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Statistical Meta-Analysis: Air Pollution & Children's Health

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Abstract

There have been numerous studies seeking to establish an association between air pollution and children's adverse health outcomes, and the ultimate findings are often varied. A few studies found a statistically significant association between an increase in a specific pollutant and an adverse health effect among children, while others find a non-significant association between the same pair of variables. These conflicting results undermine confidence in the final conclusions, and this leads naturally to a novel application of the so-called statistical meta-analysis whose primary objective is to integrate or synthesize the findings from independent and comparable studies. In this paper we first review a recent statistical meta-analysis paper by Weinmayr et al. (2010) dealing with studies on the effects of NO_2 and PM_{10} on some aspects of children's health. In the second part of this paper, we conduct our own meta-analysis focusing on the association between children's (binary) health outcomes (such as cough and respiratory symptoms) and four pollutants: PM_{10}, NO_2, SO_2, and O_3. While we find a statistically significant association with every pollutant, it turns out that for PM_{10}, NO_2, and SO_2, there is significant heterogeneity among the estimated effect sizes (odds ratios). Finally, we explore the techniques of meta-regression by incorporating distinct study features to meaningfully explain the heterogeneity.

Keywords and Phrases: Air pollution, Cochran's Chi square, DerSimonian-Laird estimate, Fixed effects model, Health effects, Meta-analysis, Random effects model.

AMS Classification: 62J02, 62P12.

1 Introduction

This paper is devoted to a study on statistical meta-analysis of the effects of air pollution on children's health. Associations between air pollution and mortality have been assessed in numerous international studies at various time periods, and many of these primary studies examined the simultaneous effects of a number of pollutants, including particulates and gases, as well as the influence of many cofounders such as age, season, and cause of death. It is hoped that our meta-analysis based on several pertinent studies dealing with some aspects of children's health (asthma, respiratory disease, cough, wheeze, etc.) will be of value to the research community. The meta-analysis includes the results from 21 primary data analyses, one being our own analysis (Stanwyck et al. 2010) based on the National Health Interview Survey data of the United States (http://www.cdc.gov/nchs/nhis.htm). We acknowledge that a recent article by Weinmayr et al. (2010) is devoted to a similar exploration based on meta-analysis (see Section 4). Our paper contributes further to this area of research by investigating the effects of two extra pollutants, SO_2 and O_3, and examining sources of heterogeneity based on meta-regression methods. A review of the standard methods of statistical meta-analysis is provided in Section 2, Section 3 gives information about the data used in the analyses, and Section 4 gives detailed results of our meta-analysis for each pollutant of interest. We conclude the paper with a summary and discussion, given in Section 5.

2 Methods of Statistical Meta-Analysis

In the context of meta-analysis, an effect size θ is a primary parameter of interest, and all studies under consideration are supposed to provide independent estimates of θ, say $T_1, \ldots, T_k$ along with their estimated standard errors $se(T_1), \ldots, se(T_k)$. Before actual pooling of different effect size estimates, it is mandatory to carry out a test of homogeneity of the underlying population effect sizes,$H_0 : \theta_1 = \cdots = \theta_k$, and the most widely used test procedure is based on Cochran's (1937) chi square statistic. We reject the homogeneity hypothesis H_0 if $Q_C > \chi^2_{k-1,\alpha}$, where

$$Q_C = \sum_{i=1}^{k} \frac{(T_i - T)^2}{\hat{\sigma}^2(T_i)} = \sum_{i=1}^{k} \frac{T_i^2}{\hat{\sigma}^2(T_i)} - \frac{(\sum_{i=1}^{k} T_i/\hat{\sigma}^2(T_i))^2}{\sum_{i=1}^{k} 1/\hat{\sigma}^2(T_i)},$$

T is defined below, and $\chi^2_{k-1,\alpha}$ is the upper α percentile of the χ^2 distribution with $k-1$ degrees of freedom. If H_0 is accepted, we follow what is known as a fixed effects model and compute a combined estimate of the common population effect size θ and its estimated variance, T and $\hat{\sigma}^2(T)$.

$$T = \tilde{\theta} = \frac{\sum_{i=1}^{k} T_i/\hat{\sigma}^2(T_i)}{\sum_{i=1}^{k} 1/\hat{\sigma}^2(T_i)}$$

$$\hat{\sigma}^2(T) = \widehat{\mathrm{Var}}(T) = \frac{1}{\sum_{i=1}^{k} 1/\hat{\sigma}^2(T_i)}$$

There are several confidence intervals that can be calculated for the common effect size estimate, including the familiar large-sample confidence interval (based on the standard normal distribution), which we denote with I_1 , as well as two intervals based on the t-distribution: one developed by Follman and Proschan (1999) and another by Hartung and Knapp (2001) and Sidik and Jonkman (2002), denoted by I_2 and I_3 respectively. When, however, the null hypothesis H_0 of homogeneity of the effect sizes is rejected, we cannot simply pool the estimated effect sizes because there is no common effect size θ . This falls into what is known as a random effects model, where we try to ascertain the causes of rejection of H_0 , i.e., variations among the population effect sizes $\theta_1, \ldots, \theta_k$, under the assumption that the θ's oscillate around a central value . We assume the following model:

$$T_i \sim N\Big(\theta \ , \ \tau^2 + \sigma_w^2(T_i)\Big),$$

where $\tau^2 \geq 0$ is the heterogeneity parameter and $\sigma_w^2(T_i)$ denotes within-study variance. There are various reasons which can lead to the heterogeneity among the θ_i's: different studies use different designs, different sets of covariates, different features of the same set of covariates, and so on. There are several ways to estimate this parameter τ^2; we use the well-known DerSimonian-Laird (1986) estimate given by

$$\hat{\tau}^2_{DSL} = \frac{Q_C - (k-1)}{\sum_{i=1}^{k} \hat{w}_i - \sum_{i=1}^{k} \hat{w}_i^2 / \sum_{j=1}^{k} \hat{w}_j}$$

where $\hat{w}_i = 1/\hat{\sigma}^2(T_i)$ and Q_C is Cochran's homogeneity test statistic defined above. Once τ^2 is estimated, an estimate of the central value and associated confidence intervals can be calculated. Estimate of the central value θ is given by

$$T_{rand} = \hat{\theta} = \frac{\sum_{i=1}^{k} \left[\hat{\tau}^2 + \hat{\sigma}_w^2(T_i)\right]^{-1} \ T_i}{\sum_{j=1}^{k} \left[\hat{\tau}^2 + \hat{\sigma}_w^2(T_j)\right]^{-1}}$$

with the estimated variance of $\hat{\theta}$ given by

$$\mathrm{Var}(T_{rand} = \hat{\theta}) = \hat{\sigma}^2_{T_{rand}} = \left\{ \sum_{i=1}^{k} \left[\hat{\tau}^2 + \hat{\sigma}_w^2(T_i)\right]^{-1} \right\}^{-1}.$$

As with the fixed effect estimate, there are several appropriate confidence intervals. The large sample $(1-\alpha)$ level confidence interval of θ is denoted by I_1 . Two alternative confidence intervals, analogous to those described above in the fixed-effect case, are also given (I_2 and I_3). Of course, the simple random-effect model described above may not capture all sources of variations among the θ_i's, and we can use the available

information on covariates and the methods of meta-regression to model the variations among the θ_i's (Hartung, Knapp, and Sinha 2008, Chapter 10). The fixed-effects meta-regression with one covariate can be written as $T_i \sim N\left(\theta + \beta x_i, \sigma_i^2\right)$, where x_i is a feature of the i^{th} study (and can be quantitative or an indicator variable). θ represents the treatment effect when $x_i = 0$ (i.e. the central value of the treatment when the study features are all set to zero) and β is the change in the treatment effect for a unit change in the study feature x_i. σ^2 is the true variance of T_i. Because the true variance of the i^{th} study is unknown, we plug in estimated values of the study variances. See Hartung, Knapp, and Sinha (2008) for details of the meta-regression. A special feature of meta-analyses with the logistic regression models is that results may be reported as regression coefficients or as odds ratios for different increases of a pollutant. Transformations must be made so that study results are comparable before any meta-analysis can be performed. Here we only consider studies that use logistic regression modeling, and show the transformation process in the simplest case. If there is only one regression coefficient, the logistic regression model is

$$\pi(x) = \frac{e^{\alpha+\beta x}}{1 + e^{\alpha+\beta x}},$$

where $\pi(x)$ is the probability of the adverse health outcome (a function of the covariate x). When we wish to calculate an odds ratio for the probability of the adverse health effect for an increase of size δ in the pollutant concentration, the calculation is as follows:

$$\text{Odds ratio } = \frac{\pi(\delta)[1-\pi(0)]}{\pi(0)[1-\pi(\delta)]} = \frac{\frac{e^{\alpha+\beta\delta}}{1+e^{\alpha+\beta\delta}}\left(\frac{1}{1+e^{\alpha}}\right)}{\frac{e^{\alpha}}{1+e^{\alpha}}\left(\frac{1}{1+e^{\alpha+\beta\delta}}\right)} = \frac{e^{\alpha+\beta\delta}}{e^{\alpha}} = e^{\beta\delta}.$$

This is the calculation that is used to transform the combined effect size estimate (calculated with regression coefficients) into an odds ratio. In the cases where an odds ratio (OR) and 95% confidence interval (LB_{OR}, UB_{OR}) are given for some increase (say δ) of a pollutant, a regression coefficient, β and its estimated standard error $\widehat{se(\beta)}$ is calculated as follows: $\beta = \frac{\ln(OR)}{\delta}$,

$$\widehat{se(\beta)} = \frac{\ln(UB_{OR}) - \ln(LB_{OR})}{2\delta z_{\alpha/2}}.$$

While the increment δ and the measurement x both refer to an amount of pollutant, different notation is used because x stands for a pollution measurement for some time period and δ indicates an **increase** in pollution measurements for which the odds ratio is computed. There is an underlying assumption that each study provides unbiased estimates of the effect size of interest; a biased or inaccurate study may have an influence on the outcome of the meta-analysis. Another assumption is that the published studies are representative of all studies on a particular topic: it can

sometimes happen that studies with significant results are more likely to be published, which can give a skewed picture to the meta-analyst. There are techniques available to detect publication bias, but in this case we felt them unnecessary since most studies included in this meta-analysis reported results for several pollutants and different models, many of which were not statistically significant.

3 Data

Our meta-analysis focuses on specific children's health outcomes (such as coughing, wheezing, and asthma symptoms), and evaluates the effects of PM_{10}, NO_2, SO_2, and O_3 including the results of our own primary study. To our knowledge, there have been no meta-analyses that connect children's health outcomes and the effects of SO_2, and O_3. Furthermore, we know of no meta-analyses on children's health that have incorporated meta-regression to explore the sources of heterogeneity among the underlying effect sizes. By now there have been more than 20 years of a multitude of primary studies seeking associations between air pollution and children's health. The studies vary wildly in scope: single-pollutant models address different specific pollutants, from PM_{10} and $PM_{2.5}$ to SO_2, NO_2, Ozone, organic carbon, black smoke and so on. Multi-pollutant models address different combinations of pollutants, sometimes measured with different metrics or at different levels. Even among studies which focus on the same pollutant, features such as study design, target population, and statistical models can be very different. These differences can create difficulties for the meta-analyst, since it may be challenging to find studies of sufficient similarity to combine estimates. On the other hand, the various studies of air pollution and children's health give differing results: some studies show an adverse effect to children's health (significant or not), while others conclude no such effect exists. This is where a meta-analysis can be the most beneficial: combining appropriate study results to find out whether or not a significant effect of air pollution on children's health exists. We take recourse to fixed- or random-effects meta-analysis, depending on the situation. There are some salient features of the many existing primary studies. Some common outcomes include cough, wheeze, FEV (forced expiry volume, a continuous measure of lung function), bronchitis, asthma, phlegm, sore throat, and mortality. Most of the studies are short-term, but lags in the models may be different from study to study. The children involved in the study come from different populations: age groups may differ, e.g. primary school students or all children from 5-18 years, and so can pre-existing conditions such as asthma or wheezing. Many studies use logistic regression to model the pollution effects, but some use Poisson regression, a log-linear model used for count data, or even linear regression in the case of continuous outcomes. Depending on the type of model being used, different effect sizes are reported: odds ratios, relative risk, a coefficient showing increase or decrease in lung function, a coefficient showing increase or decrease the in percentage of children experiencing some effect, and so on. Another important factor to consider is covariate selection. Some studies

include measurements of personal-level covariates, such as demographics and health-behavior; some studies include community-level covariates, such as humidity, average temperature, dew point, day of week, and season; while some studies include all of the above. Since climate-related covariates have been shown to be an important factor in air pollution studies, the inclusion (or not) of such information may be a source of heterogeneity between studies. As initial inclusion criteria, we chose studies that reported effect size for single-pollutant models for PM_{10}, NO_2, SO_2, and/or O_3 (ozone). Some studies reported results for all pollutants, while others focused on a single pollutant. The studies were published within the last 20 years, and the data-collection for the studies occurred between 1990 and 2003. We limited the studies under consideration to those that dealt with binary outcomes and used logistic regression modeling, and those that reported results for children (18 years and younger). These initial inclusion criteria resulted in 21 studies out of hundreds. Of these studies, 10 coincide with primary studies used by Weinmayr et a. (2010), while 11 primary studies are not included in that meta-analysis. Other studies used by Weinmayr et al. (2010) were excluded because they did not meet our inclusion criteria, they overlapped with other data sets or geographical regions, or they were not easily available. Due to the focus on single-pollutant models, results are reported by pollutant. Table 1 shows the studies we used for our meta-analysis (Stanwyck, Sinha, and Wei 2010).

Table 1: Lists of studies used in meta-analysis (by year of data collection)

Study Number	Data Collection Years	Year Published	Authors
1	1990-1991	1992	Pope, CA and D Dockery
2	1990-1991	1993	Roemer W. and G. Hoek et al.
3	1990-1993	1998	Vedal, Sverre and John Petkau, et al.
4	1991-1992	1996	Romieu, Isabelle and Fernando Meneses et al.
5	1991-1992	1997	Peters, A. and D.W. Dockery et al.
6	1992-1993	1998	Segala, C. and B. Fauroux et al.
7	1992-1994	1999	McConnell, Rob and Kiros Berhane et al.
8	1992-1995	1999	Boezen,H. and S.van der Zee et al.
9	1993	2002	Mortimer, K.M. and L.M. Neas et al.
10	1993-1995	2000	Yu, O. and L Sheppard et al.
11	1993-1995	2006	Schildcrout, Jonathan S. and Lianne Sheppard et al.
12	1994	2004	Jalaludin Bin B. and Brian I O'Toole et al.
13	1995-1996	2002	Brauer, Michael and Gerard Hoek et al.
14	1995-1996	1999	Hirsch, T and S.K. Weiland et al.
15	1996	2002	Just, J. and C. Segala et al.
16	1996-1999	2003	McConnell, Rob and Kiros Berhane et al.
17	1997-1999	2004	Mar, Therese F. and Timothy V. Larson et al.
18	1998-2001	2008	O'Connor, George T. and Lucas Neas et al.
19	2001	2004	Kim, Janice J and Svetlana Smorodinsky et al.
20	2001	2003	Gent, Janneane F. and Elizabeth W. Triche et al.
21	2001-2003	2010	Stanwyck, Elizabeth and Bimal Sinha et al.

It is worth noting that the selection of inclusion criteria is an important step in the meta-analysis and can influence results. The inclusion criteria must be narrow enough to select studies that are similar enough to be combined, yet loose enough to select a reasonable number of studies. If inclusion criteria are too narrowly defined, only a small number of studies will be selected for the meta-analysis. If, on the other hand, inclusion criteria are too widely defined, then the meta-analyst may combine unrelated studies or studies measuring different things. It is assumed that meta-analysts choose studies appropriately: all studies conforming to inclusion criteria should be included,

regardless of whether the outcome is what the analyst expects.

4 Results

4.1 PM_{10}

The studies that reported results for particulate matter included the following geographical regions within the United States: Utah Valley, Utah; Los Angeles Area, California; Spokane, Washington; Seattle, Washington; San Francisco, California; Albuquerque, New Mexico; Baltimore, Maryland; Boston, Massachusetts; Denver, Colorado; San Diego, California; and St. Louis, Missouri. Outside of the United States, the following regions were included: Toronto, Ontario, and Vancouver Island, British Columbia, Canada; Mexico City, Mexico; Australia; The Netherlands; Paris, France; and Sokolov, Czech Republic. While there was some overlap of geographical regions between studies, we made sure that studies occurring in the same geographical region were separated temporally, so that there is no duplication of information, with the possible exception of studies 19 and 21. Study 19 included data collected on children ages 8 to 12 years in the San Francisco Bay Area, while study 21 (our own study) included NHIS data collected on children up to 18 years old over the entire United States for the same year. Because the NHIS study included such a wide geographical area and a larger age group for children, we felt that any overlap of data would be minimal. All data collection for pollution data and health data occurred between 1991 and 2001. Outcomes were restricted to cough, asthma symptoms, and lower respiratory symptoms. These outcomes are similar enough to combine information, while other outcomes reported (such as bronchitis) may reflect a different pollution effect. 13 studies were similar enough to combine in a meta-analysis; effect sizes were reported as odds ratios in 11 studies, while in two studies (Study 1 and Study 21) the regression coefficient was reported. Table 2 summarizes study information for those studies included in the PM_{10} meta-analysis. Study numbers correspond to those listed in Table 1.

Table 2a: Studies used in PM_{10} meta-analysis (by year of data collection), part I

Study	Study Years	Children's Age (years)	Symptomatic?	Sample Size	Outcome
1	1990-1991	11 to 13	1	39	cough
3	1990-1992	6 to 13	0	206	cough
4	1991-1992	5 to 7	1	71	cough
5	1991-1992	6 to 14	1	89	cough
7	1992-1994	10 to 16	1	493	cough
8	1992-1995	7 to 11	1	130	lower resp
10	1993-1995	5 to 13	1	133	asthma symp
11	1993-1995	5 to 13	0	990	asthma symp
12	1994	5 to 13	1	125	cough
15	1996	7 to 15	1	82	cough
17	1997-1999	7 to 12	1	9	cough
19	2001	8 to 12	0	1109	asthma symp
21	2001	0 to 17	0	2645	resp symp

Table 2b: Studies used in PM_{10} meta-analysis (by year of data collection), part II

Study	Original Estimate	SE/CI	per $\mu g/m^3$	Transformed Estimate (effect size)	SE for Transformed Estimate
1	0.506*	0.143	100	0.00506	0.00143
3	1.07	(1.02, 1.11)	10	0.0067659	0.0021571
4	1.1	(1.06, 1.15)	20	0.0047655	0.0010395
5	1.01	(0.97, 1.06)	45	0.0002211	0.000503
7	1.1	(0.8, 1.7)	19	0.0050163	0.0101205
8	1.36	(1.13, 1.64)	100	0.0030748	0.0009502
10	1.08	(1.01, 1.17)	10	0.0076961	0.0037514
11	1.02	(0.98, 1.07)	25	0.0007921	0.0008965
12	1	(0.97, 1.02)	12.25	0	0.0010467
15	1.1	(0.88, 1.37)	10	0.009531	0.0112919
17	1.09	(1.02, 1.16)	10	0.0086178	0.0032811
19	1.02	(0.96, 1.09)	14	0.0014145	0.0023141
21	0.00436*	0.002826	1	0.00436	0.002826

The first column in table 2 gives the study number, and the second column gives the span of years in which the data were collected. The third column gives children's ages, which vary from an 18-year range (study 21) to a 2-year range (studies 1 and 4). The fourth column, "Symptomatic?" is an indicator for whether the children under study were asthmatic or symptomatic (where symptomatic is defined within each study, e.g. history of wheeze or cough). The fifth column gives the sample size (number of children involved in the study), and the sixth gives the specific outcome used in that study. The next two columns give the effect size (odds ratios in all but the first and twenty-first studies) and confidence interval (or standard error, in the case of the first and twenty-first study); these values are directly reported in the original studies. Then there is a list of the increment of PM_{10} for which each odds ratio or coefficient was calculated in the original studies (ranging from 10 to 100 $\mu g/m^3$ of PM_{10}): different studies report results based on different increases of the pollutant in question. For example, study 4 reports an odds ratio for an increase of 20 $\mu g/m^3$ of PM_{10}, while study 8 reports the odds ratio for an increase of 100 $\mu g/m^3$ of PM_{10}. Appropriate transformations are required of the reported effect size estimates for compatibility before meta-analysis can be performed; the transformations are described in section 2 above. The last two columns give the transformed effect size estimates β and their standard errors $se(\beta)$. These two columns of the table are in the same terms for each study and are thus comparable. As an example, study 10 reported an estimate almost ten times larger than that of study 11, which may very well be a sign of heterogeneity

among the effect sizes. It is important to emphasize that the weights of each study within the meta-analysis need not be inversely related to the sample size of the study. For example study 7 (493 subjects) has a much larger sample size than study 5 (89 subjects), but the subjects in study 5 recorded daily measurements over 7 months while those in study 7 had measurements taken only once for the entire previous year. The additional precision with respect to each subject's measurement in study 5 is reflected in the smaller estimated standard error. Here is a special note about study 21 (Stanwyck et al. 2010): the data analysis for this study was done on the pollutant TSP, or total suspended particulates, rather than on PM_{10}. Following Stieb et al. (2002), we transformed the effect size estimates (odds ratio) under TSP to PM_{10} by using the transformation $PM_{10} = TSP * 0.55$. All other studies under consideration reported results for PM_{10} directly, thus making all of them compatible. A forest plot of the results is depicted in Figure 1. It is evident that the reported results except study 12 show an increase in adverse health effects (i.e. coefficients greater than 0 or odds ratios greater than 1), but less than half (5 out of 13) of the studies also reveal a statistically significant result. It is not clear from a visual inspection of the studies whether or not there is a common underlying effect, or whether there is an adverse health effect. As mentioned in the introduction, a first step for meta-analysis is to apply Cochran's test for homogeneity. If the hypothesis of homogeneity cannot be rejected then a fixed-effects model will be appropriate. However, if the hypothesis is rejected a random-effects model may be more appropriate. Based on the last two columns of Table 2, the value of Cochran's χ^2 is 41.7 with a P-value smaller than 0.0001, leading to the rejection of the homogeneity hypothesis, however results for both the fixed and random effects models are reported for all pollutants to demonstrate the difference between these models. Table 3 shows combined effect size estimates (regression coefficient and its standard error) for PM_{10}, which we have converted to odds ratios for a 10 $\mu g/m^3$ of PM_{10} increase for ease of interpretation. For both regression coefficients and odds ratios, we give three confidence intervals, discussed earlier. We report results for both fixed and random effect models for comparison purposes. At the bottom of the table, the between-study variability ($\hat{\tau}^2$) is reported, calculated using the familiar DerSimonian-Laird estimate. Below that is Cochran's Q, shown with its P-value, and finally Higgins I^2 , an estimate of the proportion of total variation in the combined effect size standard error that is due to heterogeneity between studies (Higgins and Thompson, 2002).

Table 3: Combined effect size estimates for PM_{10} meta-analysis

	combined estimate (se)	95% CI I_1	Alternative CI I_2	Alternative CI I_3
Regression coefficient (fixed model)	0.0017 (0.000326)	(0.0011,0.00234)	(0.0009,0.0026)	(0.0002,0.0034)
Odds ratio (fixed model)	1.017145	(1.011, 1.024)	(1.009,1.026)	(1.002,1.034)
Regression coefficient (random model)	0.0031 (0.000811)	(0.0017,0.0048)	(0.0012,0.0054)	(0.0012,0.0053)
Odds ratio (random model)	1.03314	(1.017, 1.05)	(1.012,1.0554)	(1.012,1.055)
between-study variability [τ^2]	0.0000043			
Cochrans Q (P-value)	42.63 (<0.0001)			
Higgens I^2	71.80% (50.7%, 83.9%)			

It can be seen from Table 3 that the results are very similar whether a fixed or random effects model is used. The random effects models show a slightly larger effect than the fixed effects models, but in both cases it is clear that there is an adverse health effect on children associated with an increase in PM_{10}. Figure 1 shows a forest plot for the above meta-analysis of PM_{10} studies.

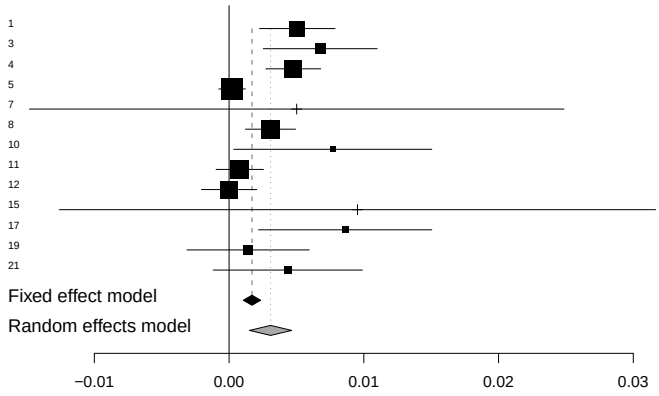

Figure 1: Forest plot for PM_{10} meta-analysis, showing the weight of each study in the meta-analysis as well as fixed and random-effects model estimates.

Table 4: Meta-regression parameter estimates for PM_{10}

variable	estimate	se	P-val	95% CI lower	95% CI upper
intercept	-0.0011	0.0038	0.7801	-0.0086	0.0065
upper age	-0.0007	0.0002	0.0005	-0.001	-0.0003
US	0.0039	0.0012	0.0013	0.0015	0.0062
outcome	0.0068	0.002	0.0005	0.003	0.0107
number of years	0.0037	0.0011	0.0008	0.0015	0.0059
number of cities	0.00005	0.00005	0.0051	0	0

A test for residual heterogeneity yielded 7.74 for Cochran's Q, corresponding to a P-value of 0.3529, an indication that significant sources of heterogeneity between studies were accounted for with the variables above. Had it not been the case, we could have used a random-effects meta-regression model (see Hartung, Knapp, and Sinha 2008 for more details). The negative value for intercept means that the estimated effect of PM_{10} when all other covariates are equal to zero is -0.0011. Upper age is a variable that ranges from 7 to 18 years; the negative estimate indicates that the adverse effect of PM_{10} is stronger on the younger age groups, as expected. The indicator variable for whether the study was conducted in the U.S. has an estimate of 0.0039, which means that studies conducted in the United States find a stronger effect of PM_{10} than those outside the United States. A positive parameter estimate for

outcome indicates that cough (outcome=1) is associated more positively with PM_{10} than other outcomes (outcome=0). The estimate for number of years is also positive, indicating that the studies conducted over more years found more of an adverse effect than shorter-term studies; this may provide an argument for long-term studies in the future. The parameter estimate for number of cities is statistically significant but so small as to be negligible. The estimated effect of PM_{10} for a particular study can be estimated as follows: -0.0011 -0.0007(upper age limit) + 0.0039 (U.S. indicator) + 0.0068 (cough indicator) + 0.0038(number of years study was conducted). A study conducted for 3 years with an upper age limit of 13 years conducted in the United States with cough as the outcome can be figured as follows: = 0.0119 = -0.0011 - 0.0007(13) + 0.0039 + 0.0068 + 0.0038(3) = 0.0119. This yields an odds ratio of 1.126 for an increase of 10 $\mu g/m^3$ of PM_{10}.

4.2 NO_2

The geographical regions in the studies of NO_2 were: Southern California; San Francisco, California; Boston, Massachusetts; the Bronx, New York; Chicago, Illinois; Dallas, Texas; New York, New York; Seattle, Washington; Tucson, Arizona; (and outside of the U.S.) Dresden, Germany; Paris, France; the Netherlands; and Australia. The two studies that have outcomes from New York were conducted in different years (1993 and 1998-2001 for the Bronx and New York City respectively), and hence do not contain overlapping information. Outcomes considered were lower respiratory symptoms, cough, and bronchitic symptoms. Odds ratios were reported in every study under consideration, but like PM_{10} the odds ratios were computed for different increases in the pollutant. Further, some odds ratios were computed for an increase calculated in $\mu g/m^3$, while others were reported in ppb (parts per billion). We used the following formula to convert all results to terms of ppb (http://www.caslab.com/Air-Testing/FAQ.php#q1):

$$ppb = \frac{\mu g/m^3 \times 24.45}{M_r} \text{ where } M_r = \text{ molecular weight in g/mol}$$

The molecular weight of NO_2 is 46.0055 g/mol, which can be seen in a Periodic Table of the Elements. Table 5 shows the study features. Notice that while some studies coincide with those used in the meta- analysis of particulate matter (studies 7, 11, 12, 15, and 19) because they provided estimates for both pollutants, others did not provide estimates of PM_{10}, and are used here for the first time.

All results are reported in terms of odds ratios, and all studies except one (study 12, as with the PM_{10} results) report odds ratios greater than 1. However, fewer than half of the studies in question show a statistically significant result. Even among non-significant results, estimates vary wildly: Study 8 shows a result nearly five times as large as that of study 16, despite similarities in outcome and symptomatic status of the children under the two studies. There are some differences in study features, the most striking of which is children's ages. The ages of children included in the study are

Table 5a: Studies used in NO_2 meta-analysis, part I

Study	Study Years	Children's Age (years)	Symptomatic?	Sample Size	Outcome
6	1992-1993	7 to 15	1	43	cough
7	1992-1994	10 to 16	1	493	cough
8	1992-1995	7 to 11	1	130	lower resp
11	1993-1995	5 to 13	0	990	asthma symp
12	1994	5 to 13	1	125	cough
13	1995-1996	0 to 2	0	3707	cough
14	1995-1996	5 to 11	0	2218	cough
15	1996	7 to 15	1	82	cough
16	1996-1999	9 to 13	1	479	bronch sympt
18	1998-2001	5 to 12	1	861	cough
19	2001	8 to 12	0	1109	bronch sympt
21	2003	0 to 17	0	5684	Resp allergies

Table 5b: Studies used in NO_2 meta-analysis, part II

Study	Original Estimate	SE/CI	per $\mu g/m^3$	Transformed Estimate (effect size)	SE for Transformed Estimate
6	1.62	(0.99, 2.64)	26.57291	0.0181548	0.009416
7	1.6	(0.9, 2.7)	24	0.0195835	0.0116774
8	1.2	(1.03, 1.39)	21.258328	0.0085765	0.003597
11	1.06	(1, 1.13)	20	0.0029134	0.0015589
12	1	(0.98, 1.03)	8.2	0	0.0015481
13	1.02	(0.89, 1.18)	5.4740194	0.0036176	0.0131441
14	1.21	(0.96, 1.52)	5.314582	0.0358674	0.0220577
15	1.22	(1.05, 1.44)	5.314582	0.0374161	0.0151611
16	1.07	(1.02, 1.12)	33.8	0.0020017	0.0007059
18	1.17	(0.99, 1.39)	20.4	0.0076963	0.0042436
19	1.02	(0.99, 1.06)	3.6	0.0055007	0.0048412
21	3.533	(¡0.0001, 999.99)	10	0.0012622	0.0065318

roughly similar except for study 13 which focuses on children aged 0-2. The reasoning for focusing on such a young age group is that these children may be more susceptible, however other primary studies focus on children older than 5 because some health outcomes are difficult to pinpoint below age 5 (e.g. asthma). Study 13 is included despite the difference in age groups with the thought that age group can be included in a meta-regression and tested to see if it is a source of heterogeneity. Cochran's Q yields a P-value of 0.0404, hence the hypothesis of homogeneity is rejected. Table 6 shows the combined effect size estimates and odds ratios, confidence intervals, an estimate of between-study variability, Cochran's Q, and Higgin's I^2.

Table 6: Combined effect size estimates for NO_2 meta-analysis

	combined estimate (se)	95% CI I_1	Alternative CI I_2	Alternative CI I_3
Regression coefficient (fixed model)	0.00235 (0.00057)	(0.0012,0.0035)	(0.0009,0.0037)	(0.0005,0.0042)
Odds ratio (fixed model)	1.024	(1.0124, 1.0353)	(1.009,1.038)	(1.005,1.043)
Regression coefficient (random model)	0.00389 (0.001071)	(0.0013,0.0064)	(0.0008,0.007)	(0.00034,0.00744)
Odds ratio (random model)	1.0397	(1.013, 1.065)	(1.008,1.0723)	(1.0034,1.0772)

between-study variability $[\tau^2]$	0.0000056
Cochrans Q (P-value)	20.38 (0.0404)
Higgens I^2	46% (0%, 72.4%)

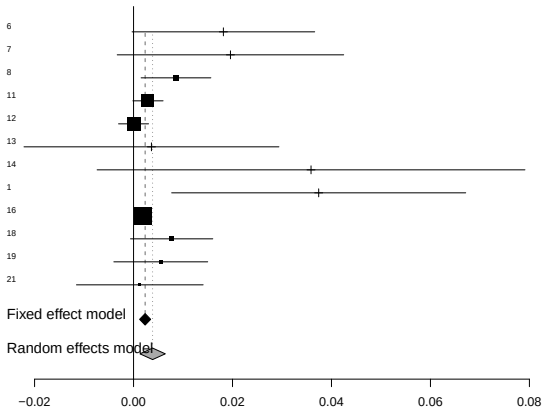

Figure 2: Forest plot for NO_2 meta-analysis

The estimated effect for the random effects models is larger than that of the fixed effects model, also seen with PM_{10}. The meta-analysis shows that there is a statistically significant adverse health effect in children associated with an increase of NO_2. As with PM_{10}, we give several confidence intervals for the combined effect size estimate. Notice that the alternative confidence intervals are both wider than the large-sample interval. Figure 2 shows a forest plot for NO_2 studies.

As with PM_{10}, we explore heterogeneity using meta-regression. The same study features were explored for NO_2, including a categorical variable used to indicate area. Rather than just indicating the United States, this variable has a value for European countries and another for Australia (Australia=0, United States=1, and European countries=2). These variables were tried exhaustively, in many combinations, and it was found that study length alone explains heterogeneity the best. Table 7 shows the parameter estimates and confidence intervals. The estimates can be interpreted as follows: estimated effect for a study of length 2 years is 0.0025(2)-0.0012 = 0.0038, which corresponds to an odds ratio of 1.0387 for a 10 ppb increase in NO_2.

Table 7: Meta-regression parameter estimates for NO_2 meta-regression

variable	estimate	se	P-val	95% CI lower	95% CI upper
intercept	-0.0012	0.0025	0.6263	-0.006	0.0036
Study length	0.0025	0.0012	0.0283	0.0003	0.0048

A test for residual heterogeneity yielded a Cochran's Q value of 15.29, which corresponds to a P-value of 0.1216. A small P-value (for instance, smaller than 0.05) would be evidence against the null hypothesis that there is a single underlying effect size, so

the P-value of 0.1216 indicates that we have nicely accounted for the heterogeneity between studies.

4.3 SO_2

The geographical regions under study for SO_2 are as follows: Baltimore, MD; St. Louis, MO.; Albuquerque, NM; Boston, MA; Denver, CO; San Diego, CA; Seattle, WA; Toronto, Ontario, Canada; Dresden, Germany; The Netherlands; Paris, France; and Sokolov, Czech Republic. Study years span 1991-2001, and outcomes include coughing, phlegm, bronchitis, asthma, runny nose, wheeze, difficulty breathing, pulmonary function, chest tightness, medication use, doctor visits, missed school, and FEV. As with NO_2, effect sizes are reported in terms of increases of SO_2 measured in both ppb and $\mu g/m^3$, so a transformation is necessary for the estimates to be compatible. The transformations were described in the NO_2 section and are very similar. The molecular weight of SO_2 is 64.07, as can be seen on the Periodic Table of the Elements. Table 8 shows the basic study features.

Table 8a: Studies used in SO_2 meta-analysis, part I

Study	Study Years	Children's Age (years)	Symptomatic?	Sample Size	Outcome
2	1990-1991	6 to 12	1	71	wheeze
5	1991-1992	6 to 14	1	89	cough
6	1992-1993	7 to 15	1	43	cough
8	1992-1995	7 to 11	1	130	lowresp
10	1993-1995	5 to 13	1	133	asthsymp
11	1993-1995	5 to 13	0	990	asthsymp
14	1995-1996	5 to 11	0	2218	wheeze
18	1998-2001	5 to 12	1	861	wheeze
21	2001	0 to 17	0	6655	Allergy sympt

Table 8b: Studies used in SO_2 meta-analysis part II

Study	Original Estimate	SE/CI	per $\mu g/m^3$	Transformed Estimate (effect size)	SE for Transformed Estimate
2	1.16	(0.69, 1.94)	19.08	0.0077785	0.0138209
5	0.99	(0.96, 1.02)	25.57	-0.0003931	0.0006049
6	1.93	(1.18, 3.15)	19.08	0.03446	0.0131275
8	1.45	(1.13, 1.85)	15.26	0.0243416	0.0082385
10	1.07	(0.9, 1.27)	10	0.0067659	0.0087851
11	1.06	(0.99, 1.13)	10	0.0058269	0.0033742
14	1.09	(0.86, 1.38)	3.82	0.0225824	0.0316129
18	1.06	(0.87, 1.3)	12.4	0.0046991	0.0082626
21	1.05	(¡0.0001, ¿999.99)	10	0.0051254	0.018592

Children's ages were very similar, and all odds ratios were greater than 1 except that of study 5, however only two studies report significant results. Cochran's test of homogeneity yields a P-value of 0.0072, and as with the other pollutants, the random effect estimate is larger than the fixed effect estimate. Table 9 gives results for the meta-analysis; showing the combined effect size estimates and odds ratios, confidence intervals, an estimate of between-study variability, Cochran's Q, and Higgin's I^2. Figure 3 is a forest plot for SO_2 studies.

Table 9: Combined effect size estimates for SO_2 meta-analysis

	combined estimate (se)	95% CI I_1	Alternative CI I_2	Alternative CI I_3
Regression coefficient (fixed model)	0.0001 (0.000586)	(-0.0011, 0.0012)	(-0.0016,0.0016)	(-0.0026,0.0026)
Odds ratio (fixed model)	1.01	(0.9891,1.01227)	(0.984, 1.016)	(0.9741,1.0267)
Regression coefficient (random model)	0.0082 (0.003597)	(0.0011, 0.0152)	(-0.00222,0.0177)	(-0.0019,0.0174)
Odds ratio (random model)	1.0807	(1.0106,1.1715)	(0.9779,1.1944)	(0.9815,1.1898)

between-study variability [τ^2]	0.000046
Cochrans Q (P-value)	20.83 (0.0076)
Higgens I^2	61.6% (20.6%, 81.4%)

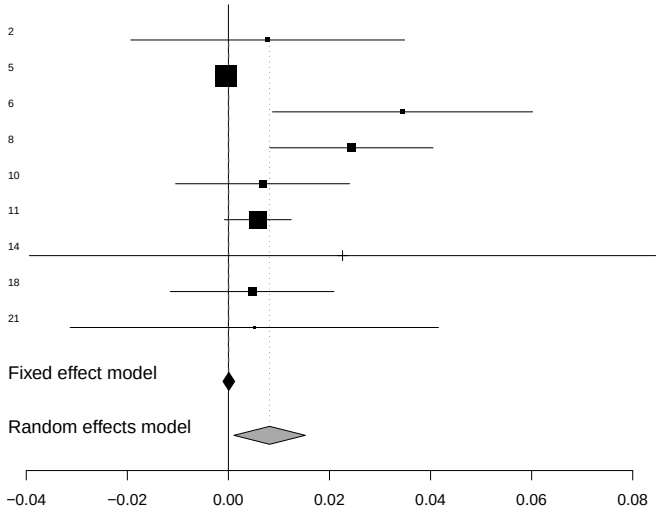

Figure 3: Forest plot for SO_2 meta-analysis

As with PM_{10} and NO_2, we explore heterogeneity with meta-analysis. The study characteristic that proves to provide the most significant sources of heterogeneity is the study length in years, as with NO_2. Table 10 gives the regression results.

As with NO_2, the positive parameter estimate for study length indicates that larger effects are found with studies that take place over a longer period of time. The estimated effect for a study lasting two years can be figured as 0.0061(2) - 0.0091 = 0.0031, corresponding to an odds ratio of 1.031 for an increase of 10 ppb of SO_2. The test of residual homogeneity yields a P-value of 0.1901 (Cochran's Q = 9.9729), indicating that these two variables account for all the heterogeneity between the studies.

Table 10: Parameter estimates for SO_2 meta-regression

variable	estimate	se	P-val	95% CI lower	95% CI upper
intercept	-0.0091	0.0114	0.4253	-0.0316	0.0133
study length	0.0061	0.0043	0.1502	-0.0022	0.0145

4.4 O_3

The geographical regions under consideration are: Bronx and East Harlem, NY; Baltimore, MD; Washington, DC; Detroit, MI; Cleveland, OH; Chicago, IL; St. Louis, MO.; Albuquerque, NM; Boston, MA; Denver, CO; San Diego, CA; Seattle, WA; Toronto, Ontario, Canada, Mexico City, Mexico; Dresden, Germany; Paris, France, and Australia. Study years span 1991-2003. Table 11 gives the study characteristics.

Table 11a: Studies used in O_3 meta-analysis, part I

Study	Study Years	Children's Age (years)	Symptomatic?	Sample Size	Outcome
4	1991-1992	5 to 7	1	71	cough
9	1993	4 to 9	1	846	asthma symp
11	1993-1995	5 to 13	0	990	resp sympt
12	1994	5 to 13	1	125	cough
14	1995-1996	5 to 11	0	2218	cough
15	1996	7 to 15	1	82	cough
16	1996-1999	9 to 13	1	479	bronch sympt
18	1998-2001	5 to 12	1	861	cough
20	2001	0 to 12	1	141	cough
21	2003	0 to 17	0	7942	Respiratory allergies

Table 11b: Studies used in O_3 meta-analysis part II

Study	Original Estimate	SE/CI	per $\mu g/m^3$	Transformed Estimate (effect size)	SE for Transformed Estimate
4	1.11	(1.05, 1.18)	50	0.0020872	0.0005955
9	1.03	(0.94, 1.12)	15	0.0019706	0.0029797
11	1.06	(0.92, 1.23)	30	0.0019423	0.0024694
12	0.97	(0.88, 1.07)	8.3	-0.0036698	0.0060085
14	0.71	(0.53, 0.96)	5.09	-0.0672346	0.0297499
15	1.04	(0.92, 1.18)	5.09	0.0076995	0.0124645
16	1.06	(1, 1.11)	37.5	0.0015538	0.0007099
18	1.03	(0.82, 1.28)	26.7	0.0011071	0.0042547
20	1.05	(0.95, 1.19)	6.7	0.0072821	0.0085762
21	1.037	(0.004, ¿999.9)	10	0.0036339	0.005902

Age ranges are roughly similar, and all but three (studies 11, 14, 21) were conducted on symptomatic children. Of the ten studies under consideration, 8 report an odds ratio greater than 1 - but only 2 of those are statistically significant. Studies 12 and 14 report odds ratios less than 1, and study 14 reports a 95% confidence interval smaller than 1. Cochran's test of homogeneity yields a P-value of 0.6043; hence the hypothesis of homogeneity is not rejected and a fixed-effects model is appropriate (however results are reported for both fixed and random effects). The common effect size is estimated to be 0.0019, which corresponds to an odds ratio of 1.019 (95% confidence interval is 1.01, 1.027) for a 10 ppb increase in O_3. Table 12 gives the results. Figure 4 shows the forest plot for O_3 studies.

Table 12: Combined effect size estimates for O_3 meta-analysis

	combined estimate (se)	95% CI I_1	Alternative CI I_2	Alternative CI I_3
Regression coefficient (fixed model)	0.0019 (0.000438)	(0.001,0.0027)	(0.0006,0.003)	(0.0007,0.0029)
Odds ratio (fixed model)	1.01877	(1.01,1.0275)	(1.006,1.0309)	(1.007,1.0303)
between-study variability [τ^2]	0			
Cochrans Q (P-value)	7.32 (0.6043)			
Higgens I^2	0% (0%, 53.7%) (50.7%, 83.9%)			

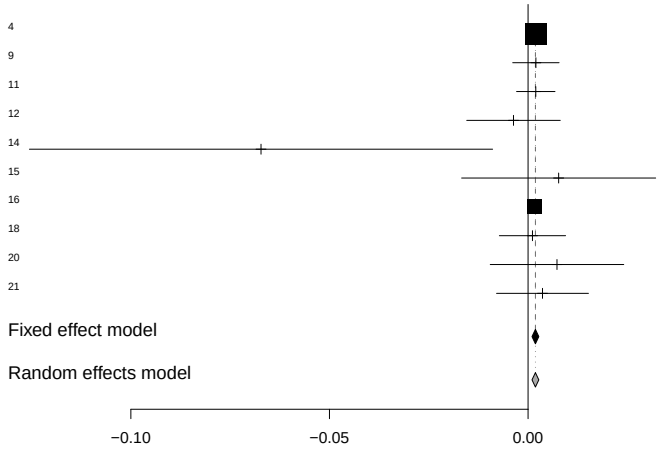

Figure 4: Forest plot for O_3 meta-analysis

Despite the negative report from study 14, it is easy to see in the forest plot that study 14 has a large variance, and contributes only a small amount to the meta-analysis. Studies 4 and 16 (the statistically significant positive results) have the smallest variance and thus contribute most to the common effect size. This explains why we find a statistically significant common underlying effect despite the varied results in primary studies.

5 Discussion and Conclusions

Table 13 summarizes the different common effect sizes estimated for each pollutant from our meta-analysis. Despite varied results within the primary studies, each meta-analysis clearly shows an adverse effect on children's health.

The odds ratio for PM_{10} is given for an incremental increase of 10 $\mu g/m^3$, but the odds ratios for the three remaining pollutants are given for an incremental increase

Table 13: Summary of common odds ratio estimates for all pollutants

Pollutant	Odds ratio	95% CI lower	95% CI upper	heterogenity
PM_{10}	1.033	1.017	1.05	0.0000043
NO_2	1.0397	1.013	1.065	0.0000056
SO_2	1.0807	1.011	1.171	0.000046
O_3	1.0188	1.01	1.027	0

of 10 ppb of the pollutant. To a limited extent, this means that the results for NO_2, SO_2, and O_3 can be compared. Among the three, it appears that SO_2 has the largest effect on children's health; however this must be interpreted cautiously because there are interactions between pollutants that are not captured with these single-pollutant models. We acknowledge a recent similar meta-analysis studying the association between air pollution and children's health. "Short-Term Effects of PM_{10} and NO_2 on Respiratory Health among Children with Asthma or Asthma-like Symptoms: A Systematic Review and Meta-Analysis" by Weinmayr et al. (2010) has many of the same goals as our own meta-analysis. Like ours, their main goal is to determine whether or not there is an effect of air pollution on children's health. While their focus was only on the pollutants PM_{10} and NO_2, ours also encompasses the pollutants SO_2 and O_3. Weinmayr et al. (2010) examined heterogeneity of common effect size estimates by stratifying according to study features, calculating common effect size estimates within strata, and then testing whether the difference between the common effect size estimates was zero. This can be contrasted with our approach, which relies on meta-regression. Meta-regression is preferable to stratification in that it can account for all study differences simultaneously, whereas stratification must be done separately for each study feature of interest.

Despite the thoroughness of the meta-analysis provided by Weinmayr et al. (2010), the authors note that there are still some factors leading to heterogeneity of the effect sizes that cannot be accounted for: use of medication among the children (including dose and frequency), the role of specific pollutants not under study in the "pollution mix" that exists in ambient outside air - not to mention the potentially very different makeup of particulate matter in different locations. The meta-analysis is further complicated by studies that may have different design aspects and protocol, occur in different geographical regions, incorporate different lag times, and possibly are comprised of different underlying subject characteristics. Despite these limitations, this meta-analysis shows strong evidence of the effect of PM_{10} on asthma symptoms and lung function of children with asthma. There is also evidence, although less pronounced, for the adverse effect of NO_2 on asthma symptoms and lung function. In conclusion, we make two important observations. 1) In spite of distinct features and differing results from primary studies, meta-analysis shows a statistically significant adverse health effect on children in the case of every pollutant. 2) Sources of heterogeneity vary from pollutant to pollutant, but significant sources of heterogeneity are identified in each case. We sincerely hope that our research on this topic will encourage other scientists to undertake further similar meta-analysis projects.

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