76:1.53:1 was applied.

Positive findings are more likely to be submitted to or published in a journal than null or negative results [102], which can result in overestimation in meta-analysis. We investigated publication bias with funnel plots, as an asymmetric distribution indicates potential publication bias among the combined estimates [103]. We used the linear regression test developed by Egger *et al* [104] to examine publication bias [105]. On the basis of the Egger's test results, we applied the 'trim and fill' approach [106] to generate overall estimates adjusted for publication bias. We compared meta-analysis results based on single-city estimates to multi-city study results, which are less subject to publication bias.

3. Results

We identified 96 articles meeting our protocol. Among these, 86 studies presented only estimates for an individual city, eight reported only combined estimates across multiple cities; [21, 78–83, 107] and two gave both estimates for an individual city and combined results across cities [65, 108]. Results were categorized by age group, type of hospital visit (i.e., general hospital admissions, emergency hospital admissions, and emergency visits), and disease category (e.g., asthma). The most commonly reported disease categories were total or general respiratory diseases, pneumonia, COPD, and asthma.

We identified a key challenge in meta-analysis or other synthesis of results in that studies used different diagnostic codes to define a disease (figure 1). For example, total respiratory disease, respiratory infection, COPD, asthma, and pneumonia were each identified through three or more different sets of ICD codes. For the meta-analysis, we used the descriptions of diseases designated by the authors to categorize estimates by disease, although the somewhat different definitions present a difficulty in comparing across studies.

Within a study, for each individual city we selected one estimate for each hospital visit type (e.g., emergency visits), disease category (e.g., COPD), and age category, and grouped the main estimates by these categories. For cases in which researchers presented more than one such result, we selected the main result identified by the authors. This indicates another challenge in meta-analysis, as the authors' choice of key result may be subject to publication bias. We generated overall estimates through meta-analysis for data groups with $\geqslant$4 estimates.

3.1. Ozone metrics

We used the 24 h mean as the ozone metric for analysis and converted results in all other ozone metrics to the 24 h mean. Separate meta-analyses were performed using three methods of converting ozone metrics, yielding similar results (supplemental table 1 available at stacks.iop.org/ERL/6/024006/mmedia). Note that although 136 estimates were identified in our literature review, a far smaller number are available for a specific cause of hospitalization, age group, and hospital visit type (general, emergency

Table 1. Percentage increase (95% interval) in risk of hospital admissions or emergency visits per 10 ppb ozone in 24 and 8 h maximum metrics. (Note: bold estimates are statistically significant.)

Disease categories	24 h mean ozone metric	8 h max ozone metric	Total # of estimates	Studies included
General hospital admissions				
Total RD[a] (all ages) [b]	2.03 (−0.21, 4.31)	1.45 (−0.04, 2.95)	6	[53, 54, 59, 75, 116, 117]
Total RD (elderly)	**2.47 (0.89, 4.07)**	**1.60 (0.58, 2.63)**	8	[9, 10, 52, 54, 85, 117, 118]
Total RD (children) [c]	0.69 (−2.03, 3.48)	0.53 (−1.46, 2.56)	4	[53, 54, 59, 72]
Pneumonia (elderly) [c]	**4.24 (2.85, 5.63)**	**2.75 (1.86, 3.64)**	5	[10, 24, 25, 60, 85]
COPD (all ages)	**5.74 (0.71, 10.96)**	**4.23 (1.18, 7.36)**	4	[30, 32, 53, 56, 117]
COPD (elderly) [d]	**2.54 (1.29, 3.80)**	**1.65 (0.84, 2.47)**	8	[10, 25, 27, 60, 62, 85, 117]
Asthma (all ages)	4.35 (−0.18, 9.10)	2.83 (−0.12, 5.85)	6	[39, 53, 56, 119–121]
Asthma (children)	−0.68 (−6.56, 5.57)	−0.68 (−6.56, 5.57)	6	[37, 53, 62, 69, 76, 122]
Emergency hospital admissions				
Total RD (all ages)	**1.90 (0.74, 3.07)**	**1.24 (0.48, 1.99)**	10	[5, 6, 11, 15, 19, 57, 74, 77, 123]
Total RD (elderly)	**4.47 (2.48, 6.50)**	**2.89 (1.60, 4.21)**	11	[6, 11, 15, 20, 57, 66, 77, 84, 123]
Total RD (15–64 years)	1.06 (−1.31, 3.47)	0.69 (−0.86, 2.26)	6	[6, 11, 57, 84, 123]
COPD (all ages)	**5.06 (1.24, 9.05)**	**3.29 (0.82, 5.82)**	6	[15, 16, 29, 84, 124]
Asthma (all ages)	**6.64 (2.60, 10.85)**	**4.29 (1.69, 6.96)**	8	[6, 15, 16, 40, 57, 71, 84, 96]
Asthma (children)	2.83 (−3.45, 9.52)	1.85 (−2.26, 6.12)	6	[6, 40, 43, 57, 71, 123]
Asthma (15–64 years)	3.63 (−2.02, 9.60)	2.46 (−1.41, 6.47)	6	[6, 40, 57, 77, 123]
Emergency visits				
Total RD (all ages)	**1.23 (0.29, 2.17)**	**0.80 (0.19, 1.42)**	5	[17, 23, 125, 126]
Total RD (children)	2.55 (−1.71, 6.98)	1.64 (−1.10, 4.48)	4	[22, 58, 126]
Asthma (all ages)	**4.50 (2.05, 6.99)**	**2.90 (1.33, 4.50)**	8	[38, 41, 42, 125–127, 50]
Asthma (children)	**3.67 (1.55, 5.81)**	**2.51 (1.15, 3.88)**	13	[36, 43, 44, 48, 49, 73, 126, 50, 47, 68, 128, 129]

[a] RD = respiratory diseases. [b] The combined estimates excluded one outlying study [130].
[c] The fixed-effect model was used. The random-effect model was used elsewhere.
[d] Estimates converted into US study ratios and specific ratios were combined in the random-effect model, but estimates converted into EPA ratios were combined in the fixed-effect model.

admission, or emergency visit). Compared with the US EPA metric conversion ratio [99], the study based on US communities [100] had a higher ratio of 8 h maximum:24 h average but a smaller value for 1 h maximum:24 h average. Results were also influenced by the magnitude of estimates in 8 h maximum and 1 h mean metrics. Combined estimates were more likely to be affected by choice of conversion ratio when study-specific central estimates were large.

Although the true relationship among ozone metrics is not constant, our overall results show little influence from the choice of metric conversion method. We applied the ratio from the US study of 78 communities (1.76:1.53:1) for the remaining analyses, as that study was a systematic analysis particularly focused on approaches to converting ozone metrics, and location-specific conversion ratios were not available for all study locations. We also used the same ratios to generate results for key findings in the 8 h maximum ozone metric.

3.2. Summary effects of ozone and respiratory hospitalizations

Table 1 presents meta-analysis results in the form of 24 and 8 h maximum ozone. Most estimates in table 1 were calculated by the random-effect model, which indicates heterogeneity across studies' results. We observed associations between ozone and hospitalization or emergency visits for all disease categories: total or general respiratory disease, pneumonia, COPD or asthma. All estimates for a 10 ppb increase in the 24 h ozone were as large as or larger than those for a 10 ppb increase in the daily 8 h maximum ozone, although a 10 ppb increase in the 24 h metric corresponds to approximately a 15 ppb increase in the 8 h maximum metric. All analyses for the elderly showed associations (total respiratory disease, pneumonia, or COPD general hospital admissions; total respiratory disease emergency hospital admissions) with effect estimates ranging from a 2.47% to 4.47% increase in risk per 10 ppb 24 h ozone. Other observed associations were for all ages for COPD (general or emergency hospital admissions) and total respiratory disease (emergency hospital admissions or emergency visits). Results did not indicate associations for total respiratory disease for general hospital admissions for all ages or children, emergency hospital admissions for adults (15–64 years), or emergency visits for children. Associations were observed for asthma for emergency hospital admissions for all ages, and emergency visits for all ages and children. Asthma emergency hospital admissions were not associated with ozone levels for children or adults (15–64 years).

Some studies adjusted for PM, using a variety of particle size distributions. Results were generally similar with and without PM adjustment. In some cases, the central effect estimate for O_3 was slightly higher with PM adjustment (e.g., [74, 30] for the age group $\geqslant$25 years); however, in many cases it was slightly attenuated (e.g., [9, 32, 37, 75]), with results that were originally statistically significant remaining so. In a few cases, some results lost statistical significance with inclusion of PM (e.g., [30] for those aged <25 years [39], for days <25 °C [76]). Effect estimates became statistically significant with inclusion of PM in a few cases (e.g., [77]).

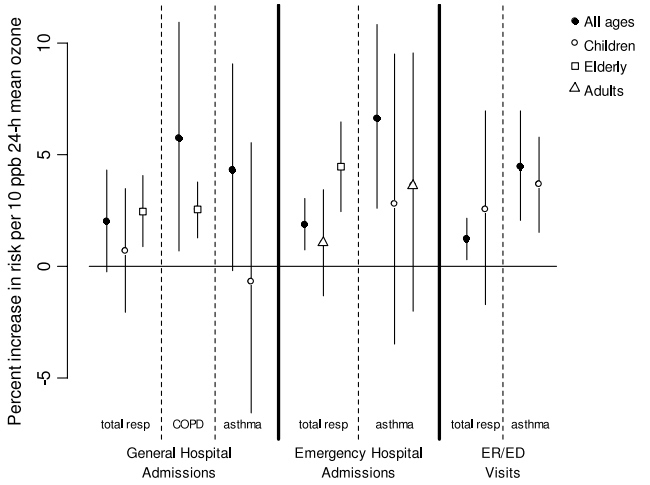

Figure 2. Comparison of overall effect estimates for total or general respiratory disease by hospital visit type, disease, and age group.

3.3. The age of the study subjects

The relationship between ozone and hospital admissions or emergency visits was influenced by the subjects' age. Figure 2 compares overall effect estimates by age group for total or general respiratory diseases by visit type. Sufficient data were not available to generate overall estimates for all hospital visit types, disease categories, and age groups. Effect estimates were slightly higher for the older age categories, with higher estimates for the elderly than children or adults for general or emergency admissions for total respiratory disease, and with higher estimates for adults than children for emergency hospitalizations for asthma.

3.4. The lag of the exposure

Studies considered different lag times between exposure and hospitalization. Data were insufficient for calculating overall effects for every lag structure; however, we were able to stratify lag selection for certain disease categories, hospitalization type, and age group combinations. Although effects were similar, effects at lag1 were consistently higher than those at lag0 for all comparisons. The increase in risk of hospital admissions for a 10 ppb increase in 24 h ozone for lag1 and lag0 was 2.51% (1.58, 3.45%) compared to 1.95% (1.08, 2.83%) for general hospital COPD admissions for the elderly; 4.14% (−1.50, 10.12%) compared to −4.06% (−11.84, 4.43%) for general hospital asthma admissions for children; and 4.96% (2.05, 7.96%) compared to 2.10% (−1.00, 5.31%) for emergency visits for asthma for children. Central estimates at lag1 and lag0–1 were similar at 2.02% (1.09, 2.93%) compared to 1.88% (0.90, 2.90%) for total or general respiratory disease emergency hospital admissions for the elderly. Central estimates were similar for lag1 and lag0–2 at 4.75% (3.71, 5.81%) compared to 5.15% (1.01, 9.45%) for emergency hospital admissions for asthma for all ages.

3.5. The exposure season

We classified estimates into three seasonal categories: (1) year round; (2) warm season (e.g., April–October, temperature >25 °C); and (3) cold season (e.g., November–March, temperature ⩽25 °C). Studies in tropical or subtropical cities (e.g., Taipei) generally defined warm and cold time periods by temperature because of a lack of distinct seasons. We identified five estimates (four from Europe, one from Hong Kong) with results for all three seasonal categories for the same disease category, hospitalization type and age group, which were total or general respiratory emergency hospital admissions for the elderly. Associations were observed in all seasonal categories. The largest effect of a 3.13% (2.04, 4.23%) increase in risk per 10 ppb 24 h ozone was found for the warm season, while 1.98% (1.17, 2.80%) and 1.67% (0.26, 3.11%) were observed for all year and the cold season, respectively. For children's asthma emergency visits the combined estimate for the warm season, 3.11% (1.08, 5.18%), was higher than that for all year round, 1.08% (3.78, 3.94%).

3.6. The study region

As most studies were conducted in North America, Europe and particular Asian cities (e.g., Hong Kong), we could make only limited comparisons by region. We combined summary estimates for asthma emergency hospital admissions among all ages in Europe and non-European countries separately. The overall estimate for the four non-European locations (Canada, Australia, two in Hong Kong) was an 8.89% (3.64, 14.45%) increase in risk per 10 ppb 24 h ozone, compared to 4.04% (−1.74, 10.16%) for the four European studies (The Netherlands, Spain, two in the UK). US and non-US estimates for children's asthma ER/ED visits were similar at 2.27% (1.17, 3.38%), based on six US studies (Portland, Maine; District of Columbia; state of Maine; St Louis; two in Atlanta) and 3.55% (−1.14, 8.46%), based on seven non-US studies (Australia, Ireland, France, Mexico, UK, two in Canada). Stratifying these cities by North America versus non-North American locations yielded results of 2.64% (1.65, 3.66%) for North American locations compared to 3.06% (−6.36, 13.43%) for non-North American studies. Overall, our analysis indicates potential differences in some effects by region; however, our ability to investigate differences by region was hindered by a lack of studies from numerous locations.

3.7. Publication bias

For the Egger linear regression test, a non-zero intercept indicates the presence of publication bias. We found that most data groups from table 1 did not indicate a statistically significant non-zero intercept, indicating lack of evidence for publication bias. Considering the small number of estimates in each data group, we used 0.10 as the significance level, and identified only three data groups with potential indication of publication bias (table 2). Figure 3 shows an example funnel plot for the association between ozone and emergency hospital admissions for total or general respiratory disease, with and without adjustment for publication bias. If no publication bias

Table 2. Percentage increase (95% interval) in risk of hospital admissions or emergency visits per 10 ppb 24 h ozone with and without adjustment for publication bias. (Note: bold estimates are statistically significant.)

Hospitalization type	Disease category	Age group	Total # of estimates	Without adjustment for publication bias	With adjustment for publication bias
General hospital admissions	Total or general respiratory disease	Elderly	9	**2.47 (0.89, 4.07)**	**2.26 (0.89, 3.64)**
Emergency hospital admissions	Total or general respiratory disease	Elderly	11	**4.47 (2.48, 6.50)**	**2.97 (1.05, 4.94)**
Emergency visits	Total or general respiratory disease	All ages	5	**1.23 (0.29, 2.17)**	**1.77 (0.66, 2.88)**

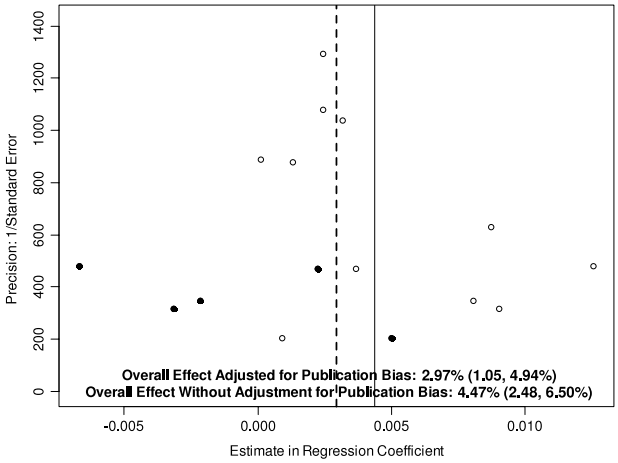

Figure 3. Funnel plot of estimates of association between ozone and total or general respiratory disease emergency hospital admissions for the elderly with and without adjustment for publication bias. Note: effect estimates show the percentage increase in risk (95% confidence interval) for a 10 ppb increase in daily ozone.

occurred, the plot of regression coefficients versus standard error would be approximately symmetrical. The 'trim and fill' approach estimates the number and results of hypothetical studies that would, if published, provide a more symmetrical distribution. In figure 3, open circles represent original studies' estimates. Filled circles represent hypothetical estimates added by the 'trim and fill' method, and mirror a subset of the actual studies (open circles). The solid line reflects the central estimate by meta-analysis random model from the original estimates; the dashed line is the central estimate after the 'trim and fill', which is adjusted for publication bias. The mirror axis is very close to the dashed line and thus not shown.

Table 2 shows overall results with and without adjustment for publication bias. After adjusting for publication bias, central estimates became smaller and confidence intervals narrowed; however, associations with ozone remained. For all ages, for total or general respiratory emergency visits, the linear regression test showed an inverse bias as the individual estimates were small or even negative. Thus after adjustment, the central estimate increased slightly.

Several multi-city studies investigated short-term ozone exposure and respiratory hospital admissions or emergency visits. Here we define multi-city studies as those that present an overall estimate across several cities, as opposed to those that only present multiple single-city estimates without an overall estimate. The multi-city study design is less subject to publication bias or between-study variation due to differences in model design, as a uniform framework is applied to all cities separately. Supplemental table 2 (available at stacks.iop.org/ERL/6/024006/mmedia) summarizes the main results from multi-city studies. We used the same conversion ratio [100] as was applied in the meta-analysis to convert multi-city estimates to a 24 h mean metric. Multi-city studies were based in Canada, Australia, Europe, or the US. The largest was for 36 US cities [82].

We compared multi-city estimates to meta-analyses results by hospitalization type, disease category and age group, with close matches to lag selection and exposure season (table 3). In five of the six comparisons, meta-analysis results exceeded multi-city studies' estimates, which provides further evidence of publication bias in single-city studies. For general hospital admissions for total or general respiratory disease among the elderly, the estimate from multi-city studies, 2.33% (0.55, 4.13%), was closer to the meta-analysis estimate adjusted for publication bias, 2.26% (0.89, 3.64%), than the unadjusted meta-analysis estimate, 2.47% (0.89, 4.07%).

4. Discussion

Several studies applied meta-analytical approaches to ozone and mortality [87–89]. To the best of our knowledge, no previous meta-analysis examined short-term ozone exposure and respiratory hospitalizations. Although multi-city studies have been conducted, our research aims to incorporate the value of previously conducted work by synthesizing evidence from single-city studies and investigating heterogeneity among study results.

We found that effects were similar by season, but higher for warm periods than year-round estimates, which were higher than cold season estimates. Individuals may have more outdoor activities in warm periods, resulting in higher exposure. Ozone's impact on respiratory morbidity may be non-linear with different relative effects depending on ozone levels, which vary by season [86]. For instance, a U-shape relationship was reported for ozone and hospital admissions [109, 110]. A threshold effect, with no or little effect at low levels, would result in different effects by season. One study found evidence of a threshold of ~40–50 ppb for 8 h maximum ozone and hospitalizations [11]. However, others found increased risk of hospitalizations at 8 h maximum ozone <50 ppb, and the shape of the concentration–response function based on quintiles of

Table 3. Percentage increase (95% interval) in risk of hospital admissions or emergency visits per 10 ppb 24 h ozone for meta-analysis and multi-city studies. (Note: bold estimates are statistically significant.)

Disease	Type of result	Location	Lag selection	Age group	Season	Estimate (95% confidence interval)
			General hospital admissions			
Total respiratory diseases	Meta-analysis result [53, 54, 59, 75, 116, 117]	6 single cities from 6 studies	Short-term lags*	All ages	All or warm	2.03 (−0.21, 4.31)
	Multi-city study [81]	16 Canadian cities	Lag1	All ages	Warm	**2.50 (1.56, 3.45)**
Total respiratory diseases	Meta-analysis result [9, 10, 52, 54, 85, 117, 118]	9 single cities from 7 studies	Short-term Lags[a]	Elderly (65+)	All or warm	**2.47 (0.89, 4.07)**
						2.26 (0.89, 3.64)[b]
	Multi-city study [81]	16 Canadian cities	Lag1	Elderly (65+)	Warm	**2.33 (0.55, 4.13)**
Asthma	Meta-analysis result [39, 53, 56, 119–121]	6 single cities from 6 studies	Short-term lags[a]	All ages	All or warm	**6.52 (1.38, 11.96)**
	Multi-city study [83]	10 cities in Canada	Not specified	All ages	All	**2.17 (1.12, 3.22)**
			Emergency hospital admissions			
COPD	Meta-analysis result [15, 16, 29, 84, 124]	6 single cities from 5 studies	Short-term lags[a]	All	All	**5.06 (1.24, 9.05)**
	Multi-city study [78]	5 cities in Europe	One-day lag	All	All	**2.60 (1.32, 3.90)**
Asthma	Meta-analysis result [6, 40, 43, 57, 71, 123]	6 cities from 6 studies	Short-term lags[a]	Children	All	2.83 (−3.45, 9.52)
	Multi-city study [79]	4 cities in Europe	Lag0 or lag1	Children	All	−0.77 (−4.14, 2.71)

[a] Multiple short-term lags in different studies. [b] Adjusted for publication bias.

ozone concentration did not suggest a threshold [6]. Few studies considered a non-linear relationship between ozone and hospitalizations, although lack of a threshold was observed for ozone and mortality [111]. Interaction with or confounding by temporally varying factors such as weather and co-pollutants could also result in different effects by season.

A meta-analysis of ozone and mortality found that the overall result from studies reporting a single lag was higher than the overall result from studies providing estimates from multiple lags [89], implying that studies were more likely to report the lag with the largest effect. We were unable to explore lag structures in this manner due to a lack of available data; however, we examined publication bias in other ways. Although funnel plot results for some groups of estimates have an asymmetrically distributed shape, suggestive of publication bias, the Egger linear regression test provides evidence of publication bias for only a few groups of estimates. Our results may be affected by the small number of estimates in data groups. Combined results from meta-analysis of single-city estimates were generally larger than corresponding results from multi-city analysis, and the difference between single-city and multi-city results narrowed after meta-analysis results were adjusted for publication bias. The discrepancy between the two kinds of results further suggests publication bias.

Our analysis revealed challenges in comparing across studies, in addition to publication bias. Many factors that could lead to heterogeneity across results were unreported or difficult to capture due to a small number of effect estimates, such as regional differences. Our protocol identified studies published over a time frame of almost 20 years. Associations between ozone and hospitalizations may have changed over this time frame, such as from changes in socioeconomic factors, and these temporal trends may vary by region. For example, prevalence of residential air conditioning, which affects exposure, has a diverse geographic distribution, is related to socioeconomic status, and is increasing [112]. Several studies demonstrated that air conditioning prevalence can modify health effect estimates for ozone [82, 113, 114].

Our ability to fully analyze differences by lag selection was limited, as many studies did not report results of all lag structures. Studies tend to report results for the lag(s) with the most statistically significant result, which may bias estimates upward [115]. However, if associations are observed in a multiple-day lag selection but not in a single-day lag selection, studies investigating single-day lag(s) might underestimate the effect [88].

Researchers applied different classifications of disease categories, even for identically worded categories (e.g., 'pneumonia'). To generate overall estimates, we combined similar disease categories, although the actual diagnosis code(s) used in previous studies varied. Researchers also used different ozone metrics; thus results must be converted to a common metric for comparison, although the actual relationship among ozone metrics differs even within a community [100]. However, we found little difference among overall meta-analysis results based on the conversion ratio applied.

In summary, we found associations between short-term ozone exposure and respiratory hospital admissions or emergency visits for several disease categories, although estimates were sensitive to study characteristics and suggest publication bias for some data groups. On the basis of our analysis of previously conducted studies, we encourage application of the same or similar approaches to future analyses to aid comparison across results. As an example, researchers using different categorizations of disease categories could perform sensitivity analysis with diagnostic codes consistent with earlier work. Authors could report results from all lags used to avoid publication bias. The ability to compare and synthesize results across studies is important for regulatory

agencies, such as the US EPA and World Health Organization, that periodically review scientific evidence on how air pollution affects human health, and establish regulations and guidelines accordingly. Our findings that suggest publication bias in single-city estimates indicate that the use of multi-city studies may be particularly useful for providing evidence for policy decisions, although an overall assessment of scientific evidence also should consider single-city studies, especially as locally important factors, such as differences in population vulnerability, may play a role in how ozone affects health.

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