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Literature Review of Air Pollution-Related Health Endpoints and Concentration-Response Functions for Ozone, Nitrogen Dioxide, and Sulfur Dioxide:

Results and Recommendations

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INTRODUCTION

Every four years, the South Coast Air Quality Management District (SCAQMD) updates the regional Air Quality Management Plan (AQMP) for Los Angeles, Orange, Riverside, and San Bernardino Counties in southern California. As part of the development of this Plan, SCAQMD considers the socioeconomic impacts of the AQMP. These estimated benefits and costs are detailed in a Socioeconomic Report that accompanies the AQMP.

A key analysis in the Socioeconomic Report is an assessment of the health benefits of the AQMP on residents of these four counties. This assessment of health impacts relies on data describing the baseline incidence of mortality and morbidity endpoints, the estimated change in air pollution concentrations, and the relationship between exposure and health outcomes. SCAQMD draws this latter input from population-based epidemiological studies. These studies provide information on which health endpoints are associated with exposure to air pollutants, and the mathematical relationship between exposure and the outcome. This report presents our review of recent studies of the health impacts associated with exposure to ozone (O_3), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2) and provides recommendations to inform SCAQMD's decisions regarding which health endpoints to include in its benefits analysis of the 2016 AQMP and which mathematical functions should be used to evaluate each endpoint.

The remainder of this document describes the methods we employed for our literature search and evaluation of the studies we identified, and presents the results of our search. Finally, we summarize our recommendations to the SCAQMD for the health endpoints to include in its 2016 Socioeconomic Report, as well as the study or studies that should serve as the basis for quantifying each of those endpoints.

METHODS

Our approach to this work consisted of three steps. First, we identified the endpoints and studies used in the U.S. Environmental Protection Agency's (U.S. EPA's) National Ambient Air Quality Standards (NAAQS) Regulatory Impact Assessments (RIA). Second, we reviewed the current evaluation of O_3, NO_2, and SO_2 effects by U.S. EPA in its most recent Integrated Science Assessment (ISA) document (U.S. EPA, 2009). Finally, we conducted a review of the health literature.

U.S. EPA NATIONAL AMBIENT AIR QUALITY STANDARDS REGULATORY IMPACT ANALYSES

Because the 2012 Socioeconomic Report for the South Coast AQMP did not include health assessments for O_3, NO_2, and SO_2, we investigated U.S. EPA's RIAs in order to better understand which studies U.S. EPA has used most recently for ozone (U.S. EPA, 2015a) and NO_2 and SO_2 (U.S. EPA, 2010a and 2010b).

U.S. EPA INTEGRATED SCIENCE ASSESSMENTS

In addition to our literature review, we also reviewed the most recent Final Integrated Science Assessments (ISAs) for O_3, NO_2, and SO_2 published by the U.S. EPA (2013, 2008, and 2008, respectively), plus the current draft final assessment for nitrogen oxides published in 2015, which was the most recent document available for NO_x at the time of this review. The comprehensive assessment of the health literature presented in the ISA provides U.S. EPA's current assessment of the strength of the evidence linking exposures to these gaseous pollutants with an array of health endpoint categories and thus serves as a suitable baseline against which we can compare the findings of recent research.

SUPPLEMENTAL LITERATURE REVIEW

In order to ensure SCAQMD uses the most current science when evaluating the health impacts of air pollution control, we conducted a literature review on mortality and morbidity impacts of O_3, NO_2, and SO_2. We searched PubMed and Google Scholar for peer-reviewed articles on these pollutants from 2003 onward (SO_2), 2007 onward (O_3), and 2012 onward (NO_2), using search terms "[pollutant] AND mortality" and "[pollutant] AND morbidity," where [pollutant] was O_3, NO_2, or SO_2.[1] We additionally performed a

[1] These years, which were specified by SCAQMD in IEc's Statement of Work, reflect the last time that SCAQMD has reviewed each of these pollutants for the AQMP Socioeconomic Analysis.

separate search on "Ozone AND Asthma AND California" to ensure we had the latest studies on this key endpoint specific to the region of study. We also included several studies that did not appear in our search, but were recommended by our scientific advisor, Dr. George Thurston. We prioritized studies to evaluate for inclusion in the Socioeconomic Report by evaluating them using the criteria described in our Evaluation Criteria Memo to SCAQMD dated August 20, 2015; these criteria are summarized in Exhibit 1. Our criteria serve as guidance for evaluating studies and weighing their strengths and limitations. No one study is likely to meet all criteria listed.

EXHIBIT 1. CRITERIA FOR EVALUATING EPIDEMIOLOGICAL STUDIES

CRITERIA
GENERAL:
1. Study is peer-reviewed. 2. Study is written in English. 3. Study measures exposure to at least one of the following pollutants: O_3, $PM_{2.5}$, PM_{10}, NO_x, SO_2, 4. Preference given to studies or groups of studies that significantly advance our understanding of the relationship between air pollution exposures and mortality and morbidity endpoints, including those endpoints previously quantified by the SCAQMD in its Air Quality Management Plans as well as new endpoints. 5. Study was published within the following timeframes: a. $PM_{2.5}/PM_{10}$: 2012 – present b. NO_2: 2012 – present c. O_3: 2007 – present d. SO_2: 2003 - present
GEOGRAPHY AND STUDY POPULATION:
6. Study measures exposures at or near ambient levels found in the South Coast Air Basin. Order of preference of study location: a. South Coast Air Basin (Los Angeles, Orange, Riverside, and San Bernardino Counties) b. Within State of California c. Within Western United States d. Within United States or Canada 7. Study uses study population with similar characteristics as found in Los Angeles, Orange, Riverside, and San Bernardino counties.
STUDY DESIGN:
8. Study is population-based, preferably using cohort or case-control epidemiological study designs. Controlled human exposure studies may be evaluated for supporting evidence, or in the absence of relevant epidemiology. Animal and in-vitro studies excluded. 9. Study controls for factors that may obscure the true concentration-response relationship, including selection bias, misclassification, recall bias, confounding (including by other pollutants), effect modification, mortality displacement, loss to follow-up, etc. 10. Study appropriately assesses any potential lag between exposure and outcomes. 11. Study appropriately assesses any potential exposure thresholds for health outcomes. 12. Study clearly presents information about uncertainty in results to facilitate evaluation and comparison with other studies. 13. Prefer studies that assess changes in the risk of incidence of disease, rather than exacerbation of existing cases or changes in symptoms.

RESULTS

In this section, we review studies found during this literature review and compare these findings to studies employed by U.S. EPA in its most recent NAAQS RIAs for ozone (U.S. EPA, 2015a), nitrogen dioxide (U.S. EPA, 2010), and sulfur dioxide (U.S. EPA, 2010). All three RIAs quantified the morbidity endpoints of asthma emergency department visits, asthma exacerbation, acute respiratory symptoms, and respiratory hospital admissions (all respiratory for O_3 and SO_2, asthma and chronic lung disease for NO_2). Only the O_3 RIA quantified impacts from school loss days and mortality. In the NO_2 RIA, where U.S. EPA used more than one study, U.S. EPA chose a random/fixed effects pooling, except for asthma studies, as described below. The pooling methods for other RIAs are detailed in each section. We do not detail those studies that only include lung function metrics (e.g., Gauderman et al. 2015) because U.S. EPA does not quantify or monetize this endpoint. Below, we detail studies from our literature review that focus on populations in California, the western U.S., or nationwide. We discuss whether the studies from U.S. EPA's RIAs are appropriate to apply to SCAQMD's assessment of air pollution-related health impacts in southern California or whether we recommend updating the concentration-response function based on our review of more recent literature.

EXHIBIT 2. OVERVIEW OF STUDIES IN U.S. EPA NAAQS RIAS FOR O_3, NO_2, AND SO_2

ENDPOINT GROUP	ENDPOINT	STUDY	AGE RANGE U.S. EPA APPLIED EFFECTS ESTIMATES
2015 Ozone NAAQS RIA			
Premature mortality	Short-term mortality	Smith et al. (2009); Zanobetti and Schwartz (2008)	All ages
	Long-term respiratory mortality incidence	Jerrett et al. (2009)	>29
Hospital admissions	Respiratory (all)	Katsouyanni et al. (2009)	>65
	Asthma-related	Glad et al. (2012); Ito et al. (2007); Mar and Koenig (2009); Peel et al. (2005); Sarnat et al. (2013); Wilson et al. (2005)	0-99
Other	Asthma Exacerbation	Mortimer et al. (2002); O'Connor et al. (2008); Schildcrout et al. (2006)	6-18
	School loss days	Chen et al. (2000); Gilliland et al. (2001)	5-17
	Acute respiratory symptoms/minor restricted activity days	Ostro and Rothschild (1989)	18-65
2010 Nitrogen Dioxide NAAQS RIA			
Hospital admissions	Asthma	Linn et al. (2000)	All ages
	Chronic lung disease	Moolgavkar (2003)	>65
Emergency department visits	Asthma	Ito et al. (2007); NYDOH (2006); Peel et al. (2005)	All ages
Other	Asthma exacerbation	O'Connor et al. (2008); Ostro et al. (2001); Schildcrout et al. (2006)	4-12
		Delfino et al. (2002)	13-18
	Acute respiratory symptoms	Schwartz et al. (1994)	7-14
2010 Sulfur Dioxide NAAQS RIA			
Hospital admissions	Respiratory (all)	Schwartz et al. (1996)	65-99
Emergency department visits	Asthma	Ito et al. (2007); Michaud (2004); NYDOH (2006); Peel et al. (2005); Wilson (2005)	All ages
Other	Asthma exacerbation	Mortimer et al. (2002); O'Connor et al. (2008); Schildcrout et al. (2006)	4-12
	Acute respiratory symptoms	Schwartz et al. (1994)	7-14

MORTALITY

CAUSALITY - OZONE

In its 2013 ISA document, the U.S. EPA concludes that there is likely to be a causal relationship between short-term ozone exposures and mortality, and that the evidence linking long-term ozone exposure with mortality is suggestive of a causal relationship. U.S. EPA based its findings for short-term mortality effects on the addition of a number of multicity studies and a multi-continent study to the base of literature that previously suggested a short-term effect. The newer studies found consistent, positive associations of short-term ozone exposure with both total and cause-specific mortality, typically showing stronger effects in the warm season. Associations between long-term ozone exposure and mortality are not as conclusive at this time; results for cardiovascular mortality are mixed, and evidence of a link to total mortality is limited. The strongest evidence for long-term exposure to ozone is for a link to respiratory mortality. These mixed findings and limited database led U.S. EPA to classify the evidence linking long-term exposure to ozone and mortality as only suggestive of a causal relationship. These findings largely echo the findings of a 2008 National Academy of Sciences (NAS) panel that reviewed the ozone/mortality relationship. The NAS panel found the array of multi-city time series studies and meta-analyses conducted in the early 2000s provided "robust statistical evidence of an association," leading them to conclude that short-term ozone exposure "is likely to contribute to premature deaths" (NAS, 2008). They also indicated that the evidence did not support modeling of a threshold for these impacts.

NAS notes potential concern over confounding of the ozone-mortality relationship with PM, but also notes that the PM/ozone correlations show considerable variation from location to location. Thus, the assessment of any degree of confounding is far from straightforward and may vary spatially. A reanalysis of NMMAPS data for 98 urban communities by Bell et al. (2007) found no evidence that PM_{10} or $PM_{2.5}$ confounds the short-term ozone/mortality relationship, while an analysis of 18 U.S. communities by Franklin and Schwartz in 2008 showed some confounding of this relationship by sulfate particles, which are largely comprised of secondary pollution formed in the atmosphere, like ozone. Given the lower concentrations of sulfate particles in the South Coast study area, these two studies suggest that assessing an independent mortality effect of ozone, at least on short-term deaths, is reasonable for the 2016 Socioeconomic Report.

The studies we found in our supplemental literature review were consistent with the above U.S. EPA and NAS findings regarding causality and threshold.

CAUSALITY - NO2 AND SO2

U.S. EPA's 2008 ISA document for NO_2 found that the evidence linking short-term NO_2 to total nonaccidental and cardiopulmonary mortality was "suggestive but not sufficient" to infer a causal relationship. While U.S. EPA found that studies generally reported positive associations, it found little evidence to evaluate the coherence and plausibility of these findings, especially given difficulties teasing out the effects of NO_2, which contributes to the nitrate portion of PM, from the effects of the overall PM mass. They

found the evidence supporting a mortality association with long-term exposure to be "inadequate to infer the presence or absence of a causal relationship" (U.S. EPA, 2008a) because of inconsistent results in U.S. and European cohort studies and issues of co-pollutant confounding between NO_2 and PM. As of the second review draft ISA for nitrogen oxides, EPA was maintaining the same assessment for short-term NO_2 exposure and mortality, but was proposing to upgrade the assessment of long-term exposure and mortality to "Suggestive, but not sufficient, to infer a causal relationship" (2015b).

Findings for SO_2 are similar to those for NO_2; U.S. EPA found consistently positive associations with SO_2 on all-cause and cardiopulmonary mortality, but these results were not robust in multipollutant models. Thus, they classified the evidence as only suggestive of a causal relationship between short-term SO_2 exposures and mortality. They found evidence for associations between long-term SO_2 exposure and mortality to be less compelling, due to a lack of consistency across studies and difficulty addressing confounding by copollutants, and therefore rated the evidence as "inadequate to infer a causal relationship" (U.S. EPA, 2008b). The recent draft 2015 ISA upgrades the long-term mortality assessment to "suggestive but not sufficient to infer a causal relationship," based on "improved consistency between long-term exposure to SO2 and both respiratory and total mortality that comes from the inclusion of recent cohort studies" (U.S. EPA, 2015c).

Our supplemental literature review did not find sufficient evidence to make a different determination as to whether there is a causal relationship involving mortality impacts of either NO_2 or SO_2, independent of $PM_{2.5}$.

STUDIES FROM U.S. EPA RIAS

In its most recent RIA for the Ozone NAAQS, the U.S. EPA pooled the results of two studies for short-term ozone mortality. The first, Smith et al., 2009, conducted an extensive meta-analysis of time series studies of the short-term ozone-mortality effect from around the world. While we agree this is a high quality study, a large proportion of the inputs from the meta-analysis come from international studies, which may or may not be as relevant for application to a specific U.S. city. Thus, we focus our review for SCAQMD on the pool of Los Angeles-specific estimates we found from similarly high quality studies, including that used in the second pooled study: Zanobetti and Schwartz, 2008.

STUDIES FROM LITERATURE REVIEW: MORTALITY

Our supplemental literature review found two studies addressing ozone exposure and infant mortality and 26 studies addressing ozone exposure and mortality in adults that reported results for the city of Los Angeles, all or part of California, or the U.S. as a whole including western U.S. cities. All studies identified in our search are listed in Appendix A.

Infant mortality

Of the two studies addressing infant mortality, one (Ritz et al, 2006) was conducted in the South Coast Air Basin, but the authors did not find associations between ozone exposure and all cause death or sudden infant death syndrome (SIDS) in infants. The other study by Woodruff et al (2008) did not find an association with infant respiratory deaths and ozone, but did find an association between ozone exposure and SIDS. These studies do not provide sufficient evidence to recommend evaluating infant mortality from ozone exposures.

Adult mortality - ozone

Of the 28 studies addressing ozone exposure and mortality, three addressed only long-term exposures, one (Smith et al., 2009) addressed both, and the remainder addressed short-term exposure.

Of the 24 short-term studies, we eliminated two that focused on addressing specific issues of susceptible populations (Medina-Ramon and Schwartz 2008 and Zanobetti and Schwartz 2011) and one that focused on deaths only from chronic lower respiratory disease (Hao et al., 2015). Within the remaining set, we focused on studies in Exhibit 3 that reported an estimate of effect in Los Angeles or Southern California, either as an part of a multi-city analysis or meta-analysis, or as an input to a meta-analysis.

- **Bell and Dominici, 2008** reanalyzed data from 1987 to 2000 for 98 U.S. urban communities from the National Morbidity, Mortality, and Air Pollution (NMMAPS) dataset to identify whether community characteristics modified the effect of ozone on mortality found in past NMMAPS analyses. They found higher estimates associated with factors such as higher unemployment, larger fraction of African American population, public transportation use, and lower prevalence of air conditioning use. This study also presents region-specific mortality effect estimates from NMMAPS results, including one for Southern California for a 0.21 percent (-0.46 – 0.88) increase in mortality for a 10 ppb increase in the previous week's daily O_3.
- **Bell et al 2004 and 2005**. The first of these studies present the results of a multi-city analysis of the NMMAPS data for short-term ozone mortality impacts across 95 U.S. urban communities, using distributed lag models to estimate community-specific rates adjusted for key time-varying confounding factors, such as PM, weather, season, and long-term trends. The 2004 study also applies hierarchical Bayesian methods to integrate community-specific findings into an overall national average rate, controlling for spatial heterogeneity. The second study conducts a meta-analysis of time-series studies of ozone and mortality and compares the results to the 2004 NMMAPS findings. The 2005 study found that meta-analysis results were consistently larger than the NMMAPS results. Los Angeles was among the eight cities for which both results were generated and, while the meta-analysis central effect estimate was higher, the difference in the

central estimates was considerably smaller than for other cities, as were the reported confidence intervals for both results.

- **Huang et al, 2005** is another multi-city time series study analyzing NMMAPS data. This study uses Bayesian hierarchical distributed lag models to estimate the effect of daily summer O_3 concentrations specifically on cardiovascular and respiratory mortality in 19 large U.S. cities, including Los Angeles. Results were sensitive to adjustment for PM_{10}, but not influenced by other potential confounders such as long-term trends and other gaseous pollutants. The study reports significant positive associations in LA for models of lags 0, 1, and 2 days (values not reported in study), as well as a positive, but not statistically significant association for the distributed lag result, which is presented in Exhibit 3.
- **Ito et al, 2005** includes a meta-analysis of short-term ozone mortality studies across a wide range of cities from 1990-2003 and conducts additional time-series analysis for 7 U.S. cities. The latter analysis does not include Los Angeles, and focuses primarily on East coast or Midwest cities. We nonetheless include this study in Exhibit 3 because it provides estimates from past studies of ozone mortality in LA as inputs to its meta-analysis.
- **Levy et al. 2005** is another meta-analysis that combines 48 estimates from 28 studies of short-term mortality impacts of ozone using Bayesian metaregression methods to adjust for variation in study design (e.g., statistical methods, inclusion of specific confounding factors). The authors found an overall increase of 0.21% (0.16 – 0.26) in mortality associated with a 10 ppb change in one-hour maximum ozone concentrations, and that air pollution use and lag time explained the greatest proportion of inter-study variability. The study includes estimates of mortality impacts from past studies of ozone mortality in LA as inputs to its meta-analysis.
- **Zanobetti and Schwartz, 2008** is a study that analyzes whether there is mortality displacement (i.e., advancing deaths by a few days) due to ozone exposure that is responsible for the ozone mortality signal. This analysis of results across 48 US cities between 1989 and 2000 found increasing mortality impacts with larger ozone exposure windows, suggesting that use of a single day's ozone concentration is more likely to underestimate the mortality impact of ozone. This paper does include a figure with LA-specific estimates of the mortality effect, though exact numbers are not provided in the text.

All the studies in Exhibit 3 are high-quality studies that are well-documented. In several cases, the LA-specific results are not statistically significant, though the central effect estimates are consistently positive and of similar magnitude. The lack of statistical significance may reflect the impact of extracting city-specific results, with smaller sample size, from larger multi-city studies originally designed to report integrated U.S. estimates. We note, for example, that studies focused on LA that are used as inputs to meta-analyses

(Kinney et al., 1995 and Moolgavkar, 2003) have findings that are both positive and statistically significant.

RECOMMENDATIONS: ADULT MORTALITY - OZONE

Of the studies in Exhibit 3, we recommend an equal weight pooling of LA-specific mortality estimates based on the meta-analysis and NMMAPS results in Figure 2 of Bell et al., 2005 for the 2016 Socioeconomic Analysis. The Bell et al. study has the advantage that the meta-analytic results already incorporate results from LA studies by Kinney et al. 1995, Moolgavkar 2003, and others, and both the meta-analysis and NMMAPS estimates have relatively tight confidence intervals compared with the other studies in the Exhibit. We propose to develop a C-R function applicable to a change in the 8-hour max ozone metric (vs. 24-hour average or 1-hour max), using the conversion specified in the Bell et al. paper.

We do not recommend quantifying mortality associated with long-term exposures to ozone at this time. Despite U.S. EPA's inclusion of a long-term study in the RIA for the most recent ozone NAAQS (2015a) we continued to see mixed results in the recent studies we reviewed and are concerned about the potential for a double-counting of long-term mortality results with PM effects. Of the studies we found, Smith et al. (2009) found no association between ozone and mortality in their analysis of ACS cohort data, and Krewski et al., 2009 had similar results, with the exception of a few associations with deaths from ischemic heart disease (IHD). Jerrett et al., 2013 found associations of ozone with IHD deaths in California, but not with all-cause, respiratory, or cardiovascular categories. These results became insignificant when combined in a model with $PM_{2.5}$; however, they were significant in a model with both $PM_{2.5}$ and NO_2. In sum, while the results for IHD are potential suggestive of an association, it is not clear whether the effect being measured is attributable to ozone or PM, particularly in California. At this time, we find the evidence is not strong enough for us to recommend quantifying this endpoint for ozone at this time in the South Coast Air Basin.

RECOMMENDATIONS: ADULT MORTALITY NO_2 AND SO_2

Appendix A presents the studies we found addressing mortality impacts of NO_2 and SO_2. In short, we do not see compelling evidence in the studies we found to argue for estimating independent mortality impacts of these gaseous pollutants. Given the previous causality determinations in U.S. EPA's ISAs for these pollutants, there would need to be substantial advances in the overall numbers of studies, in the consistency of results, and in the studies that focus on addressing the co-pollutant issues raised by U.S. EPA to be able to distinguish separate mortality impacts for NO_2 and SO_2.

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EXHIBIT 3. STUDIES THAT REPORT SHORT-TERM OZONE MORTALITY IMPACTS FOR SOUTHERN CALIFORNIA OR LOS ANGELES

STUDY	LA ESTIMATE (% CHANGE IN MORTALITY)	OZONE INCREMENT/METRIC	NOTES
Bell and Dominici, 2008	0.21 (-0.46 - 0.88) for Southern CA	10 ppb daily O_3 previous week	
Bell et al., 2004	~0.2	10 ppb daily O_3 previous week	Estimated from Fig. 2; confidence interval includes zero
Bell et al., 2005	~0.3, ~0.5	lag 0 (NMMAPS); 10 ppb daily O_3 lag 0-2 (meta-analysis)	Estimated from Fig 2; lower value from NMMAPS, higher value from meta-analysis; both significant; need data to get specific values and CIs
Huang et al., 2005	0.79 (-0.69, 2.28)	10 ppb daily O_3	CVD and RESP deaths only
Ito et al., 2005	~0.4 , ~0.8	per 20 ppb 24-hr avg. O_3	Estimated from Fig 5; estimates from Kinney et al., 1991, 1995
Levy et al., 2005	0.07 (0-0.17) , 0.1 (0.02 - 0.19)	per 10 µg/m3 increase in 1-h max ozone	From Kinney et al, 1995 and Moolgavkar, 2003, respectively
Zanobetti and Schwartz, 2008	between 0 and 0.3	Per 10 ppb increase in 8-hr ozone	Estimated from Fig 1; appears positive but not significant

MORBIDITY

CAUSALITY – OZONE

In the final U.S.EPA 2013 ISA, EPA finds that respiratory morbidity has a causal relationship with short-term O_3 exposures and a likely causal relationship with long-term exposures. Cardiovascular effects were likely to be causal following short-term exposures, and "suggestive of a causal relationship" following long-term exposures. Central nervous system effects were also "suggestive of a causal relationship" for all durations of exposure. Long-term exposure's effects on reproductive and developmental endpoints, including premature birth, low birth weight, and birth defects, are also suggestive of an association. However, the evidence for long-term exposures leading to cancer is not adequate to determine a relationship (U.S. EPA 2013).

CAUSALITY – NITROGEN DIOXIDE

In the External Review Draft of the 2015 ISA, the U.S. EPA determined that there is a causal relationship between respiratory health endpoints and short-term NO_2 exposure (minutes to one month exposure duration). Long-term respiratory health effects (over one month to multiple year exposure duration) are deemed likely to be a causal relationship. Both of these statuses are updates from the last NO_2 ISA published in 2008, which stated that short-term respiratory effects were "sufficient to infer a likely causal relationship" and that long-term effects were "suggestive, but not sufficient" to determine a relationship (U.S. EPA 2008a, 2015b).

The U.S. EPA has also updated their understanding of the weight of the evidence for non-respiratory endpoints. Both short- and long-term NO_2 exposures are considered "suggestive, but not sufficient" for cardiovascular and metabolic effects; this designation was a change from the "inadequate" designation given in 2008. In the 2015 ISA, the U.S. EPA considered birth outcomes to be "suggestive, but not sufficient" of an association. However, U.S. EPA determined that the related outcomes of fertility, reproduction, pregnancy, and post-natal development still do not have adequate evidence to understand potential associations. Finally, the U.S. EPA changed the designation for cancer endpoints from "inadequate" to "suggestive, but not sufficient" for long-term NO_2 exposures (U.S. EPA 2008a, 2015b).

CAUSALITY – SULFUR DIOXIDE

U.S. EPA reported in its 2008 ISA for sulfur oxides that epidemiologic studies show evidence of respiratory symptoms in children, especially children with underlying respiratory diseases, such as asthma. It determined that there is a causal relationship between short-term SO_2 exposures and respiratory morbidity. However, U.S. EPA determined that there is "inadequate" evidence for long-term exposures to SO_2 leading to respiratory morbidity. For cardiovascular morbidity and short-term SO_2 exposures, U.S. EPA reports that the available literature is not adequate to determine a relationship (U.S. EPA 2008b). The 2015 external review draft of the ISA for SO_2 upgrades this finding to "suggestive of, but not sufficient to infer, a causal relationship," based on new evidence

linking SO_2 with cardiovascular effects in models that control for other pollutants (U.S. EPA, 2015c).

RESPIRATORY HOSPITAL ADMISSIONS

STUDIES FROM U.S. EPA RIA'S

All three RIA's assessed the impacts of air pollutants on respiratory hospital admissions. The O_3 and SO_2 RIA's quantified all respiratory hospital admissions, using results from Katsouyanni et al. (2009) and Schwartz et al. (1996), respectively. The NO_2 RIA did not quantify impacts from all respiratory admissions, but it instead calculated the change in hospital admissions only for asthma (Linn et al. 2000) and chronic obstructive pulmonary disease (COPD) causes (Moolgavkar 2003).

- **Katsouyanni et al. (2009)** is a multi-country assessment of the impact of air pollutant on mortality and morbidity (90 U.S. cities, 32 European cities, and 12 Canadian cities). It reports U.S.-specific results for respiratory and cardiovascular morbidity and mortality and uses pollution data from U.S. EPA's Aerometric Information Retrieval System and AirData System (Air Quality System) for all criteria pollutants except lead. To prevent double counting, the authors calculate total (rather than disease-specific) respiratory hospital admissions in the summer season for individuals ages 65-99. This publication reports 1-hour maximum O_3 effect estimates, which U.S. EPA converted to 8-hour maximum effect estimates to match their analysis in the 2015 O_3 RIA. EPA used equal-weight averaging to pool results of natural and penalized splines models. U.S. EPA only relied on results from the single-pollutant O_3 model because the multiple pollutant models were for the full year.
- **Schwartz et al. (1996)** is a review paper using an example of an elderly population in Cleveland, OH. Data were collected in 1988-1990. Because of the location of this study and the availability of newer studies, we do not recommend the use of this publication in SCAQMD's assessment.
- **Linn et al. (2000)** regressed the rate of hospital admissions for asthma on same day exposures to NO_2 (daily average) for populations 0-29 years and 30-99 years in Los Angeles.
- **Moolgavkar (2003)** calculated the impact of daily NO_2 averages on COPD hospital admissions in Los Angeles and Cook counties. This study used lags of 0-5 days and focused only on those 65 years or older. The strongest association was seen with a daily lag of 0 (i.e., the same day). We judge that assessing the impact of specific respiratory diseases in elderly adults may lead to a strong risk of double counting hospital admissions when combined them with studies that provide C-R functions for all respiratory hospital admissions.

STUDIES FROM LITERATURE REVIEW: ALL RESPIRATORY HOSPITAL ADMISSIONS

- **Karr et al. (2007)** assessed the effects of $PM_{2.5}$, NO_2, CO, and O_3 exposure on severe bronchiolitis on infants three weeks to one year. This study measured 18,595 hospital discharges in the South Coast Air Basin and matched each case to 10 controls (169,472) based on age and gestational age. Authors assigned monitoring stations by ZIP code, and controlled for weather (humidity and temperature), and sociodemographic factors. Authors measured exposure both by mean lifetime expo sure (mean of monthly averages) and by mean concentrations the month before admission (average of daily levels over the month). However, in single pollutant models, $PM_{2.5}$ was the only pollutant significantly associated with bronchiolitis.
- **Rodopoulou et al. (2014)** studied respiratory and cardiovascular HA and ED visits associated with PM_{10}, $PM_{2.5}$, and O_3 in adults (18 years or older) in Doña Ana County New Mexico. Exposure data came from three monitoring stations in the study area. The paper controlled for sex, age, and race/ethnicity. The mean 8-hour maximum O_3 was 43.2 ppbv. However, the study did not find significant associations with 10 ppbv increase in maximum O_3 on the previous day. Additionally, authors note that windblown dust and fires are the source of much of the pollution in this area. These sources of air pollution may make this study less transferrable to other areas of the country.

STUDIES FROM LITERATURE REVIEW: ASTHMA-RELATED HOSPITAL ADMISSIONS

NO_2

- **Delfino et al. (2014)** assessed asthma-related hospital encounters (HA and ED visits) in a case-crossover study of over 11,000 children ages 0-18 years in Orange County, CA. This study measured $PM_{2.5}$, UFP, NO_X, and CO exposures at 1, 3, 5, and 7 day lags. The mean NO_2 concentrations were 26.6 ppb in the warm season and 16.1 ppb in the cool season. NO_2 and NO_X were significantly associated with these health endpoints only for 5- and 7-day lags. Less evidence exists on the biological plausibility of longer lag periods for acute effects of air pollution (e.g., see Roy et al. 2014).
- **Delamater et al. (2012)** is an ecological study of asthma hospitalizations in Los Angeles County. Authors developed a kriging model based on monitor data in Los Angeles to estimate exposures within 3 km x 3 km grid cells. They used data from California's Office of Statewide Health Planning and Development (OSHPD) and interpolated annual state population data to calculate the average daily hospitalization rate by month. The study found that a one percent change in monthly average NO_2 was associated with a 0.37% (95% critical interval=0.22, 0.52) increase in hospitalizations.

Ozone

- **Meng et al. (2009)** analyzed the effects of annual average of O_3, $PM_{2.5}$, and PM_{10} exposures on asthmatics (all ages) in the San Joaquin Valley in CA, using California Health Interview Survey data. The two endpoints assessed were 1) experiencing daily or weekly symptoms in the past year and 2) asthma-related HA or ED visit in the past year. Exposure was measured from monitors within a five mile radius of residence of 1,502 participants. The authors calculated the annual average concentrations from hourly measurements of O_3. The study adjusted for age, gender, race, and poverty; smoking was assessed but not included in the final model. In the year prior to the study, the odds ratio of an asthma-related ED visit or hospital admission was 1.49 (95%: 1.05, 2.11) per 10 ppb annual average increase of O_3.
- **Moore et al. (2008**) analyzed the relationship between warm season O_3 concentrations and hospital discharges in children (birth - 19 years) over a period of 18 years in the South Coast Air Basin. This region is home to about 4 million children. Authors developed a 10km x 10km grid over the study area. To each grid cell, they assigned ZIP-level hospital discharge data, quarterly average O_3, SO_2, NO_2, CO, and PM_{10} concentrations, and demographic data from the 1980, 1990, and 2000 U.S. Census (smallest area available). This study controlled for race, income, temperature, humidity, income, and birth location. O_3 decreased over the course of the study. Every 10 ppb increase in the mean quarterly 1-hour maximum O_3 above the median value of 87.7 ppb was associated with a 4.6% increase in hospital discharges.

RECOMMENDATION

Based on our assessment of the U.S. EPA's most recent NAAQS RIA's and our literature review on respiratory HA, we recommend SCAQMD use two studies in their assessment of O_3 effects: Katsouyanni et al. (2009) for all respiratory HA in individuals ages 65-99 years and Moore et al. (2008) for asthma HA in children. Katsouyanni et al. provides the most comprehensive assessment of total respiratory HA across the U.S. and is the only study chosen by U.S. EPA to calculate O_3-related respiratory HA estimates. We do not recommend including studies that assessed disease-specific endpoints in individuals 65-99 years for this outcome, as this approach would lead to double counting the effects of exposure (i.e., Delamater et al., Meng et al., and Moolgavkar et al.). Also, while the Meng et al. study was conducted in California, we believe the use of self-reported data on asthma exacerbation and HAs is less preferred than studies based on hospital admissions data.

To include the effect of O_3 exposure on children's asthma-related HA, we recommend the C-R function from Moore et al. (2008). This study includes individuals from birth to 19 years and thus does not overlap with the population assessed in Katsouyanni et al. We recommend that SCAQMD adjust the risk estimate reported in that study, which is based on changes in the 1-hour maximum concentration, to a risk estimate based on changes in the 8-hour maximum, which would correspond to SCAQMD's air quality data. We

propose to do this using by dividing the reported risk estimate of $1.4x10^{-6}$ for a unit change in the 1-hour maximum ozone by the 1-hr max/8-hr max ratio of 1/1.3279 reported in the footnote to Table 3 of the Moore et al. paper.

Because NO_2 is often a marker of traffic-related air pollution, and is often highly correlated with $PM_{2.5}$ exposures near roadways (Beckerman et al. 2007), we do not recommend that SCAQMD assess asthma-related hospital admissions separately for NO_2, since it is already being evaluated for $PM_{2.5}$.

Using the reported C-R functions for both $PM_{2.5}$ and NO_2 may lead to double counting of the same cases. In our PM report, we recommended the use of Delfino et al. (2014) for asthma-related HA and ED visits.

RESPIRATORY ED VISITS

For all three pollutants, U.S. EPA quantified the impacts to asthma-related ED visits. As presented in Exhibit 3, the U.S. EPA pooled multiple studies in each RIA using random effects pooling. However, the majority of these studies assessed populations in the eastern U.S.: Atlanta (Peel et al., Sarnat et al.), New York (Ito et al., New York State Department of Health), Pittsburgh (Glad et al. 2012), Portland, ME (Wilson et al.) or in Hawai'i (Michaud 2004). Only Mar and Koenig (2009) analyzed a population living the western U.S. (Seattle). Studies in the east coast may not accurately reflect pollution patterns in southern California. For the study based in Hawaii, SO_2 was used to measure "vog" (volcanic fog). This phenomenon is not found in the study area.

STUDIES FROM LITERATURE REVIEW: RESPIRATORY ED VISITS

Ozone studies

- **Mar and Koenig (2009)** studied the effects of O_3 and $PM_{2.5}$ exposures on asthma-related ED visits for adults and children (<18 years) in Seattle. O_3 data from May-October came from two stations; $PM_{2.5}$ data came from three stations. Over the four years of study, the 1-hour maximum O_3 was 39 ppb, and the 8-hour maximum was 32 ppb. This authors did not control for potentially confounding factors (demographics, smoking, etc.); because these factors do not change over the several day lag between exposure and response. The authors did not find an association with $PM_{2.5}$, but did find the following results for a 10ppb increase in O_3:
    - Children, same day:
        - Maximum daily average O_3 concentrations; RR 1.10 (95% CI: 1.02-1.18)
        - Maximum 8-hour 1.11 (95% CI: 1.01-1.19)
    - Children, three day lag:
        - Maximum daily average O_3 concentrations; RR 1.08 (95% CI: 1.00-1.18)

        - Maximum 8-hour 1.11 (95% CI: 1.02-1.21)
        - Similar results for 2 and 4 day lags.
    - Significant, but smaller associations for adults:
        - Lags of 4-5 days significant for 1-hour maximum
        - Lags of 2, 4, 5 days significant for 8ihour maximum

- **Meng et al. (2009)** assessed the effects of ozone exposure on asthma-related ED visits; see description above for further information.

RECOMMENDATION

We recommend that SCAQMD apply the Mar and Koenig study to assess the impact of O_3 exposure on asthma-related ED visits in southern California. This study assessed both adults and children, was located in the western U.S., and was included in the U.S. EPA RIA for O_3. The concentration-response selected from this study is an 11% increase in asthma-related ED visits for each 10ppb increase in O_3 (95% CI: 1.01-1.19) based on the 8-hour maximum O_3 concentration. While this study does not assess populations in California, it does analyze a west coast city (Seattle), which is likely to have more similar air pollution composition to the Los Angeles region than cities in the eastern part of the U.S. We did not find studies that show a clear relationship between NO_2 and SO_2 exposures and this outcome.

ASTHMA EXACERBATION

All three RIAs assessed the effect of asthma exacerbation in children. This endpoint is defined as worsening symptoms of asthma, including wheeze, cough, medication usage, and/or asthma exacerbation (attack), as indicated in some research on the use of unscheduled rescue medications. The U.S. EPA did not separately quantify this endpoint for adults because it was assumed that adult asthma exacerbation effects are accounted for in work loss days and minor restricted activity days. The O_3 RIA used equal weight pooling for Mortimer et al. (2002), O'Connor et al. (2008), and Schildcrout et al. (2006). The NO_2 RIA used random/fixed effects pooling for ages 4-12 years for O'Connor et al., Schildcrout et al., and Ostro et al. (2001) and then summed these results with the results of Delfino to include 13-18 year olds. Based on findings from a U.S. EPA Scientific Advisory Board (SAB-HES (2004)) and the National Research Council (NRC 2002), it was decided to apply the effect estimates to ages 6-18, regardless of the specific population included in individual studies.

- Although **Delfino et al. (2002)** analyzed participants in southern California, the small sample size of 22 leads us to recommend pooling this result with other larger studies.
- **Mortimer et al. (2002)** studied 846 asthmatic children ages 4-9 years from the National Cooperative Inner-City Asthma Study involving eight U.S. cities: New York; Baltimore; Washington, DC; Detroit; Cleveland; Chicago; and St. Louis.

The study assessed areas with at least 30% of residents below the federal poverty line and measured asthma symptoms and lung function. Pollution measures (O_3, SO_2, NO_2, PM_{10}) came from U.S. EPA's Aerometric Information Retrieval System. In single pollutant models:

- O_3: OR per IQR four day average, 1.16 (95% CI: 1.02, 1.30)
- SO_2: 1.32 (95% CI: 1.03, 1.70) per IQR two day average
- NO_2: 1.48 (95% CI: 1.02, 2.16) per IQR six day average

- **O'Connor et al. (2008)** followed 861 children ages 5-12 years with persistent asthma and atopy from low-income Census tracts in Boston, the Bronx, Chicago, Dallas, New York, Seattle, and Tucson. For two weeks every six months, participants kept a journal where they recorded lung function, symptoms (wheeze/cough days, nighttime asthma, slow play, missed school days per two week period) and missed school days. Pollution concentrations were pulled from U.S. EPA's Aerometric Information Retrieval System; the median distance to monitors was 2.3km. About half of the children lived with adult smoker. In single pollutant models, O_3 and SO_2 were not significantly associated with symptoms. NO_2 was significant for nighttime asthma, slow play, and missed school over two week periods. The odds ratios for the 10^{th} to 90^{th} percentile change (20.4 ppb NO_2) were:
  - Nighttime asthma: 1.37 (95% CI: 1.08, 1.73)
  - Slow play: 1.26 (95% CI: 1.04, 1.54)
  - Missed school: 1.67 (95% CI: 1.18, 2.36)
- **Schildcrout et al. (2006)** analyzed daily symptoms and rescue inhaler use over the warm season in 990 children in eight North American cities (Albuquerque, Baltimore, Boston, Denver, San Diego, Seattle, St. Louis, Toronto) over two years as part of the Childhood Asthma Management Program. This study assessed short-term exposures to SO_2, PM_{10}, and O_3, with exposure-response lags of up to two days. The authors used monitor data from U.S. EPA's Aerometric Retrieval System and Environment Canada. The study controlled for race/ethnicity, annual family income, age, and sensitivity to rescue meds. O_3 (1-hour maximum) was not significant for any lag. For increases of 20 ppb for NO_2 (24 hour average):
  - NO_2 odds ratios: 1.09 (95% CI: 1.03, 1.15) for 2 day lag; 1.06 (95% CI: 1.0, 1.13) same day; 1.04 (95% CI: 1.01, 1.07) 3 day moving sum
  - NO_2 rate ratio for use of rescue inhaler: 1.05 (95% CI:1.01, 1.09) for 2 day lag
  - SO_2: 1.04 (95% CI: 1.00, 1.08) 3 day moving sum

- **Ostro et al. (2001**) studied the risk of asthma exacerbation and air pollution exposure for 138 African-American children (8-13 years) with doctor-diagnosed asthma in central Los Angeles. The study lasted for 13 weeks. The study included PM_{10}, $PM_{2.5}$, NO_2, and O_3 and controlled for age, income, time trends, and temperature. Subjects completed a daily diary, including symptoms, medication usage, and lung function measurements. Asthma exacerbation was defined as "probability of a day with symptoms" and "onset of symptom episodes." Wheeze incidence (1.08 (95% CI: 1.02, 1.15) and wheeze prevalence (1.13 (95% CI: 1.04, 1.24) were associated with an increase of 5pphm in 1-hour maximum NO_2; no endpoints were associated with O_3. No pollutants were associated with additional medication usage in the full study population.

STUDIES FROM LITERATURE REVIEW: ASTHMA EXACERBATION

Ozone studies

- **Akinbami et al. (2010**) analyzed the effect of annual NO_2, SO_2, O_3, $PM_{2.5}$, and PM_{10} averages by county across the U.S. on asthma attack risk and asthma prevalence in children ages 3-17. The authors used the 2001-2004 National Health Interview Survey (n=34,073). Pollution data came from the U.S. EPA Aerometric Information Retrieval System (AIRS). Twenty-four hour measurements for all pollutants were averaged quarterly, except O_3, which was averaged quarterly using the 8-hour maximum. Quarterly averages were then averaged to obtain rolling annual averages. The model was adjusted for presence of adult smoker, race, education, age, sex, poverty, region, and single parent household. This study found no association with NO_2 or SO_2 in adjusted models. For every 5 ppb increase in O_3, the odds ratio for asthma attack in the previous year was 1.07 (95% CI: 1.00, 1.13).
- In addition to HA and ED visits, **Meng et al. (2009)** also analyzed the effects of annual average of O_3, $PM_{2.5}$, and PM_{10} exposures asthma exacerbation. In the year prior to the study, the odds ratio for daily or weekly asthma symptoms (coughing, wheezing, shortness of breath, chest tightness, phlegm) was 1.23 (95%: 0.94, 1.60) per 10 ppb of O_3.
- **Meng et al. (2009)** assessed the effects of traffic density, and annual averages of O_3, CO, NO_2, $PM_{2.5}$, and PM_{10} on the risk of poorly controlled asthma in adults in Los Angeles and San Diego counties. Pollution concentration data was obtained from monitoring stations within a five mile radius of residence. This paper used the California Health Interview Survey data. Authors defined poorly controlled asthma as daily or weekly symptoms (coughing, wheezing, shortness of breath, chest tightness, phlegm) or two or more HA or ED visits in the prior year. This paper reported the percent of current smokers (18.6%) but does not adjust for smoking in the model. Authors found no association with NO_2, $PM_{2.5}$, or CO. Poorly controlled asthma was associated with higher O_3 exposure only in men and

elderly individuals. Per 1pphm increase in O_3, the risk of poorly controlled asthma was 1.70 (95% CI: 0.91-3.18) in the elderly and 1.76 (95% CI: 1.05-2.94) in men.

- **Young et al. (2014)** investigated the association between air pollution exposure and the incidence of doctor-diagnosed asthma, and self-reported wheeze and chronic cough in adult women (≥ 35 years) without symptoms or asthma diagnoses at the start of the study. Study participants were from the nationwide, 50,884 subject Sister Study, a cohort of women with one sister diagnosed with breast cancer but who do not have the disease themselves. NO_2 exposure estimates were based on a national kriging and land-use regression model for the year 2006. For each interquartile range of NO_2 (5.8 ppb), the odds of wheeze in the fully adjusted model were 1.08 (95% CI: 1.00-1.17). Other asthma symptom endpoints were not significant. Authors controlled for age, body mass index, race, education, occupational exposures, smoking, health insurance, and fiber consumption.

RECOMMENDATION

We recommend that SCAQMD use the same set of studies as the U.S. EPA NO_2 NAAQS RIA to assess the impact of air pollution exposures on asthma exacerbation in children younger than 18 years. U.S. EPA pooled effect estimates from O'Connor et al. (2008); Ostro et al. (2001); Schildcrout et al. (2006); and Delfino et al. (2002). We judge that this approach provides a reasonable combination of studies that assessed this impact in the Los Angeles area with larger multi-city studies that included locations in the western U.S. We do not recommend that SCAQMD conduct a separate analysis of the effects of O_3 on this endpoint in order to avoid double counting.

ACUTE RESPIRATORY SYMPTOMS

In the 2015 O_3 RIA, the U.S. EPA used minor restricted activity days (MRAD) as the metric to account for acute respiratory symptoms. U.S. EPA relied on results from **Ostro and Rothschild (1989)**, which is the same study as employed in the 2008 O_3 RIA. Ostro and Rothschild assessed 50,000 participants in the National Health Interview Survey, ages 18-65 years. This survey relied on participants' two week recall of their health status, which the RIA noted may have introduced a fair amount of error. The study controlled for age, sex, race, education, income, season, marital status, chronic health issue, and temperature. It did not control for smoking, but did not find a significant association between smoking status and air pollution. Previous studies have shown that not controlling for smoking does not necessarily bias the results. Exposures were taken from U.S. EPA's SAROAD monitors (O_3, $PM_{2.5}$). Weighting by the inverse of variance leads to a pooled estimate of MRAD of 0.185% for O_3 per 1 µg pollutant. Because this estimate is derived from multipollutant risk models, including both ozone and fine particulates, and because we recommend using the same study to quantify the impacts of $PM_{2.5}$ exposure on MRADs, we assess that it would not double count benefits to quantify MRADs for both ozone and $PM_{2.5}$.

Schwartz et al. (1994) assessed respiratory illness in 1,844 children ages 7-14 years in six U.S. cities (Watertown, MA; Kingston-Harriman, TN; St. Louis, MO; Steubenville, OH; Portage, WI; and Topeka, KS) in the warm months. In single pollutant models, exposure to $PM_{2.5}$, NO_2 (1.27 (95% CI: 1.04, 1.56) per 10ppb increase), and O_3 (1.23 (95% CI: 0.99, 1.54) per 30 ppb increase) were associated with incidence of cough and SO_2 was associated with lower respiratory symptoms (1.28 (95% CI: 1.13, 1.46) per 10 ppb increase).

RECOMMENDATION

We recommend that SCAQMD continue to follow U.S. EPA's guidance on using MRADs to assess acute respiratory symptoms for O_3 (Ostro and Rothschild). In BenMAP, U.S. EPA provides the following C-R function for the 8-hour maximum O_3 concentration:

- (1-(1/EXP(Beta*DELTAQ)))*A*POP
    - Beta=0.002596
    - A= 0.02137 (MRAD for ages 18 to 64)
    - DeltaQ=Difference in O_3 exposure between baseline and control scenarios

We also recommend that SCAQMD applies the Schwartz et al. (1994) study to assess acute respiratory symptoms cough (NO_2) and lower respiratory symptoms (SO_2). Quantifying these endpoints for NO_2 and SO_2 may double count benefits with $PM_{2.5}$, thus we recommend that SCAQMD quantifies these endpoints for either NO_2/SO_2 or $PM_{2.5}$, but not both.

SCHOOL LOSS DAYS

Only the 2015 O_3 RIA assessed missed days of school. Based on recommendations from the National Research Council (NRC 2002), the U.S. EPA applied the random effects pooled estimates from Gilliland et al. (2001) and Chen et al. (2000) to children 5-17 years. These studies are the same as used in the 2008 O_3 RIA.

- **Gilliland et al. (2001)** calculated the incidence of periods of absence from school associated with air pollution exposures in 2,081 fourth graders in communities within 200 miles of Los Angeles over 10 years. One central monitor in each of 12 communities measured O_3, NO_2, and PM_{10}. Hourly O_3 measurements were averaged over the eight hours between 10am and 6pm. Authors assessed smoking exposure, medical conditions, demographics, and outdoor activity level. U.S. EPA converted incidence to daily rates (absence periods x average duration) leading to 1.6 days for each period of absence. This study reports that short-term increases in O_3 were associated with school absences. No association was seen with NO_2 and PM_{10}. For each 20 ppb increase in O_3:
    - Illness-related absences increased 62.9% (95% CI: 18.4, 124.1%)

  - Respiratory illness: 82.9% (95% CI: 3.9, 222.0%)
  - Upper respiratory illnesses: 45.1% (95% CI: 21.3, 73.7%)
  - Lower respiratory illnesses with wet cough: 173.9% (95% CI: 91, 292.3%)

- **Chen et al. (2000)** similarly assessed daily rates of absence in Washoe County, Nevada, at 57 elementary schools encompassing nearly 28,000 students. Data on PM_{10}, O_3, and CO was taken from seven monitoring stations. The average O_3 concentration was 37.5ppb. The analysis controlled for weather and other confounders, and found that school absences increased by 13.01% (95% CI: 3.41-22.61%) for each 50ppb increase in O_3.

RECOMMENDATION

Because Gilliland et al. assesses missed school days in the South Coast Air Basin region, we recommend using the C-R function from Gilliland et al. as currently used in BenMAP for the 8-hour maximum O_3 concentration:

- (1-(1/EXP(Beta*DELTAQ)))*Incidence*POP*A*B
  - Beta = 0.007824
  - A= Scalar for % of school days in ozone season (0.3929)
  - B= Population of school children at-risk for a new absence (0.945)
  - DeltaQ= Difference in O_3 exposure between baseline and control scenarios

NEW ENDPOINTS

This review identified studies on multiple health endpoints not previously quantified by U.S. EPA. These include autism, asthma incidence, birth weight, birth defects, cardiovascular disease, diabetes, hypertension, respiratory ED visits, rheumatoid arthritis, and stroke. Of these new endpoints, we recommend the addition of new asthma disease incidence to the 2016 Socioeconomic Report. The remaining endpoints lack sufficient data to establish causality between exposure and morbidity. Below, we summarize our findings on studies of these endpoints in California, the western U.S., or nationwide.

NEW ASTHMA DISEASE INCIDENCE

This review found three articles on asthma incidence in California, one in Texas, and one nationwide. Wendt et al. (2014) assessed the effects of O_3, NO_2, and $PM_{2.5}$ in children in Harris County, Texas. The one nationwide study (Young et al., 2014) was the first publication to find an association with air pollution and asthma incidence in adult women, but, because of the lack of supporting studies, we recommend that SCAQMD focus on asthma incidence in children only. Because we found similar studies that focus on southern California, we recommend that SCAQMD use the area-specific studies:

- **Islam et al. (2007)** followed 2,057 children 9-10 years without asthma or wheeze for eight years in southern California. Authors assessed exposure to O_3 and a "non-ozone package" consisting of NO_2, $PM_{2.5}$ and PM_{10}, acid vapor, elemental carbon, and organic carbon in "high" (90^{th} percentile) and "low" (10^{th} percentile) communities. The study assessed lung function changes. Over the course of the study, 212 cases of asthma developed. However, authors found no significant difference between high and low concentration O_3 communities for asthma incidence.
- **McConnell et al. (2010)** assessed the impact of exposures of traffic related air pollution (TRAP), NO_2, O_3 (8-hour average), PM_{10}, and $PM_{2.5}$ on doctor-diagnosed, new onset asthma in a cohort of nearly 2,500 kindergarten and first grade students followed for three years. TRAP was defined as distance to nearest freeway or major road and traffic density within 150m of a student's residence and school. Students were free from asthma or wheeze at the start of the study. Pollution was measured at a single monitor in each community and weather (temperature and humidity) assessed. The study population was from Southern California Children's Health Study. For the single pollutant NO_2 model, the study reported a hazard ratio of 2.17 (95% CI: 1.18-4.00) for a range of NO_2 exposure of 23.6ppb. Mean NO_2 was 20.4ppb, with a range of 8.7-32.3ppb and an interquartile range of 12.8ppb. However, the effects of NO_2 were attenuated when assessed with a multipollutant model with both TRAP and NO_2. O_3 and PM were not associated with asthma incidence. Authors found higher incidence of asthma in those children with higher rates in maternal smoking during pregnancy, history of allergies, and/or family history of asthma.
- **Nishimura et al. (2013)** analyzed early-life (first year) NO_2 exposure in 4,320 Latino and African American children ages 8 to 21 who were part of the GALA II and SAGE II studies. The former is a study on Latinos from Chicago, the Bronx, Houston, the San Francisco Bay area, and Puerto Rico) and the latter included African Americans from the San Francisco Bay area. Authors calculated average annual exposures to NO_2, SO_2, PM_{10}, $PM_{2.5}$, and O_3 for each year of life based on U.S. EPA's Air Quality System. The study controlled for family history of asthma, IgE (high/low), and sex. Over all geographic areas in the study, NO_2 exposure during the first year of life and the first three years of life was associated with onset of asthma (OR of 1.17 (95% CI: 1.04, 1.31) and OR of 1.26 (95%: 1.07, 1.48), respectively) per 5ppb increase. The mean NO_2 concentration over the study was 19.3 ppb.

Recommendation

We recommend that SCAQMD use McConnell et al. to assess the impact of NO_2 exposures on the incidence of new asthma disease in children, using the following C-R function: hazard ratio of 2.17 (95% CI: 1.18-4.00) for a range of NO_2 exposure of 23.6ppb. This study focused on a southern California-specific population and assessed factors such as family history of asthma and allergies and maternal smoking. Nishimura

et al. analyzed exposures from multiple locations across the U.S. and the only city in California assessed was San Francisco. Islam et al.'s use of percentiles, rather than incremental changes, and their combination of NO_2 with other air pollutants, makes this study less appropriate for assessing the impact of specific air pollutions on asthma incidence.

AUTISM

- **Becerra et al. (2013)** assessed the impact of $PM_{2.5}$, O_3, CO, NO, and NO_2 exposure on the odds of developing autism for children living in Los Angeles. This study included 7,603 cases which were matched with 10 controls per case by sex, birth year, and gestational age. Exposure was measured via the nearest monitoring station and by two land-use regression models for NO_2. The first model estimated annual average pollutant concentrations and the second adjusted for each season. Results were adjusted by maternal age, education, race, maternal place of birth, type of birth, parity, insurance, and gestational age. For single pollutant models, the results were:
    - NO_2, annual average: 1.07 (95% CI: 1.03, 1.12); interquartile range of 5.41 ppb
    - NO_2, adjusted for seasons: 1.05 (95% CI: 0.98, 1.12); interquartile range of 9.70 ppb
    - NO_2, monitoring data: 1.04 (95% CI: 0.98, 1.10); interquartile range of 10.47 ppb
    - O_3, annual average: 1.06 (95% CI: 1.01, 1.12); interquartile range of 11.54 ppb
- **Volk et al. (2013)** conducted a case-control study on children enrolled in the Childhood Autism Risks from Genetics and the Environment (CHARGE) study in California. The study included 279 autistic children and 245 without autism. $PM_{2.5}$, PM_{10}, O_3, and NO_2 exposures were assessed from interpolating all monitor data within 50 km of residence, with data from U.S. AQS and University of Southern California Children's Health Study. Ozone was not significantly associated with any outcome. The model adjusted for sex, ethnicity, parental education, maternal age, and prenatal smoking. For every 14.1 ppb increase in NO_2, the odds of having autism increased by 2.06 (95% CI: 1.37, 3.09) for exposures during the first year of life and by 1.81 (95% CI: 1.23, 2.65) for exposure during pregnancy. Stratifying outcomes by trimester led to odds ratios that were significant but smaller in magnitude. Risk did not change when population density and urban vs. rural areas were added to the model.

Recommendation

Despite the findings of these two studies, we do not recommend the use of autism as an endpoint in the 2016 Socioeconomic Report. Very few other studies have reported on the association of autism and air pollutant exposures, and only limited data exists on the

possible mechanism (Hertz-Picciotto et al. 2008). Because of these issues, we suggest that autism not be assessed in the 2016 report.

BIRTH DEFECTS

Gilboa et al. (2005) is a population-based case-control study investigating the association between maternal exposure to air pollutants (NO_2, O_3, SO_2) during weeks 3-8 of pregnancy and the risk of selected cardiac birth defects and oral clefts in livebirths and fetal deaths between 1997 and 2000 in seven Texas counties (n=5,338). When the highest quartile of exposure was compared with the lowest, the authors observed positive associations between SO_2 and isolated ventricular septal defects (odds ratio = 2.27, CI: 1.51, 3.09). There were inverse associations between ozone and isolated ventricular septal defects. Evidence that air pollution exposure influences the risk of oral clefts was limited. Suggestive results support a previously reported finding of an association between ozone exposure and pulmonary artery and valve defects.

Padula et al. (2014) looked at the association between environmental contaminants (7 ambient air pollutant and traffic exposures in California during the first two months of pregnancy, 1997-2006) and congenital anomalies (N=813 cases and N=828 controls). No change in risk of congenital heart defects were associated with NO_2 or O_3. There are some incongruities between this study and previous studies. Two previous studies reported an association between ozone and pulmonary artery value defects. The current study did not find positive associations of ozone with any heart defect grouping. The explanation for these discrepancies is unknown.

Stingone et al. (2014) investigated maternal exposures to air pollutants during weeks 2-8 of pregnancy and their associations with congenital heart defects in mothers from the National Birth Defects Prevention Study (a nine-state [including California] case control study). Positive associations were observed between exposure to NO_2 and coarctation of the aorta (OR = 2.5) and pulmonary valve stenosis (OR = 2.03). They also observed a positive association between SO_2 exposure and PVS, although it was attenuated at the highest exposure level (OR=2.34). Associations between left ventricular outflow tract obstructions and NO_2 were supported by findings from the multipollutant analyses, although estimates were attenuated at the highest exposure levels.

Vinikoor-Imler et al. (2015) performed an exploratory analysis of ozone and fine particulate matter concentrations during early pregnancy and multiple types of birth defects on data from births in the Texas Birth Defects Registry and the National Birth Defects Prevention Study in Texas. Both databases had inverse associations between O_3 and septal heart defects as well as a positive association between O_3 and craniosynostosis in adjusted and co-pollutant models. To their knowledge, no other studies have reported on the relationship between O_3 concentrations and craniosynostosis. Multiple studies have been conducted examining the association between O_3 concentration and various heart defects. An earlier study performed in Texas also reported an inverse association between O_3 concentration and ventricular septal defects and null associations between O_3

concentrations and other cardiovascular defects. Further research needs to be done to fully understand the associations.

Zhu et al. (2015) studied criteria air pollutant exposure during three months preconception and gestational weeks 3-8 in relation to orofacial defects using data from the Consortium on Safe Labor (2002-2008). SO_2 was associated with isolated cleft lip with or without cleft palate (OR=1.93; CI: 1.16, 3.21). During gestational weeks 3-8, NOx were related to the risk for isolated cleft palate. Analyses by individual week revealed that positive associations of NOx with isolated cleft palate were most prominent from weeks 3-6 and 3-5 respectively. Exposure to several criteria air pollutants preconception and during early gestation was associated with elevated odds for isolated cleft palate while isolated cleft lip with or without cleft palate was only associated with preconception SO_2 exposure. According to Zhu et al., this study is the first time positive associations of exposure to NOx with isolated cleft palate, and SO_2 with isolated cleft lip, with or without cleft palate during the three months preconception exposure window, as a proxy of chronic exposure to air pollution.

Recommendation

While several of these birth defect studies find positive associations with gaseous air pollutants, we do not recommend adding this endpoint. These studies investigated a wide range of birth defects and it is unclear of these myriad endpoints have similar etiologies. These studies report contradictory findings. For example, Vinikoor-Imler et al. found positive associations with cardiac defects, whereas Padula et al. found none. Finally, a potential biologically plausible mechanism is not known.

BIRTH WEIGHT/PRETERM BIRTH

- **Laurent et al. (2014)** studied over 960,000 births in Los Angeles County and assessed exposure to NO_2 and O_3 via monitoring data from the California Air Resources Board. Hourly measurements were converted to daily means. For O_3, only measurements from 10 AM to 6 PM. Concentrations were then interpolated by a Bayesian kriging model. For exposures over an entire pregnancy, neither O_3 nor NO_2 was significantly associated with LBW (for an interquartile range (8.62 ppb) increase in O_3, the OR was 0.992 (95% CI: 0.984, 1.001); for and interquartile range (7.36 ppb) increase in NO_2, the OR was 1.008 (95% CI: 0.999, 1.017). This study controlled for many of the same factors as previously mentioned, although it did not control for smoking.

- **Morello-Frosch et al. (2010)** assessed over 3.5 million births over 10 years in California. Air pollution (CO, NO_2, O_3, SO_2, PM_{10}, $PM_{2.5}$, PM_{coarse}) was averaged by Census tract and ZIP code. Results are reported by monitor distances of 3, 5, and 10 km for both change in birth weight and odds of birth weight under 2,500g.

  For multivariate models using a distance of 3km, authors found a decrease in birth weight of 98.3g (95% CI: 7.0, 9.6) per 1 ppm NO_2 and a decrease of 8.9g (95% CI: 7.1, 10.6) per 1 ppm of O_3 for full-term births (>37 weeks). NO_2 slightly

increased the odds of birth weight below 2,500g (OR of 1.03 (95% CI: 1.01, 1.05) per ppb; SO_2 had similar associations, but was only significant at 10km distance1.01 (95% CI: 1.00, 1.02) per ppb. The model controlled for sex, gestational age, season, year of birth, parity, and maternal race/ethnicity, education, marital status, prenatal care, birth place, and age. Authors state a decrease of this magnitude is unlikely to affect the health of an individual infant, but could have population-level impacts due to the widespread exposure to air pollutants across California.[2]

- **Ritz et al., (2007)** conducted a case-control study of about 58,000 births in Los Angeles County to assess the effect of air pollution exposure on the risk of preterm birth. About 2,500 mothers were interviewed to assess confounders. Air pollution exposure was based on ZIP code. This study adjusted for mother's age, race, education, season, birth season, and parity and for the interviewed cohort, smoking, alcohol use, and marital status. For women exposed to average NO_2 between 2.62-3.12 (second quartile) pphm, odds of preterm birth increased 22% (95% CI 1.13, 1.31) (birth cohort) to 4% (95% CI 0.83, 1.30) (interviewed cohort). For concentrations above 3.13 pphm, OR was 1.09 (1.00, 1.19) (birth cohort) to non-significant for interviewed cohort. O_3 was not significantly associated with preterm birth.
- **Symanski et al. (2015)** studied the relationship between preterm birth and mean 8-hour maximum O_3 exposure for each 4 week period of each pregnancy in Harris County, Texas. O_3 data came from local monitoring data. The study assessed exposure during pregnancy for mothers who had singleton births in the Houston area from 2005-2007 (n=152,214). Authors assessed potential confounders including smoking status, race/ethnicity, education, age, body mass index, prenatal care, parity, insurance, and participation in Women, Infants, and Children services. Authors found statistically significant associations with O_3 exposures. For a 10ppb increase in county-wide O_3, authors reported the following odds ratios for a give four week period of pregnancy:
    - Late preterm birth (33-36 weeks gestation)
        - Fifth 4-week period: OR=1.08 (95%CI: 1.04, 1.12)
        - Sixth: OR=1.05 (95% CI: 1.01, 1.09)
        - Seventh: OR=1.07 (95% CI: 1.03, 1.10)
    - Moderate preterm birth (29-32 weeks gestation)
        - Fifth: OR=1.13 (95% CI: 1.02, 1.25)
        - Seventh: OR=1.15 (95% CI: 1.04, 1.27)

[2] For a discussion of the adverse impacts of shifts in population risk distributions, see American Thoracic Society. What constitutes an adverse health effect of air pollution? Official statement of the American Thoracic Society. Am J Respir Crit Care Med. 2000 Feb;161(2 Pt 1):665-73.

- Severe preterm birth (20-28 weeks gestation)
  - Fifth: OR=1.21 (95% CI: 1.08, 1.36).

- **Trasande et al. (2013)** assessed the impact of air pollutants on low birth weight across the U.S. This study used the Kids Inpatient Database (KID), which records in-hospital births from up to 38 states (depending on year). Authors used pollutant concentrations from the U.S. EPA Aerometric Information Retrieval System (AIRS) coupled with random subsampling of over 2.6 million births in KID for 2000, 2003, and 2006. Authors controlled for gestational age, birth month, gender, race, socioeconomic variables. They were able to link one third of births in KID to AIRS data (lead, PM_{10}, NO_2, SO_2, CO and $PM_{2.5}$, and reactive volatile organic compounds). Single pollutant models of NO_2 showed an association with odds of preterm birth (OR of 1.02 (95% CI of 1.01, 1.04)) and preterm LBW (OR of 1.26 (95% CI of 1.06, 1.50)). O_3 is associated with very LBW (OR of 2.60 (95% CI: 1.40, 4.82). In the multi-pollutant models, neither birth weight as a continuous variable, nor as a categorical variable (i.e., <2,500g and <1,500g) showed significant associations with NO_2 or O_3.

Recommendation

Although there is a general coherence of associations between adverse impacts on infants and pre-birth air pollution exposure to the mother, because of the limited number of studies assessing birth weight and preterm birth, and the inconsistencies in the specific pollutant and exposure time of most effect, we do not yet recommend quantifying these endpoints to the 2016 Socioeconomic Report. Laurent et al. did not find statistically significant associations with low birth weight risk. Morello-Frosch et al. found small decreases in birth weight, but the authors state that these small changes may not have any significant health impact. The upper range of their estimated decreases were under four tenths of an ounce. While Ritz et al., Symanski et al., and Trasande et al. all report significant associations with air pollutant exposures and preterm birth, their studies differ on most associated pollutant, and when during pregnancy an exposure has the greatest impact.

CARDIOVASCULAR DISEASE

- **Ensor et al. (2013)** assessed over 11,500 cases of out of hospital cardiac arrest in adults (18 years and over) in Houston, TX. Authors analyzed hourly and daily O_3, $PM_{2.5}$, NO_2, SO_2, and CO exposures and controlled for weather. Cardiac arrests were included in the study only if the patient was not dead on arrival, based on data from the Houston emergency services. Results were stratified by age, sex, race, and preexisting conditions. "A 20-ppb ozone increase for the 8-hour average daily maximum was associated with an increased risk of OHCA on the day of the event (1.039; 95% confidence interval, 1.005–1.073). Each 20-ppb increase in ozone in the previous 1 to 3 hours was associated with an increased risk of OHCA (1.044; 95% confidence interval, 1.004–1.085). Relative risk estimates were

higher for men, blacks, or those aged >65 years." Limitations of this study include the use of citywide-averaged PM data, as well as a lack of control for pre-existing conditions and risk factors.

- **Koken et al. (2013)** analyzed the effect of air pollution levels (PM_{10}, O_3, NO_2, SO_2, CO) and maximum daily temperature (*T*max) on daily HA for cardiovascular diseases in men and women ages 65 and older in July and August between 1993 and 1997 in Denver, Colorado. Unit of analysis was daily admissions >65 years old per 10,000 residents. The eligible population (>65 years) in Denver started at 64,000 at the beginning of the study and declined to 60,000 by the end. Admissions data for males and females (38% and 62%, respectively) for acute myocardial infarction (AMI), coronary atherosclerosis, pulmonary heart disease, cardiac dysrhythmias, and congestive heart failure were collected for a total of 310 days. Daily HA data were provided by the Agency for Healthcare Research and Quality (AHRQ; Rockville, MD) which maintains state-specific hospital discharge databases as part of the Healthcare Cost and Utilization Project (HCUP 2001). Air pollution data were extracted from the U.S. EPA) Aerometric Information Retrieval System (AIRS) (U.S. EPA 2002). Daily concentrations of the U.S. EPA's criteria air pollutants were obtained from all of the monitoring stations in Denver County. Daily 24-hr meteorological measurements such as *T*max and DPT were provided by the National Climate Data Center (NCDC 2002). HA data was adjusted for yearly trends, day-of-week effects, ambient maximum temperature, and dew point temperature (DPT). To account for potential delays in disease incidence after exposures, lag times of 1–4 days for each of the environmental variables were included as additional model covariates. This study found a "marginal" positive association between SO_2 and cardiac dysrhythmias at lag day zero for males and females combined. An increase in the daily average level of SO_2 from the 25th percentile (3.8 ppb) to the 75th percentile (7.2 ppb) is associated with an increased risk of hospital admission for cardiac dysrhythmias of 8.9%, with a 95% CI of –0.34–18.93% ($p = 0.055$). Positive associations were also found between O_3 and some endpoints at various lag days (coronary atherosclerosis at lag day 2, and pulmonary heart disease at lag day 1), and a negative association was found between O_3 and AMI at lag day zero. No association was found between PM_{10} or NO_2 and any of the health outcomes.
- **Rodopoulou et al. (2014):** as noted above, this study did not find significant associations with cardiovascular HA and ED visits and O_3.

Recommendation

The association between $PM_{2.5}$ exposure and cardiovascular outcomes has been well-established, as discussed in our $PM_{2.5}$ report to SCAQMD. However, exposures to gaseous pollutants and cardiovascular morbidity are less clearly understood. Of the three studies detailed above, one (Rodopoulou et al.) found no association between exposure and cardiovascular endpoints. Koken et al. found several moderate associations, depending on the lag time used. However, as reported in Roy et al. (2014),

cardiovascular effects from air pollution exposure are biologically more likely to occur at lags within several days. Ensor et al. analyzed emergency medical services data on out of hospital cardiac arrests, but because this paper states that nearly 90% of people who experience these cardiac arrests die, using the results of this paper may lead to double counting with mortality endpoints. Based on the limited amount of data on these associations, we recommend that SCAQMD continue to assess the effects of cardiovascular endpoints with $PM_{2.5}$ exposures, and not yet add gaseous effect estimates at this time.

HYPERTENSION AND DIABETES

Coogan et al., (2012) is a study of African American women in LA for incident hypertension and type II diabetes associated with exposure to $PM_{2.5}$ and NOx. The authors found a statistically significant association of both with NO_2 exposure. This was the first study of incident hypertension with air pollution and the third study to address diabetes incidence and air pollution.

Eze et al. (2015) conducted a **r**eview and meta-analysis of 13 studies in either Europe or North America of air pollutant exposure and type II diabetes risk. They found overall a positive association, but also identified a high risk of bias in results. A similar review by Balti et al. in 2014 also found a generally positive association of type II diabetes with NO_2 and $PM_{2.5.}$

Mobasher et al. (2013) evaluated the effects of ambient air pollution on the odd of hypertensive disorder of pregnancy and whether these associations varied by body mass index in a case-control study among 298 predominantly Hispanic women in the LA county area during 1996-2008. There was a significantly positive association between exposure to O_3 in the second trimester and hypertensive disorder of pregnancy (OR per 15ppb=2.05; CI: 1.22-3.46). While there are currently no studies investigating the role of O_3 in predisposing to hypertensive disorders of pregnancy, Liu et all showed a significant association between O_3 and Intrauterine growth restriction during the 2nd trimester of pregnancy. The exact mechanism by which ozone acts to increase risk is unknown; however, it is likely that increased levels of O_3 leads to increased lipid peroxidation, resulting in the release of pro-inflammatory cytokines into the circulation. Exposure to NO_2 in any trimester was not significantly associated with hypertensive disorder of pregnancy. This is consistent with previous findings.

Robledo et al. (2015) looked at the impact of preconception and early pregnancy air pollution on gestational diabetes mellitus risk. Data from electronic medical records was obtained for 219,952 singleton deliveries without pregestational diabetes among women between 2002 and 2008 based in 12 clinical centers across 15 hospital referral regions. Preconception maternal exposure to NOx (RR=1.09, CI: 1.04, 1.13) and SO_2 (RR=1.05, 1.01, 1.09) were associated with increased risk of subsequent GDM and risk estimates remained elevated for first trimester exposure. Preconception O_3 was associated with lower risk of subsequent GDM (RR=0.93, 0.90, 0.96) but risks increased later in pregnancy. Findings for NO_x were consistent with prior studies of GDM and air quality

but they added new information on the preconception exposure window and have evaluated the association between GDM with all criteria pollutants, including constituents of $PM_{2.5}$. They identified novel associations between preconception SO_2 exposure and second trimester ozone exposure and increased GDM risk.

Recommendation

Our literature review found a limited number of studies on the link between exposures to air pollutants and chronic cardiovascular and metabolic diseases, such as hypertension and type II diabetes. The review finds suggestive new evidence for both of these endpoints, but literature findings are not yet sufficient to support quantification of these endpoints.

RHEMATOID ARTHRITIS

- **Hart et al. (2013)** examined whether long-term exposures to specific air pollutants were associated with rheumatoid arthritis risk among women in the Nurses' Health Study (n=111,425). Overall, they found no evidence of increased risks of RA, seronegative or seropositive RA, with exposure to the different pollutants (including SO_2 and NO_2), and little evidence of effect modification by socioeconomic status or smoking status, geographic region, or calendar period. While there were no consistent overall associations between air pollution and risk for RA, they did observe a suggestion that selected pollutants (NO_2 and SO_2) were associated with increased risk of RA.

Recommendation

We do not recommend adding rheumatoid arthritis as an endpoint. The one national study discovered during the literature review found no evidence that air pollutants are associated with the risk of development of arthritis.

STROKE

We identified two studies assessing the relationship between stroke and O_3, NOx, or SO_2: one found a borderline association with short term levels of PM and ozone and ischemic stroke risk in Corpus Christi, TX, a city with relatively low pollution levels. The other found a relationship across 9 US cities with Ischemic stroke only (not hemorrhagic) and PM, NOx, and SO_2.

Recommendation

We assess that these impacts are likely already captured in our recommended C-R function for PM and ischemic stroke.

RECOMMENDATIONS SUMMARY

Exhibit 4 summarizes our recommended health endpoints for ozone, and three proposed NO_2/SO_2 endpoints for consideration for the 2016 Socioeconomic Report. In summary, we propose evaluation of the same endpoints evaluated in the 2015 U.S. EPA Ozone NAAQS RIA. We also recommend consideration of two endpoints from the 2010 U.S. EPA Nitrogen Dioxide NAAQS RIA, and 2010 U.S. EPA Sulfur Dioxide NAAQS RIA, , plus new cases of asthma in children younger than 18 years of age associated with NO_2 exposure. Our recommendations for which studies to use differ in several cases from the recommended studies used in the NAAQS RIAs. Most of these changes involve using more locally relevant studies conducted in southern California; others are more recent studies considered more appropriate. The U.S. EPA RIAs considered the entire U.S., whereas the focus of the 2016 Socioeconomic Report will be the South Coast Air Basin. Gray-highlighted rows indicate changes in recommended studies from the U.S. EPA NAAQS RIAs.

We note that the use of the Bell et al study values for estimating avoided all-cause mortality associated with ozone exposure will require estimating incremental mortality risk increases for Los Angeles from Figure 2 in that study. In the course of our review we requested, but were not able to obtain, the data underlying that figure from the lead author. Nonetheless, we continue to recommend the Bell et al. estimates and find Figure 2 of that paper to be clear and undistorted, which will allow us to generate an interpolated estimate of risk based on the center point of the symbols employed for the NMMAPS and meta-analysis estimates. Use of this interpolated estimate will, however, introduce additional uncertainty into SCAQMD's calculations; we estimate the error to be no more than one tenth of a percentage point in the Bell et al. risk estimate.

We caution that quantifying the endpoints specified in Exhibit 4 for NO_2 and SO_2 changes may double count benefits with those estimated for $PM_{2.5}$. We recommend that SCAQMD quantify these endpoints for either NO_2 / SO_2 or for $PM_{2.5}$, but not both. SCAQMD should consider the sources targeted by their AQMP and the predicted effects of their control measures on co-exposures when deciding whether to focus on the gaseous pollutants or $PM_{2.5}$.

Note that all C-R functions and related parameters were developed in accordance with the EPA's BenMAP-CE User's Manual Appendix C (U.S. EPA, 2015d). Specific functional forms and input parameters were delivered to the SCAQMD and are consistent with the recommendations of studies and risk models specified in this report.

EXHIBIT 4. RECOMMENDED HEALTH ENDPOINTS FOR GASEOUS POLLUTANTS

ENDPOINT	POLLUTANT	STUDY	STUDY POPULATION
Premature Mortality, Short-term Exposure			
Deaths, All-Cause	O_3 (8-hour max)	Pooled estimate: Bell et al., 2005 (meta-analysis result for LA) Bell et al., 2005 (NMMAPS result for LA)	All ages
Hospital Admissions			
Respiratory, all	O_3 (8-hour max)	Katsouyanni et al. (2009)	65-99 years
Respiratory, asthma	O_3 (8-hour max)	Moore et al. (2008)	0-19 years
Emergency Department Visits			
Respiratory, asthma	O_3 (8-hour max)	Mar and Koenig (2009)	<18 years
Other Health Endpoints			
Asthma incidence (new cases)	NO_2 (annual average)	McConnell et al. (2010)	<18 years
School loss days	O_3 (8-hour max)	Gilliland et al. (2001)	5-17 years
Acute respiratory symptoms/Minor restricted-activity days	O_3 (8-hour max)	Ostro and Rothschild (1989)	18–65 years
Asthma exacerbation*	NO_2	Pooled estimate: O'Connor et al. (2008); Ostro et al. (2001); Schildcrout et al. (2006)	4 - 12
		Delfino et al. (2002)	13 - 18
Acute respiratory symptoms*	NO_2; SO_2	Schwartz et al. (1994)	7-14 years

* Quantifying these endpoints for NO_2 and SO_2 changes may double count benefits with $PM_{2.5}$. We recommend that SCAQMD quantify these endpoints for either NO_2 / SO2 or for $PM_{2.5}$, but not both. We present them for completeness and for SCAQMD's consideration. We recommend that SCAQMD quantify these endpoints for either NO_2 / SO_2 or for $PM_{2.5}$, but not both, based on consideration of the predicted effects of their control measures.

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APPENDIX A:

RESULTS OF GASEOUS POLLUTANTS HEALTH EFFECTS LITERATURE REVIEW FOR SCAQMD SOCIOECONOMIC ANALYSIS OF 2016 AQMP

Table 1. NO_2 Mortality

Authors	Title	Year Published	Journal Published	Pollutant(s) Studied	Causes of Mortality or Morbidity Considered	Geographic scope	Population studied	Study question	Statistically significant relationships?	Analysis method	Controls for factors that could obscure relationship?	Assesses potential lag between exposure and outcome?	Reports uncertainty?	Abstract
Hart, J.E., Rimm, E.B., Rexrode, K.M., Laden, F.	Changes in Traffic Exposure and the Risk of Incident Myocardial Infarction and All-Cause Mortality	2014	Epidemiology	NO2	All-cause, myocardial infarction	United States	Nurses' Health Study, 30-55 ye	Assessed the effects of changes in traffic exposure with incident myocardial infarction and all-cause mortality	Used prospective time-varying Cox proportional hazards models. Calculated person-months of follow-up from 1 July 1990 until censoring, date of death, or the end of follow-up. Models were based on a biennial time scale and were used to estimate hazard ratios. Primarily used exposure to traffic by distance to road, but also look at NO2 concentrations.	Controlled for age and calendar year, estimating separate baseline hazards for age in months and calendar year in the Cox models. Examined possible confounding by age, race, physical activity, BMI, alcohol consumption, hypertension, diagnosed diabetes, hypercholesterolemia, family history of MI. Also controlled for smoking, alcohol consumption, diet, education level, parents' occupation, marital and employment status. Look at effect modification by diet, physical activity, outdoor physical activity, BMI, smoking status.	Predicted ambient NO2 levels in 2000	Yes	Yes	Background: Traffic related exposures, such as air pollution and noise, have been associated with increased cardiovascular morbidity and mortality. Few studies, however, have been able to examine the effects of changes in exposure on changes in risk. Our objective was to explore the associations of changes in traffic exposure with changes in risk 1990–2008 in the Nurses' Health Study. Methods: Incident myocardial infarction (MI) and all-cause mortality were prospectively identified. As a proxy for traffic exposure, we calculated residential distance to roads at all residential addresses 1986–2006, and considered addresses to be "close" or "far" based on distance and road type. To examine the effect of changes in exposure, each consecutive pair of addresses was categorized as: (1) consistently close, (2) consistently far, (3) change from close to far, and (4) change from far to close. We also examined the change in NO2 levels between address pairs. Results: In time-varying Cox proportional hazards models adjusted for a variety of risk factors, women living at residences consistently close to traffic were at a higher risk of an incident MI (HR= 1.11; 95% confidence interval = 1.01 – 1.22) and a higher risk of all-cause mortality (1.05; 1.00 – 1.10), compared with those consistently far. The highest risks were seen among women who moved from being far from traffic to close (incident MI: HR=1.50 (95%CI: (1.11–2.03); all-cause mortality: HR=1.17 (95%CI: 1.00–1.37)). Each 1ppb increase in NO2 compared with the previous address was associated with a HR=1.22 for incident MI (95%CI: 0.99–1.50). 1.03 for all-cause mortality (95%CI: 0.92–1.15). Conclusions: Our results suggest that changes in traffic exposure (measured as roadway proximity or change in NO2 levels) are associated with changes in risk of MI and all-cause mortality.
Jerrett, M., Burnett, R.T., Beckerman, B.S., Turner, M.C., Krewski, D., Thurston, G., Martin, R.V., van Donkelaar, A., Hughes, E., Shi, Y., Gapstur, S.M., Thun, M.J., Pope, C.A.	Spatial Analysis of Air Pollution and Mortality in California	2013	Respiratory and Critical Care Medicine	PM2.5, O3, NO2	Mortality from Cardiovascular disease (ICD-9: 390-429, ICD-10:I01-I59), ischemic heart disease (ICD-9: 410-414, ICD-10:I20-I25), stroke (ICD-9: 430-438, ICD-10: I60-I69), respiratory disease, lung cancer (ICD-9: 162, ICD-10: C34), all-cause	California	California adults from American Cancer Society Cancer Prevention II Study	Assesses the associations of PM2.5, O3, and NO2 with the risk of mortality in California adults	Yes (with ischemic heart disease mortality and all causes combined)	Assigned exposure for PM2.5 to subjects' addresses using an advanced remote sensing model coupled with atmospheric modeling, applied to monthly average monitoring data from 112 sites. Assessed the association between air pollution and mortality (CVD, IHD, stroke, respiratory disease, lung cancer, all other, all causes) using standard and multilevel Cox proportional hazards models.	Controlled for individual-level variables for lifestyle, diet, demographics, ocupation, and education and ecological variables at the county level. Also control for residence in a metropolitan area. Acknowledges the potential for bias from intercorrelation among the various pollutants.	Used long-term averaged exposure rates. Exposures appear to be averaged over different year ranges for different pollutants. For PM2.5, seems to be over 1998 to 2002	Yes	Rationale: Although substantial scientific evidence suggests that chronic exposure to ambient air pollution contributes to premature mortality, uncertainties exist in the size and consistency of this association. Uncertainty may arise from inaccurate exposure assessment. Objectives: To assess the associations of three types of air pollutants (fine particulate matter, ozone [O3], and nitrogen dioxide [NO2]) with the risk of mortality in a large cohort of California adults using individualized exposure assessments. Methods: For fine particulate matter and NO2, we used land use regression models to derive predicted individualized exposure at the home address. For O3, we estimated exposure with an inverse distance weighting interpolation. Standard and multilevel Cox survival models were used to assess the association between air pollution and mortality. Measurements and Main Results: Data for 73,711 subjects who resided in California were abstracted from the American Cancer Society Cancer Prevention II Study cohort, with baseline ascertainment of individual characteristics in 1982 and follow-up of vital status through to 2000. Exposure data were derived from government monitors. Exposure to fine particulate matter, O3, and NO2 was positively associated with ischemic heart disease mortality. NO2 (a marker for traffic pollution) and fine particulate matter were also associated with mortality from all causes combined. Only NO2 had significant positive association with lung cancer mortality. Conclusions: Using the first individualized exposure assignments in this important cohort, we found positive associations of fine particulate matter, O3, and NO2 with mortality. The positive associations of NO2 suggest that traffic pollution relates to premature death.

Table 1. NO_2 Mortality

Authors	Title	Year Published	Journal Published	Pollutant(s) Studied	Causes of Mortality or Morbidity Considered	Geographic scope	Population studied	Study question	Statistically significant relationships?	Analysis method	Controls for factors that could obscure relationship?	Assesses potential lag between exposure and outcome?	Reports uncertainty?	Abstract
Moolgavkar, S.H., McClellan, R.O., Dewanji, A., Turim, J., Luebeck, E.G., Edwards, E.	Time-Series Analyses of Air Pollution and Mortality in the United States: A Subsampling Approach	2013	Environmental Health Perspectives	PM10, O3, CO, NO2, SO2	All-cause non-accident	108 United States cities	All deaths, 1987-2000, from NMMAPS	Estimates maximum likelihoods of the common national effects of criteria pollutants on mortality	Use subsampling, where they randomly choose 4 cities without replacement from the 108 cities, and estimate the common pollutant effect for each sample. Ran 5,000 bootstrap cycles. Fit an over-dispersed Poisson model to the randomly chosen 4 cities. Investigate the shape of the concentration-response relationship	Control for temperature and relative humidity in each of the 4 cities in each sample. Also control for day of the week, temporal trends, mean temperature on the previous day, and mean dew-point temperature--should control for city-specific confounders, day of week effects, and time trends	Use a 1-day lag for pollutant exposure, i.e. 24-hr average pollutant concentration	Yes	No	Background: Hierarchical Bayesian methods have been used in previous papers to estimate national mean effects of air pollutants on daily deaths in time-series analyses. Objectives: We obtained maximum likelihood estimates of the common national effects of the criteria pollutants on mortality based on time-series data from ≤ 108 metropolitan areas in the United States. Methods: We used a subsampling bootstrap procedure to obtain the maximum likelihood estimates and confidence bounds for common national effects of the criteria pollutants, as measured by the percentage increase in daily mortality associated with a unit increase in daily 24-hr mean pollutant concentration on the previous day, while controlling for weather and temporal trends. We considered five pollutants [PM10, ozone (O3), carbon monoxide (CO), nitrogen dioxide (NO2), and sulfur dioxide (SO2)] in single- and multipollutant analyses. Flexible ambient concentration–response models for the pollutant effects were considered as well. We performed limited sensitivity analyses with different degrees of freedom for time trends. Results: In single-pollutant models, we observed significant associations of daily deaths with all pollutants. The O3 coefficient was highly sensitive to the degree of smoothing of time trends. Among the gases, SO2 and NO2 were most strongly associated with mortality. The flexible ambient concentration–response curve for O3 showed evidence of nonlinearity and a threshold at about 30 ppb. Conclusions: Differences between the results of our analyses and those reported from using the Bayesian approach suggest that estimates of the quantitative impact of pollutants depend on the choice of statistical approach, although results are not directly comparable because they are based on different data. In addition, the estimate of the O3-mortality coefficient depends on the amount of smoothing of time trends.

Table 2. NO_x Respiratory Morbidity

Authors	Title	Year Published	Journal Published	Pollutant(s) Studied	Causes of Mortality or Morbidity Considered	Geographic scope	Population studied	Study question	Statistically significant relationships?	Analysis method	Controls for factors that could obscure relationship?	Assesses potential lag between exposure and outcome?	Reports uncertainty?	Abstract
Delamater, P.L., Finley, A.O., Banerjee, S.	An Analysis of Asthma Hospitalizations, Air Pollution, and Weather Conditions in Los Angeles County, California	2012	Science of the Total Environment	CO, NO2, O3, PM10, PM2.5	Extrinsic, intrinsic, other asthma (ICD-9-CM: 493.0x, 493.1x, 493.8x)	Los Angeles County, CA	Daily hospital admissions	Examines the relationship between asthma morbidity, air pollution, and weather conditions at a county-level scale.		Generated monthly rates of asthma hospitalizations and then mean daily hospitalization rate for each month. Removed yearly trend and seasonal trends. Then experimented with a number of diferent model specifications, using Bayesian regression models with temporal random effects.	Controls for time trends and seasonality, but perhaps not other controls typically used.	Uses monthly average pollutant exposure	Yes	There is now a large body of literature supporting a linkage between exposure to air pollutants and asthma morbidity. However, the extent and significance of this relationship varies considerably between pollutants, location, scale of analysis, and analysis methods. Our primary goal is to evaluate the relationship between asthma hospitalizations, levels of ambient air pollution, and weather conditions in Los Angeles (LA) County, California, an area with a historical record of heavy air pollution. County-wide measures of carbon monoxide (CO), nitrogen dioxide (NO(2)), ozone(O(3)), particulate matter<10 µm (PM(10)), particulate matter<2.5 µm (PM(2.5)), maximum temperature, and relative humidity were collected for all months from 2001 to 2008. We then related these variables to monthly asthma hospitalization rates using Bayesian regression models with temporal random effects. We evaluated model performance using a goodness of fit criterion and predictive ability. Asthma hospitalization rates in LA County decreased between 2001 and 2008. Traffic-related pollutants, CO and NO(2), were significant and positively correlated with asthma hospitalizations. PM(2.5) also had a positive, significant association with asthma hospitalizations. PM(10), relative humidity, and maximum temperature produced mixed results, whereas O(3) was non-significant in all models. Inclusion of temporal random effects satisfies statistical model assumptions, improves model fit, and yields increased predictive accuracy and precision compared to their non-temporal counterparts. Generally, pollution levels and asthma hospitalizations decreased during the 9 year study period. Our findings also indicate that after accounting for seasonality in the data, asthma hospitalization rate has a significant positive relationship with ambient levels of CO, NO(2), and PM(2.5).
Delfino, R.J., Wu, J., Tjoa, T., Gullesserian, S.K., Nickerson, B., Gillen, D.L.	Asthma Morbidity and Ambient Air Pollution: Effect Modification by Residential Traffic-Related Air Pollution	2014	Epidemiology	PM2.5, NO2, NOx, CO, O3	"Hospital encounters" (ER visits and hospital admissions) from asthma	Orange County, CA	Subjects aged 0-18 with hospital encounters with a primary diagnosis of asthma between 2000 and 2008	Assesses the association between ambient air pollution and asthma-related hospital admissions and ER visits and investigates whether this association is modified by exposure to residential traffic-related air pollutants (NO2, NOx, CO)		Estimated long-term traffic-related NO2, NOx, CO, PM2.5 for each residence. Then evaluated associations of asthma-related hospital morbidity with air pollution exposure using a case-crossover design with conditional logistic regression. Exposures are sampled from each subject's time-varying distribution of exposure, so each person is his or her own control. Use semisymmetric bidirectional referent selection design	Case-crossover design controls for time-invariant subject characteristics, and using sufficiently narrow reference windows for controls avoids bias from seasonal confounding. To reduce serial correlation and avoid confounding from temporally adjacent exposures, did not select referent days within 7 days of exposure. Controlled for overlap bias between two sample hospitals, and controlled for within-subject correlation. Controlled for mean temperature and relative humidity over same lag period as pollutants. Tested effect modification by 6-month seasonal average residential air pollution. Addressed confounding in this analysis by doing secondary analysis to assess influence of race/ethnicity or health insurance status on differences in association with traffic-related air pollution strata	Estimates average traffic pollutant exposure for 6-month seasonal periods, and looks at PM2.5 exposure over 7 days before hospitalization, and tested other lags	Yes	**Background:** Ambient air pollution has been associated with asthma-related hospital admissions and emergency department visits (hospital encounters). We hypothesized that higher individual exposure to residential traffic-related air pollutants would enhance these associations. **Methods:** We studied 11,390 asthma-related hospital encounters among 7492 subjects 0-18 years of age living in Orange County, California. Ambient exposures were measured at regional air monitoring stations. Seasonal average traffic-related exposures (PM2.5, ultrafine particles, NOx, and CO) were estimated near subjects' geocoded residences for 6-month warm and cool seasonal periods, using dispersion models based on local traffic within 500 m radii. Associations were tested in case-crossover conditional logistic regression models adjusted for temperature and humidity. We assessed effect modification by seasonal residential traffic-related air pollution exposures above and below median dispersion-modeled exposures. Secondary analyses considered effect modification by traffic exposures within race/ethnicity and insurance group strata. **Results:** Asthma morbidity was positively associated with daily ambient O3 and PM2.5 in warm seasons and with CO, NOx, and PM2.5 in cool seasons. Associations with CO, NOx, and PM2.5 were stronger among subjects living at residences with above-median traffic-related exposures, especially in cool seasons. Secondary analyses showed no consistent differences in association, and 95% confidence intervals were wide, indicating a lack of precision for estimating these highly stratified associations. **Conclusions:** Associations of asthma with ambient air pollution were enhanced among subjects living in homes with high traffic-related air pollution. This may be because of increased susceptibility (greater asthma severity) or increased vulnerability (meteorologic amplification of local vs. correlated ambient exposures).

Table 2. NO_x Respiratory Morbidity

Authors	Title	Year Published	Journal Published	Pollutant(s) Studied	Causes of Mortality or Morbidity Considered	Geographic scope	Population studied	Study question	Statistically significant relationships?	Analysis method	Controls for factors that could obscure relationship?	Assesses potential lag between exposure and outcome?	Reports uncertainty?	Abstract
Gauderman, W.J., Urman, R., Avol, E., Berhane, K., McConnell, R., Rappaport, E., Chang, M.S., Lurmann, F., Gilliland, F.	Association of Improved Air Quality with Lung Development in Children	2015	N Engl J Med	NO2, O3, PM2.5, PM10, PM10-PM2.5	Lung function impairment (FEV1 and FVC) in children with and without asthma	Southern California (Long Beach, Mira Loma, Riverside, San Dimas, and Upland)	A total of 2120 children between the ages of 11 and 15 recruited from three separate Children's Health Study cohorts, including 669 in cohort C, 588 in cohort D, and 863 in cohort E. The two earlier cohorts (cohorts C and D) enrolled fourth-grade students in 1992–1993 and 1995–1996, respectively, from elementary schools in 12 southern California communities. The third cohort (cohort E) enrolled kindergarten and first-grade students in 2002–2003 from 13 communities, 9 of which overlapped with the 12 cohort C and D communities.	The goal of the analyses was to examine the association between long-term improvements in ambient air quality and lung-function development in children from 11 to 15 years of age, measured as the increases in FEV1 and FVC during that period (referred to as 4-year growth in FEV1 and FVC).	Yes	All available pulmonary-function measurements were used to estimate lung-function growth curves, including measurements at ages ranging from approximately 9 to 19 years in cohorts C and D and 10 to 16 years in cohort E. A previously developed linear-spline model, with knots placed at ages 12, 14, and 16 years, was used to capture the nonlinear pattern of growth during adolescence (see the Supplementary Appendix for details). In addition to examining 4-year growth from 11 to 15 years of age, we analyzed the cross-sectional pulmonary-function measurements obtained for 1585 children at the end of this period (mean age, 15 years) to determine whether changes in air quality over time were associated with clinically important deficits in attained FEV1 and FVC. Using data from all three cohorts, we developed a linear prediction model for FEV1 that included adjustments for age, sex, race and ethnic background, height, height squared, BMI, BMI squared, and the presence or absence of respiratory illness. For each child, we determined whether the ratio of observed to predicted FEV1 and FVC fell below each of three cutoffs for defining low lung function: 90%, 85%, and 80%. Logistic regression was used to test for temporal trends in the proportion of children with low lung function across cohorts after adjustment for community. A P value of less than 0.05 was considered to indicate statistical significance, under the assumption of a two-sided alternative hypothesis.	The model included adjustments for sex, race, Hispanic ethnic background, height, height squared, body-mass index (BMI, the weight in kilograms divided by the square of the height in meters), BMI squared, and presence or absence of respiratory-tract illness on the day of the pulmonary-function test.	Yes (indirectly)	Yes (qualitatively - discusses sensitivity analyses and study limitations)	BACKGROUND—Air-pollution levels have been trending downward progressively over the past several decades in southern California, as a result of the implementation of air quality– control policies. We assessed whether long-term reductions in pollution were associated with improvements in respiratory health among children. METHODS—As part of the Children's Health Study, we measured lung function annually in 2120 children from three separate cohorts corresponding to three separate calendar periods: 1994–1998, 1997–2001, and 2007–2011. Mean ages of the children within each cohort were 11 years at the beginning of the period and 15 years at the end. Linear-regression models were used to examine the relationship between declining pollution levels over time and lung-function development from 11 to 15 years of age, measured as the increases in forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) during that period (referred to as 4-year growth in FEV1 and FVC). RESULTS—Over the 13 years spanned by the three cohorts, improvements in 4-year growth of both FEV1 and FVC were associated with declining levels of nitrogen dioxide (P<0.001 for FEV1 and FVC) and of particulate matter with an aerodynamic diameter of less than 2.5 μm (P = 0.008 for FEV1 and P<0.001 for FVC) and less than 10 μm (P<0.001 for FEV1 and FVC). These associations persisted after adjustment for several potential confounders. Significant improvements in lung-function development were observed in both boys and girls and in children with asthma and children without asthma. The proportions of children with clinically low FEV1 (defined as <80% of the predicted value) at 15 years of age declined significantly, from 7.9% to 6.3% to 3.6% across the three periods, as the air quality improved (P = 0.001). CONCLUSIONS—We found that long-term improvements in air quality were associated with statistically and clinically significant positive effects on lung-function growth in children. (Funded by the Health Effects Institute and others.)
Islam, T., Gauderman, W.J., Berhane, K., McConnell, R., Avol, E., Peters, J.M., Gilliland, F.D.	Relationship between air pollution, lung function and asthma in adolescents	2007	Thorax	O3, NO2, PM10, PM2.5, acid vapour and elemental carbon	Air pollution as an effect modifier of the relationship between lung function (as measured by FEV1, FVC and FEF25-75) and asthma diagnosis	Southern California	Adolescents who participated in the Children's Health Study (CHS) who did not have asthma at entry into the cohort in 1993 (n=2057)	Study hypothesis is that higher lung function is associated with reduced risk for childhood asthma, but that ambient air pollution attenuates this effect.	Yes (The modifying effect of PM2.5, PM10 and organic carbon was statistically significant (p(0.05) and that of NO2, elemental carbon and acid vapour was marginally significant (p(0.08). Of all the pollutants, PM2.5 appeared to have the strongest modifying effect on the association between lung function with asthma as it had the highest R2 value (0.42).	The authors fitted Cox proportional hazards models with sex- and age specific (age defined as integer age at study entry) baseline hazards to investigate the association between new onset asthma and lung function at study entry. The authors report results using lung function as a continuous term. The hazard ratio (HR) can be interpreted as the change in risk of new onset asthma as the lung function increases over the 10th–90th percentile range of the corresponding lung function. They also fitted proportional hazard models treating annual lung function as 1- or 2-year lagged time-dependent covariates. To assess the effect of ambient air pollution on the relationship between lung function and new onset asthma, authors estimated the heterogeneity of association using community levels of air pollutants measured at one monitor in each community. To address this issue they fitted hierarchical two stage models to these time-dependent data (for details see Methods section in online supplement available at http://thorax.bmj.com/supplemental).	All models adjusted for community and race/ethnicity. Additional covariates (birth weight, premature birth, maternal smoking, maternal allergies, family history of asthma, BMI,parental education, health insurance and personal characteristics and househo ld and indoor exposures such as pets or second hand smoke exposure or humidifier use), were considered for inclusion in the model based on whether their inclusion changed the lung function effect estimate by more than 10%.	Yes	Discusses sensitivity analyses, alternative hypotheses and study limitations	Background: The interrelationships between air pollution, lung function and the incidence of childhood asthma have yet to be established. A study was undertaken to determine whether lung function is associated with new onset asthma and whether this relationship varies by exposure to ambient air pollutants. Methods: A cohort of children aged 9–10 years without asthma or wheeze at study entry were identified from the Children's Health Study and followed for 8 years. The participants resided in 12 communities with a wide range of ambient air pollutants that were measured continuously. Spirometric testing was performed and a medical diagnosis of asthma was ascertained annually. Proportional hazard regression models were fitted to investigate the relationship between lung function at study entry and the subsequent development of asthma and to determine whether air pollutants modify these associations. Results: The level of airway flow was associated with new onset asthma. Over the 10th–90th percentile range of forced expiratory flow over the mid-range of expiration (FEF25–75, 57.1%), the hazard ratio (HR) of new onset asthma was 0.50 (95% CI 0.35 to 0.71). This protective effect of better lung function was reduced in children exposed to higher levels of particulate matter with an aerodynamic diameter ,2.5 mm (PM2.5). Over the 10th–90th percentile range of FEF25–75, the HR of new onset asthma was 0.34 (95% CI 0.21 to 0.56) in communities with low PM2.5 (,13.7 mg/m3) and 0.76 (95% CI 0.45 to 1.26) in communities with high PM2.5 (>13.7 mg/m3). A similar pattern was observed for forced expiratory volume in 1 s. Little variation in HR was

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Klea Katsouyanni, Jonathan M. Samet, H. Ross Anderson, Richard Atkinson, Alain Le Tertre, Sylvia Medina, Evangelia Samoli, and Giota Touloumi, Richard T. Burnett, Daniel Krewski, Timothy Ramsay, Francesca Dominici, Roger D. Peng, Joel Schwartz, and Antonella Zanobetti	Air Pollution and Health: A European and North American Approach (APHENA)	2009	Health Effects Institute	PM10, O3, SO2, NO2, CO	Mortality (all-cause, respiratory, cardiovascular): morbidity (respiratory, cardiovascular hospital admissions)	90 U.S. cities, 32 European cities, and 12 Canadian cities	Ages 65-99	The study evaluated the effects of air pollutant exposures on morbidity and mortality in the U.S., Canada, and Europe.	Yes	Time series analysis	Yes	Lags of 0 and 1 day	Yes	This report provides the methodology and findings from the project: Air Pollution and Health: a European and North American Approach (APHENA*). The principal purpose of the project was to provide an understanding of the degree of consistency among findings of multicity time-series studies on the effects of air pollution on mortality and hospitalization in several North American and European cities. The project included parallel and combined analyses of existing data. The investigators sought to understand how methodological differences might contribute to variation in effect estimates from different studies, to characterize the extent of heterogeneity in effect estimates, and to evaluate determinants of heterogeneity. The APHENA project was based on data collected by three groups of investigators for three earlier studies: (1) Air Pollution and Health: A European Approach (APHEA), which comprised two multicity projects in Europe. (Phase 1 [APHEA1] involving 15 cities, and Phase 2 [APHEA2] involving 32 cities); (2) the National Morbidity, Mortality, and Air Pollution Study (NMMAPS), conducted in the 90 largest U.S. cities; and (3) multicity research on the health effects of air pollution in 12 Canadian cities.
McConnell, R., Islam, T., Shankardass, K., Jerrett, M., Lurmann, F., Gilliland, F., Gauderman, J., Avol, E., Kunzli, N., Yao, L., Peters, J., Berhane, K.	Childhood Incident Asthma and Traffic-Related Air Pollution at Home and School	2010	EHP	NOX, O3	New-onset asthma resulting from traffic-related pollution near homes and schools	Southern California	2,497 children who were pariticipants of the Southern California Childrens Health Study	Study evaluated the relationship of new-onset asthma with traffic-related pollution near homes and schools.	Yes	Authors fitted a multilevel Cox proportional hazards model that allows for assessment of residual variation in time to asthma onset and also for clustering of children around schools and communities (Ma et al. 2003). The model allowed for joint evaluation of the effects of exposure to traffic-related pollutants at homes and at schools and to ambient pollutants measured at community central sites, with effects scaled to the interquartile range (IQR) for each metric of residential exposure (e.g., for TRP from the line source dispersion model) and to the total range across the 13 communities, respectively. Traffic exposure at homes and school were correlated. Therefore, in models including both exposures, home traffic estimates were deviated from the corresponding school metric to minimize the chance of collinearity and allow for valid independent effect estimates. The authors assessed heterogeneity of traffic pollution effects by level of community central site regional pollutant measurements by comparing nested models using a partial likelihood ratio test with and without interaction terms. They examined any potential nonlinearity in the exposure–response relationship using cubic spline terms, piecewise polynomials joined smoothly at a number of break points (Hastie and Tibshirani 1990), for the exposure terms and comparing the nested models using a partial likelihood ratio test.	All models included race/ethnicity. Other individual covariates included secondhand smoke exposure, pets in the home, and other possible confounders.	Yes	Discusses sensitivity analyses and study limitations	Background: Traffic-related air pollution has been associated with adverse cardiorespiratory effects, including increased asthma prevalence. However, there has been little study of effects of traffic exposure at school on new-onset asthma. Objectives: We evaluated the relationship of new-onset asthma with traffic-related pollution near homes and schools. Methods: Parent-reported physician diagnosis of new-onset asthma (n = 120) was identified during 3 years of follow-up of a cohort of 2,497 kindergarten and first-grade children who were asthma- and wheezing-free at study entry into the Southern California Children's Health Study. We assessed traffic-related pollution exposure based on a line source dispersion model of traffic volume, distance from home and school, and local meteorology. Regional ambient ozone, nitrogen dioxide (NO2), and particulate matter were measured continuously at one central site monitor in each of 13 study communities. Hazard ratios (HRs) for new-onset asthma were scaled to the range of ambient central site pollutants and to the residential interquartile range for each traffic exposure metric. Results: Asthma risk increased with modeled traffic-related pollution exposure from roadways near homes [HR 1.51; 95% confidence interval (CI), 1.25–1.82] and near schools (HR 1.45; 95% CI, 1.06–1.98). Ambient NO2 measured at a central site in each community was also associated with increased risk (HR 2.18; 95% CI, 1.18–4.01). In models with both NO2 and modeled traffic exposures, there were independent associations of asthma with traffic-related pollution at school and home, whereas the estimate for NO2 was attenuated (HR 1.37; 95% CI, 0.69–2.71). Conclusions: Traffic-related pollution exposure at school and homes may both contribute to the development of asthma.

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Meng, Y.Y, Wilhelm, M., Rull, R.P., English, P., Ritz, B.	Traffic and outdoor air pollution levels near residences and poorly controlled asthma in adults	2007	AnnAllergy Asthma Immunol.	O3, NO2, PM2.5, PM10, CO	Prevalence of poorly controlled asthma in adults as indicated by daily or weekly asthma symptoms or at least one ED vistit or hospitalization due to asthma in the previous 12 months.	Los Angeles and San Diego counties	1,609 adults (age 18 and older) with asthma in Los Angeles and San Diego counties using 2001 California Health Intrview Survey (CHIS) Data	Study investigated association between traffic density (TD) and outdoor air pollution levels near residences and poorly controlled asthma (defined poorly controlled asthma during the preceding 12 months as having (1) daily or weekly asthma symptoms or (2) at least 1 ED visit or hospitalization because of asthma) among adults previously diagnosed with asthma by a physician.	Yes	We used logistic regression to evaluate associations between TD and annual average air pollution concentrations and poorly controlled asthma. The analyses incorporated sampling weights that adjusted for unequal probabilities of selection into the CHIS sample. Measured air pollutants were evaluated as continuous measures, as well as categorical measures, by comparing respondents with annual average concentrations in the 90th percentile or higher to those with concentrations in the less than 90th percentile based on the distribution in the study population. Age, sex, race/ethnicity, and poverty level are included in our final models. In stratified analyses, we examined whether pollutant association measures were modified by age and sex. We also performed analyses that included multiple pollutants in the same model.	Age, sex, socioeconomic status, access to care, health behaviors, overall health status, race/ethnicity, poverty level, insurance status, smoking behavior, employment, asthma medication use, and county (covriates included in the analysis were from CHIS).	no	yes	Background: Air pollution may exacerbate asthma. Objective: To investigate associations between traffic and outdoor air pollution levels near residences and poorly controlled asthma among adults diagnosed as having asthma in Los Angeles and San Diego counties, California. Methods: We estimated traffic density within 500 ft of 2001 California Health Interview Survey respondents' reported residential cross-street intersections. Additionally, we assigned annual average concentrations of ozone, nitrogen dioxide, particulate matter 2.5 and 10 micrometers or less in diameter, and carbon monoxide measured at government monitoring stations within a 5-mile radius of the reported residential cross-street intersections. Results: We observed a 2-fold increase in poorly controlled asthma (odds ratio [OR], 2.11; 95% confidence interval [CI], 1.38 –3.23) among asthmatic adults in the highest quintile of traffic density after adjusting for age, sex, race, and poverty. Similar increases were seen for nonelderly adults, men, and women, although associations seemed strongest in elderly adults (OR, 3.00; 95% CI, 1.13–7.91). Ozone exposures were associated with poorly controlled asthma among elderly adults (OR, 1.70; 95% CI, 0.91–3.18 per 1 pphm) and men (OR, 1.76; 95% CI, 1.05–2.94 per 1 pphm), whereas particulate matter 10 micrometers or less seemed to affect primarily women (OR, 2.06; 95% CI, 1.17–3.61), even at levels below the national air quality standard. Conclusions: Heavy traffic and high air pollution levels near residences are associated with poorly controlled asthma.
Mortimer,K.M ., L.M. Neas, D.W. Dockery, S. Redlinez, I.B. Tager	The effect of air pollution on inner-city children with asthma	2002	Eur Respir J	O3, SO2, NO2, PM10	Peak expiratory flow rate (PEFR) and asthma symptoms (cough, chest tightness, wheeze).	Participants are from one of the following 8 urban areas: Bronx and East Harlem, NY; Baltimore, MD; Washington, DC; Detroit, MI; Cleveland, OH; Chicago, IL; and St. Louis, MO.	Children aged 4-9 yrs old with asthma from the National Cooperative Inner-City Asthma Study (NCICAS).	Study evaluated air pollution-related health effects in a large cohort of inner-city children with asthma.	Yes	The per cent change in PEFR was analysed using linear mixed effect models (SAS Proc Mixed), while the incidence of symptoms and incidence of a 10% decline in median PEFR were modelled with generalized estimating equations, using a logistic link. Change-in-estimate criteria and likelihood ratio tests were used to determine the choice of covariates, with an alpha level of 0.05. AIC was used to evaluate the best correlation structure and to determine if a covariate should be entered as a fixed or random effect. Models with the AIC closest to zero were considered to best fit the data. Standard errors were insensitive to the use of several covariance structures, therefore results from models assuming the most simple structure (independence) were reported. Lagged air pollution effects were evaluated using moving averages, unrestricted distributed lags, and polynomial distributed lags. Within-model lag-specific estimates were combined to create a cumulative effect over a specified interval and estimates were then compared across models.	Yes	Yes	Yes	ABSTRACT: The effect of daily ambient air pollution was examined within a cohort of 846 asthmatic children residing in eight urban areas of the USA, using data from the National Cooperative Inner-City Asthma Study. Daily air pollution concentrations were extracted from the Aerometric Information Retrieval System database from the Environment Protection Agency in the USA. Mixed linear models and generalized estimating equation models were used to evaluate the effects of several air pollutants (ozone, sulphur dioxide (SO2), nitrogen dioxide (NO2) and particles with a 50% cut-off aerodynamic diameter of 10 mm (PM10) on peak expiratory flow rate (PEFR) and symptoms in 846 children with a history of asthma (ages 4–9 yrs). None of the pollutants were associated with evening PEFR or symptom reports. Only ozone was associated with declines in morning % PEFR (0.59% decline (95% confidence interval (CI) 0.13–1.05%) per interquartile range (IQR) increase in 5-day average ozone). In single pollutant models, each pollutant was associated with an increased incidence of morning symptoms: (odds ratio (OR)=1.16 (95% CI 1.02–1.30) per IQR increase in 4-day average ozone, OR=1.32 (95% CI 1.03–1.70) per IQR increase in 2-day average SO2, OR=1.48 (95% CI 1.02–2.16) per IQR increase in 6-day average NO2 and OR=1.26 (95% CI 1.0–1.59) per IQR increase in 2-day average PM10. This longitudinal analysis supports previous time-series findings that at levels below current USA air-quality standards, summer-air pollution is significantly related to symptoms and decreased pulmonary function among children with asthma.

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Nishimura, K.K., Joshua M. Galanter, Lindsey A. Roth, Sam S. Oh, Neeta Thakur, Elizabeth A. Nguyen, Shannon Thyne, Harold J. Farber, Denise Serebrisky, Rajesh Kumar, Emerita Brigino-Buenaventura, Adam Davis, Michael A. LeNoir, Kelley Meade, William Rodriguez-Cintron, Pedro C. Avila, Luisa N. Borrell, Kirsten Bibbins-Domingo, Jose R. Rodriguez-	Early-Life Air Pollution and Asthma Risk in Minority Children: The GALA II and SAGE II Studies	2013	Am J Respir Crit Care Med	O3, NO2, SO2, PM10, PM2.5	Physician-diagnosed asthma plus two or more symptoms of coughing, wheezing, or shortness of breath	Participants from Chicago, IL; Bronx, NY; Houston, TX; San Francisco Bay Area, CA) and Puerto Rico	Latino (n = 3,343) and African American (n = 977) children (ages 8-21 years old) with and without asthma from five urban regions in the mainland United States and Puerto Rico who are participants in the Genes–environments and Admixture in Latino Americans (GALA II) and the Study of African Americans, Asthma, Genes and Environments (SAGE II) studies.	Study seeks to assess the relationship between traffic-related air pollution and childhood asthma, in high-risk racial/ethnic minorities (African Americans and Puerto Ricans)	Yes	To account for regional characteristics, the authors used a two-stage analysis, allowing us to measure the between-region heterogeneity and to obtain a representative estimate across all regions. In the first stage, associations for each pollutant were determined separately for each study and region. Unadjusted logistic regression models and models adjusted for age, sex, ethnicity, and composite socioeconomic status (SES) were used to calculate the association between pollutant exposures during the first 3 years of life and subsequent asthma diagnosis as a dichotomous outcome. We also performed a sensitivity analysis examining additional potential covariates for maternal in utero smoking, environmental tobacco smoke in the household between 0 and 2 years old, and maternal language of preference (as an indicator of acculturation). These variables were included in the final site-specific adjusted models if the sample size was large enough and their inclusion improved the fit of the model as indicated by the Akaike Information Criterion (AIC). In the second stage, the regression coefficients for each region were combined, using a random-effects meta-analysis with a restricted maximum-likelihood estimator to generate a summary OR for each pollutant. The authors performed three stratified analyses: with or without family history of asthma, male or female sex, and high or low total IgE (above/ below 200 IU/ml, the approximate median among case subjects).	Yes: age, sex, ethnicity, and composite SES (calculated for each participant by assigning a low, medium, or high score for income, level of education, and insurance type, and then by taking the sum of these three values). The investigators also performed a sensitivity analysis examining additional potential covariates for maternal in utero smoking, environmental tobacco smoke in the household between 0 and 2 years old, and maternal language of preference (as an indicator of acculturation).	Yes (through study design)	Yes (reports confidence intervals around Ors and discusses study limitations)	Rationale: Air pollution is a known asthma trigger and has been associated with short-term asthma symptoms, airway inflammation, decreased lung function, and reduced response to asthma rescuemedications. Objectives: To assess a causal relationship between air pollution and childhood asthma using data that address temporality by estimating air pollution exposures before the development of asthma and to establish the generalizability of the association by studying diverse racial/ethnic populations in different geographic regions. Methods: This study included Latino (n = 3,343) and African American (n = 977) participants with and without asthma from five urban regions in the mainland United States and Puerto Rico. Residential history and data from local ambient airmonitoring stationswere used to estimate average annual exposure to five air pollutants: ozone, nitrogen dioxide (NO2), sulfur dioxide, particulatematter not greater than 10 mm in diameter, and particulatematter not greater than 2.5 mmindiameter. Within each region, we performed logistic regression to determine the relationship between early-life exposure to air pollutants and subsequent asthma diagnosis. A random-effects model was used to combine the region specific effects and generate summary odds ratios for each pollutant. Measurements and Main Results: After adjustment for confounders, a 5-ppb increase in average NO2 during the first year of life was associated with an odds ratio of 1.17 for physician-diagnosed asthma (95% confidence interval, 1.04–1.31). Conclusions: Early-life NO2 exposure is associated with childhood asthma in Latinos and African Americans. These results add to a growing body of evidence that traffic-related pollutants may be causally related to childhood asthma.
George T. O'Connor; Lucas Neas; Benjamin Vaughn; Meyer Kattan; Herman Mitchell; Ellen F. Crain; Richard Evans, III; Rebecca Gruchalla; Wayne Morgan; James Stout; G. Kenneth Adams; and Morton Lippmann	Acute respiratory health effects of air pollution on children with asthma in US inner cities	2008	U.S. Environmental Protection Agency Papers	PM2.5, NO2, SO2, CO, and O3	Acute respiratory morbidity	Low-income Census tracts in Boston, the Bronx, Chicago, Dallas, New York, Seattle, and Tucson	Low-income children	The association between changes in ambient air pollutants and asthma morbidity in inner city children.	Yes	Mixed-effects models; both single and three pollutant models	No	Yes; 1-, 3-, and 5-day lags	Yes	Background: Children with asthma in inner-city communities may be particularly vulnerable to adverse effects of air pollution because of their airways disease and exposure to relatively high levels of motor vehicle emissions. Objective: To investigate the association between fluctuations in outdoor air pollution and asthma morbidity among inner-city children with asthma. Methods: We analyzed data from 861 children with persistent asthma in 7 US urban communities who performed 2-week periods of twice-daily pulmonary function testing every 6 months for 2 years. Asthma symptom data were collected every 2 months. Daily pollution measurements were obtained from the Aerometric Information Retrieval System. The relationship of lung function and symptoms to fluctuations in pollutant concentrations was examined by using mixed models. Results: Almost all pollutant concentrations measured were below the National Ambient Air Quality Standards. In singlepollutant models, higher 5-day average concentrations of NO2, sulfur dioxide, and particles smaller than 2.5 mm were associated with significantly lower pulmonary function. Higher pollutant levels were independently associated with reduced lung function in a 3-pollutant model. Higher concentrations of NO2 and particles smaller than 2.5 mm were associated with asthma-related missed school days, and higher NO2 concentrations were associated with asthma symptoms. Conclusion: Among inner-city children with asthma, short-term increases in air pollutant concentrations below the National Ambient Air Quality Standards were associated with adverse respiratory health effects. The associations with NO2 suggest that motor vehicle emissions may be causing excess morbidity in this population.

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Wendt, J.K., Symanski, E., Stock, T.H., Chan, W., Du., X.L.	Association of Short-Term Increases in Ambient Air Pollution and Timing of Initial Asthma Diagnosis Among Medicaid-Enrolled Children in a Metropolitan Area	2014	Environmental Research	O3, NO2, PM2.5	Diagnosis of new-onset asthma	Harris County, Texas	Incident asthma cases among Medicaid-enrolled children between 2005-2007	Investigates whether short-term increases in O3, NO2, and PM2.5 levels were related to timing of initial diagnosis in children with asthma		Used a time-stratified, case-crossover design. Specified forty 28-day strata, matching each asthma case-day with the three referent dates in the pre-defined strata that were the same weekday. Ran conditional logistic regression to estimate Ors for each exposure metric and pollutant. Ran various lags and average cumulative exposures, and tested for non-linearity of effect using restricted cubic splines.	Case-crossover design allowed them to control for person-level factors and design also controlled for time-dependent exposures. Adjusted for temperature, mean relative humidity, and all aeroallergen variables. Also ran both single and co-pollutant models. Stratified analysis by age group, gender, race, and season.	Considered various lags and average cumulative exposures, with single-day values lagged 1 through 5 days, cumulative values averaged over 2 day through 6 days	Yes	**Objective:** We investigated associations of short-term changes in ambient ozone (O3), fine particulate matter (PM2.5) and nitrogen dioxide (NO2) concentrations and the timing of new-onset asthma, using a large, high-risk population in an area with historically high ozone levels. **Methods:** The study population included 18,289 incident asthma cases identified among Medicaid-enrolled children in Harris County Texas between 2005-2007, using Medicaid Analytic Extract enrollment and claims files. We used a time-stratified case-crossover design and conditional logistic regression to assess the effect of increased short-term pollutant concentrations on the timing of asthma onset. **Results:** Each 10 ppb increase in ozone was significantly associated with new-onset asthma during the warm season (May-October), with the strongest association seen when a 6-day cumulative average period was used as the exposure metric (odds ratio [OR]=1.05, 95% confidence interval [CI], 1.02-1.08). Similar results were seen for NO2 and PM2.5 (OR=1.07, 95% CI, 1.03-1.11 and OR=1.12, 95% CI, 1.03-1.22, respectively), and PM2.5 also had significant effects in the cold season (November-April), 5-day cumulative lag (OR=1.11. 95% CI, 1.00-1.22). Significantly increased ORs for O3 and NO2 during the warm season persisted in co-pollutant models including PM2.5. Race and age at diagnosis modified associations between ozone and onset of asthma. **Conclusion:** Our results indicate that among children in this low-income urban population who developed asthma, their initial date of diagnosis was more likely to occur following periods of higher short-term ambient pollutant levels.
Young, M.T., Sandler, D.P., DeRoo, L.A., Vedal, S., Kaufman, J.D., London, S.J.	Ambient Air Pollution Exposure and Incident Adult Asthma in a Nationwide Cohort of U.S. Women	2014	American Journal of Respiratory and Critical Care Medicine	PM2.5, NO2	Development of asthma and incident respiratory symptoms	United States	Sister Study cohort (sisters of v	Assesses the effect of long-term exposure to PM2.5 on adult incident asthma	Yes (for incident wheeze and almost for incident asthma, not with cough)	Estimated annual average PM2.5 and NO2 concentration at participants' addresses using a national land-use/kriging model incorporating roadway information. Evaluate outcomes at follow-up between 2008 and 2012, including incident self-reported wheeze, chronic cough, and doctor-diagnosed asthma in women without baseline symptoms		Uses average ambient PM2.5 and NO2 concentrations from 2006	Yes	**Rationale:** Limited prior data suggest an association between traffic-related air pollution and incident asthma in adults. No published studies assess the effect of long-term exposures to particulate matter less than 2.5 µm in diameter (PM2.5) on adult incident asthma. **Objectives:** To estimate the association between ambient air pollution exposures (PM2.5 and nitrogen dioxide, NO2) and development of asthma and incident respiratory symptoms. **Methods:** The Sister Study is a U.S. cohort study of risk factors for breast cancer and other health outcomes (n = 50,884) in sisters of women with breast cancer (enrollment, 2003-2009). Annual average (2006) ambient PM2.5 and NO2 concentrations were estimated at participants' addresses, using a national land-use/kriging model incorporating roadway information. Outcomes at follow-up (2008-2012) included incident self-reported wheeze, chronic cough, and doctor-diagnosed asthma in women without baseline symptoms. **Measurements and Main Results:** Adjusted analyses included 254 incident cases of asthma, 1,023 of wheeze, and 1,559 of chronic cough. For an interquartile range (IQR) difference (3.6 µg/m(3)) in estimated PM2.5 exposure, the adjusted odds ratio (aOR) was 1.20 (95% confidence interval [CI] = 0.99-1.46, P = 0.063) for incident asthma and 1.14 (95% CI = 1.04-1.26, P = 0.008) for incident wheeze. For NO2, there was evidence for an association with incident wheeze (aOR = 1.08, 95% CI = 1.00-1.17, P = 0.048 per IQR of 5.8 ppb). Neither pollutant was significantly associated with incident cough (PM2.5: aOR = 0.95, 95% CI = 0.88-1.03, P = 0.194; NO2: aOR = 1.00, 95% CI = 0.93-1.07, P = 0.939). **Conclusions:** Results suggest that PM2.5 exposure increases the risk of developing asthma and that PM2.5 and NO2 increase the risk of developing wheeze, the cardinal symptom of asthma, in adult women.

Table 3. NO_x Other Morbidity

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Balti, E.V., Echouffo-Tcheugui, J.B., Yako, Y.Y., Kengne, A.P.	Air Pollution and Risk of Type 2 Diabetes Mellitus: a Systematic Review and Meta-Analysis	2014	Diabetes Research and Clinical Practice	NO2, Nox, PM2.5, PM10, PM10-2.5	Type 2 diabetes mellitus	6 of 10 studies are in the US or Canada. Others are in Europe	All studies assessed adult	Investigates whether exposure to relatively high levels of air pollution is associated with diabetes occurrence	Yes	Looked for cross-sectional, case-control, and cohort studies repoting a quantitative measure of the association between exposure to air pollution and risk of T2DM, only studies using humans but no language restrictions. Pooled estimates using random-effects meta-analysis, and assessed heterogeneity using I-squared test. Ultimately used 10 studies	Most studies used single-pollutant mdoels, so they don't take into account potential interaction between pollutants. Controls commonly included were age, sex, BMI, smoking. Possible misclassification of diabetes diagnoses. Acknowledges potential for bias from heterogeneity in assessment strategies used to assess exposure.	Looks at long-term exposure studies, but none look at lifetime exposure	Yes	**Aim:** Whether exposure to relatively high levels of air pollution is associated with diabetes occurrence remains unclear. We sought to assess and quantify the association between exposure to major air pollutants and risk of type 2 diabetes. **Methods:** PubMed and EMBASE databases (through September 2013) were searched using a combination of terms related to exposure to gaseous (NO2 and NOx) or particulate matter pollutants (PM2.5, PM10 and PM10-2.5) and type 2 diabetes. Descriptive and quantitative information were extracted from selected studies. We used random-effects models meta-analysis to derive overall risk estimates per type of pollutant. **Results:** We included ten studies (five cross-sectional and five prospective), assessing the effects of air pollutants on the occurrence of diabetes. In prospective investigations, the overall effect on diabetes occurrence was significant for both NO2 (adjusted hazard ratio [HR], 1.13; 95% confidence interval [95%CI], 1.01-1.22; p < 0.001; I(2) = 36.4%, pheterogeneity = 0.208) and PM2.5 (HR, 1.11; 95%CI, 1.03-1.20; p < 0.001; I(2) = 0.0%, pheterogeneity = 0.827). Odds ratios were reported by two cross-sectional studies which revealed similar associations between both NO2 and PM2.5 with type 2 diabetes. Across studies, risk estimates were generally adjusted for age, gender, body mass index and cigarette smoking. **Conclusions:** Available evidence supports a prospective association of main air pollutants with an increased risk for type 2 diabetes. This finding may have implications for population-based strategies to reduce diabetes risk.
Becerra, T.A., Wilhelm, M., Olsen, J., Cockburn, M., Ritz, B.	Ambient Air Pollution and Autism in Los Angeles County, California	2013	Environmental Health Perspectives	CO, NO2, O3, PM10, PM2.5	Autism Disorder	Los Angeles County, CA	Children born 1995-2006 to mothers living in LA County at time of giving birth	Examines associations between measured and modeled exposures to prenatal air pollution and autism in children		First calculated Pearson's correlation coefficients to examine relations between various pollutant measures. Then looked at associations between air pollution exposure and odds of AD diagnosis using one- and two-pollutant models.	Adjusted for maternal age, maternal place of birth, race/ethnicity, and education, type of birth, parity, insurance type, gestational age at birth. Also excluded control for gestational age, since that might be a step on the causal pathway. Looks at potential confounding by co-pollutant exposure.	Estimated pollutant exposure for full pregnancy and for each trimester	Yes	Background: The prevalence of autistic disorder (AD), a serious developmental condition, has risen dramatically over the past two decades, but high-quality population-based research addressing etiology is limited. Objectives: We studied the influence of exposures to traffic-related air pollution during pregnancy on the development of autism using data from air monitoring stations and a land use regression (LUR) model to estimate exposures. Methods: Children of mothers who gave birth in Los Angeles, California, who were diagnosed with a primary AD diagnosis at 3–5 years of age during 1998–2009 were identified through the California Department of Developmental Services and linked to 1995–2006 California birth certificates. For 7,603 children with autism and 10 controls per case matched by sex, birth year, and minimum gestational age, birth addresses were mapped and linked to the nearest air monitoring station and a LUR model. We used conditional logistic regression, adjusting for maternal and perinatal characteristics including indicators of SES. Results: Per interquartile range (IQR) increase, we estimated a 12–15% relative increase in odds of autism for ozone [odds ratio (OR) = 1.12, 95% CI: 1.06, 1.19; per 11.54-ppb increase] and particulate matter ≤ 2.5 μm (OR = 1.15; 95% CI: 1.06, 1.24; per 4.68-μg/m3 increase) when mutually adjusting for both pollutants. Furthermore, we estimated 3–9% relative increases in odds per IQR increase for LUR-based nitric oxide and nitrogen dioxide exposure estimates. LUR-based associations were strongest for children of mothers with less than a high school education. Conclusion: Measured and estimated exposures from ambient pollutant monitors and LUR model suggest associations between autism and prenatal air pollution exposure, mostly related to traffic sources.

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Coogan, P.F., White, L.F., Jerrett, M., Brook, R.D., Su, J.G., Seto, E., Burnett, R., Palmer, J.R. Rosenberg, L.	Air Pollution and Incidence of Hypertension and Diabetes Mellitus in Black Women in Los Angeles	2012	Circulation	PM2.5, NOx	Incident hypertension, diabetes	Los Angeles	Participants in the Black Wome	Assesses the risks of incident hyperension and diabetes associated with eposure to PM2.5 and NOx	Very close to significant for PM2.5 in single pollutant model	Used Cox proportional hazards models to estimate incidence rate ratios associated with increases in pollutant concentrations. Calculated person-time from start of follow-up in 1995 until occurrence of hypertension or diabetes, loss to follow-up, moving from study aea, death, or end of follow-up. Used both single and co-pollutant models.	Adjusted IRRs for both hypertension and diabetes by age, BMI, years of education, household income, number of people supported by household income, smoking status, alcohol consumption, hours per week of vigorous exercise, and neighborhood SES score. Adjusted hypertension IRRs with neighborhood noise level. Analyzed co-pollutant models, and looked at interactions of noise with both pollutants in hypertension analysis.	Look at long-term exposure, annual values	Yes	**Background:** Evidence suggests that longer-term exposure to air pollutants over years confers higher risks of cardiovascular morbidity and mortality than shorter term exposure. One explanation is that cumulative adverse effects that develop over longer durations lead to the genesis of chronic disease. Preliminary epidemiological and clinical evidence suggest that air pollution may contribute to the development hypertension and type 2 diabetes. **Methods and Results:** We used Cox proportional hazards models to assess incidence rate ratios (IRRs) and 95% confidence intervals (CI) for incident hypertension and diabetes associated with exposure to fine particulate matter (PM2.5) and nitrogen oxides (NOx) in a cohort of African American women living in Los Angeles. Pollutant levels were estimated at participant residential addresses with land use regression models (NOx) and interpolation from monitoring station measurements (PM2.5). Over follow-up from 1995-2005, 531 incident cases of hypertension and 183 incident cases of diabetes occurred. When pollutants were analyzed separately, the IRR for hypertension for a 10 µg/m3 increase in PM2.5 was 1.48 (95% CI 0.95-2.31) and the IRR for the interquartile range (12.4 parts per billion) of NOx was 1.14 (95% CI 1.03-1.25). The corresponding IRRs for diabetes were 1.63 (95% CI 0.78-3.44) and 1.25 (95% CI 1.07-1.46). When both pollutants were included in the same model, the IRRs for PM2.5 were attenuated and the IRRs for NOx were essentially unchanged for both outcomes. **Conclusions:** Our results suggest that exposure to air pollutants, especially traffic-related pollutants, may increase the risk of type 2 diabetes and possibly of hypertension.
Ensor, K.B., Raun, L.H., Persse, D.	A Case-Crossover Analysis of Out-of-Hospital Cardiac Arrest and Air Pollution	2013	Circulation	PM2.5, O3, NO2, SO2, CO	Out of hospital cardiac arrest (ER visits)	Houston, TX	All non-dead-on-arrival adults >	Studies the association between air pollution and risk of out-of-hospital cardiac arrest.	Yes	Used a time-stratified case-crossover design coupled with conditional logistic regression. Uses ambient air pollution concentrations at times when the study individual is not experiencing the OHCA health event as reference for each case. Use conditional logistic regression to estimate the association of pollution and increased relative risk of health event. Did sensitivity analysis with single lag models to look at hour and day time scales. Implemented constrained distributed lag models to estimate the cumulative effect over 2-hour average or 2-day average increments.	Case-crossover design should control for individual-level confounders. When there was a significant association between individual pollutants and OHCA, looked at potential confounding between pollutants by estimating correlations and including pollutants as covariates in the model. Looked at effect modification by age, sex, race, and season. Acknowledge the possibility of exposure time misclassification and selection bias from not including individuals dead on arrival.	Assessed lags on hourly and daily time scale, for 1-8 lag hours and 1-5 day lags	Yes	**Background:** Evidence of an association between the exposure to air pollution and overall cardiovascular morbidity and mortality is increasingly found in the literature. However, results from studies of the association between acute air pollution exposure and risk of out-of-hospital cardiac arrest (OHCA) are inconsistent for fine particulate matter, and, although pathophysiological evidence indicates a plausible link between OHCA and ozone, none has been reported. Approximately 300 000 persons in the United States experience an OHCA each year, of which >90% die. Understanding the association provides important information to protect public health. **Methods and Results:** The association between OHCA and air pollution concentrations hours and days before onset was assessed by using a time-stratified case-crossover design using 11 677 emergency medical service–logged OHCA events between 2004 and 2011 in Houston, Texas. Air pollution concentrations were obtained from an extensive area monitor network. An average increase of 6 µg/m3 in fine particulate matter 2 days before onset was associated with an increased risk of OHCA (1.046; 95% confidence interval, 1.012–1.082). A 20-ppb ozone increase for the 8-hour average daily maximum was associated with an increased risk of OHCA on the day of the event (1.039; 95% confidence interval, 1.005–1.073). Each 20-ppb increase in ozone in the previous 1 to 3 hours was associated with an increased risk of OHCA (1.044; 95% confidence interval, 1.004–1.085). Relative risk estimates were higher for men, blacks, or those aged >65 years. **Conclusions:** The findings confirm the link between OHCA and fine particulate matter and introduce evidence of a similar link with ozone.

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Eze, I.C., Hemkens, L.G., Bucher, H.C., Hoffmann, B., Schindler, C., Kunzli, N., Schikowski, T., Probst-Hensch, N.M.	Association Between Ambient Air Pollution and Diabetes Mellitus in Europe and North America: Systematic Review and Meta-Analysis	2015	Environmental Health Perspectives	PM2.5, Nox	Type 2 diabetes mellitus	Europe and North American	Electronic literature databases	Reviewed epidemiological evidence on the association between air pollution and diabetes, and synthesized results of studies on type 2 diabetes mellitus (T2DM)	Yes	Evaluated risk of bias and role of potential confounders in all studies. Synthesized reported associations with T2DM in meta-analyses using random-effects models and conducted various sensitivity analyses.	Controlled for air pollution, sex, BMI, age, type of study	Different lag times across different studies	Yes	**Background**: Air pollution is hypothesized to be a risk factor for diabetes. Epidemiological evidence is inconsistent and has not been systematically evaluated. **Objectives:** We systematically reviewed epidemiological evidence on the association between air pollution and diabetes, and synthesized results of studies on type 2 diabetes mellitus (T2DM). **Methods:** We systematically searched electronic literature databases (last search, 29 April 2014) for studies reporting the association between air pollution (particle concentration or traffic exposure) and diabetes (type 1, type 2, or gestational). We systematically evaluated risk of bias and role of potnetial confounders in all studies. We synthesized reported associations with T2DM in meta-analyses using random-effects models and conducted various sensistivity analyses. **Results:** We included 13 studies (8 on T2DM, 2 on type 1, 3 on gestational diabetes), all conducted in Europe or North America. Five studies were longitudinal, 5 cross-sectional, 2 case-control, and 1 ecologic. Risk of bias, air pollution assessment, and confounder control varied across studies. Dose-response effects were not reported. Meta-analyses of 3 studies on PM2.5 and 4 studies on NO2 showed increase risk of T2DM by 8-10% per 10 ug/m3 increase in exposure [PM2.5:1.10 (95% CI: 1.02, 1.18); NO2: 1.08 (95% CI: 1.00, 1.170]. Associations were stronger in females. Sensitivity analyses showed similar results. **Conclusion:** Existing evidence indicates a positive association of air pollution and T2DM risk, albeit there is high risk of bias. High-quality studies assessing dose-response effects are needed. Research should be expanded to developing countries where outdoor and indoor air pollution are high.
Hart, J.E., Kallberg, H., Laden, F., Costenbader, K.H., Yanosky, J.D., Klareskog, Alfredsson, L., Karlson, E.W.	Ambient Air Pollution Exposures and Risk of Rheumatoid Arthritis in the Nurses' Health Study	2014	Arthritis Care Research	PM10, PM2.5, SO2, NO2	Rheumatoid arthritis	United States	Nurses' Health Study participa	Considers the possible association between air pollution and risks of rheumatoid arthritis		Used time-varying Cox proportional hazards models with each air pollutant in a separate model. Person-time accrued from baseine until diagnosis of RA, loss to follow-up, date of death, or end of follow-up. Stratified all models by age in months and calendar year.	Controlled for age, race, age at menarche, parity, total months of lactation, current menopausal status, menopausal hormone use, oral contraceptive use, physical activity, and BMI. Controlled for smoking and individual level SES using education levels. Also included census tract-level median income and house value. Looked at effect modification by age in months and calendar year. Also looked at effect modification by SES and smoking status, as well as by census region.	Looked at time-varying annual exposure the 6th- and 10th-year prior to each questionnaire cycle. Also looked at time-varying cumulative average exposure during the follow-up period	Yes	Objective: Environmental factors may play a role in the development of rheumatoid arthritis (RA), and we have previously observed increased RA risk among women living closer to major roads (a source of air pollution). We examined whether long-term exposures to specific air pollutants were associated with RA risk among women in the Nurses' Health Study. Methods: The Nurses' Health Study (NHS) is a large cohort of U.S. female nurses followed prospectively every two years since 1976. We studied 111,425 NHS participants with information on air pollution exposures as well as data concerning other lifestyle and behavioral exposures and disease outcomes. Outdoor levels of different size fractions of particulate matter (PM10 and PM2.5) and gaseous pollutants (SO2 and NO2) were predicted for all available residential addresses using monitoring data from the USEPA. We examined the association of time-varying exposures, 6 and 10 years before each questionnaire cycle, and cumulative average exposure with the risks of RA, seronegative (rheumatoid factor [RF] and anti–citrullinated peptide antibodies [ACPA]) RA, and seropositive RA. Results: Over the 3,019,424 years of follow-up, 858 incident RA cases were validated by medical record review by two board-certified rheumatologists. Overall, we found no evidence of increased risks of RA, seronegative or seropositive RA, with exposure to the different pollutants, and little evidence of effect modification by socioeconomic status or smoking status, geographic region, or calendar period. Conclusion: In this group of socioeconomically-advantaged middle-aged and elderly women, adult exposures to air pollution were not associated with an increased RA risk.

Table 3. NO_2 Other Morbidity

Authors	Title	Year Published	Journal Published	Pollutant(s) Studied	Causes of Mortality or Morbidity Considered	Geographic scope	Population studied	Study question	Statistically significant relationships?	Analysis method	Controls for factors that could obscure relationship?	Assesses potential lag between exposure and outcome?	Reports uncertainty?	Abstract
Laurent, O., Hu, J., Li, L., Cockburn, M., Escobedo, L., Kleeman, M.J., Wu, J.	Sources and Contents of Air Pollution Affecting Term Low Birth Weight in Los Angeles County, California, 2001-2008	2014	Environmental Research	PM2.5, NO2, O3	Low Birth Weight	Los Angeles County, CA	Singleton livebirths with plausit	Studies the relationships between LBW in term born infants and exposures to particles by size fraction, source, and chemical composition, and complementary components of air pollution	Yes (with significant effect modification by socioeconomic status, chronic hypertension, diabetes, BMI)	Estimated generalized additive models, using a logistic link function with a quasi-binomial distribution. Did sensitivity analysis looking at the effect of adjustent for population density, diabetes, chronic hypertension, and preeclampsia.	Adjusted for maternal race/ethnicity, education level, parity, trimester of pregnancy during which primary care began and infant's gender. Also adjusted for maternal age, length of gestation and median household income by census block group. Tried controlling for both seasonal and long-term temporal trends using a smoothed function of the day of conception. Looks at adjustment for maternal height, BMI, and weight gain during pregnancy. Looked at effect modification by maternal race/ethnicity, education, median block group income, hypertension, diabetes, and preeclampsia. Evaluated correlation between pollutants, but seems to use single pollutant models--unsure	Looked at average pollutant concentration for entire pregnancy and for each trimester	Yes	Background: Low birth weight (LBW, <2500 g) has been associated with exposure to air pollution, but it is still unclear which sources or components of air pollution might be in play. The association between ultrafine particles and LBW has never been studied. Objectives: To study the relationships between LBW in term born infants and exposure to particles by size fraction, source and chemical composition, and complementary components of air pollution in Los Angeles County (California, USA) over the period 2001–2008. Methods: Birth certificates (n=960,945) were geocoded to maternal residence. Primary particulate matter (PM) concentrations by source and composition were modeled. Measured fine PM, nitrogen dioxide and ozone concentrations were interpolated using empirical Bayesian kriging. Traffic indices were estimated. Associations between LBW and air pollution metrics were examined using generalized additive models, adjusting for maternal age, parity, race/ethnicity, education, neighborhood income, gestational age and infant sex. Results: Increased LBW risks were associated with the mass of primary fine and ultrafine PM, with several major sources (especially gasoline, wood burning and commercial meat cooking) of primary PM, and chemical species in primary PM (elemental and organic carbon, potassium, iron, chromium, nickel, and titanium but not lead or arsenic). Increased LBW risks were also associated with total fine PM mass, nitrogen dioxide and local traffic indices (especially within 50 m from home), but not with ozone. Stronger associations were observed in infants born to women with low socioeconomic status, chronic hypertension, diabetes and a high body mass index. Conclusions: This study supports previously reported associations between traffic-related pollutants and LBW and suggests other pollution sources and components, including ultrafine particles, as possible risk factors.
Mobasher, Z., Salam, M.T., Goodwin, T.M., Lurmann, F., Ingles, S.A., Wilson, M.L.	Associations Between Ambient Air Pollution and Hypertensive Disorders of Pregnancy	2013	Environmental Research	CO, NO2, O3, PM10, PM2.5	Hypertensive Disorders of Pregnancy	Southern California	Women giving birth in Los Angeles 1999-2008 at Los Angeles County+USC Women's and Children's Hospital, predominately Hispanic	Investigates the role of trimester-specific ambient air pollution on risk for hypertensive disorder of pregnancy	Yes (with 1st trimester exposure, modified by BMI)	Retrospective case-control study. Performed correlation analysis to determine Pearson's correlation coefficients for all air pollutants. Then used unconditional logistic regression to examine the association between ambient air pollution and odds of hypertensive disorder of pregnancy	Adjusted analysis for maternal age, parity, maternal smoking status, exposure to secondhand smoke during pregnancy, indicator of calendar year of pregnancy, BMI. Acknowledge the possibility of exposure misclassification, response rate may introduce bias.	Uses average pollution in each trimester	Yes	**Background:** Exposure to ambient air pollution is linked to adverse pregnancy outcomes. Previous reports examining the relationship between ambient air pollution and Hypertensive Disorders of Pregnancy have been inconsistent. **Objectives:** We evaluated the effects of ambient air pollution on the odds of Hypertensive Disorder of Pregnancy and whether these associations varied by body mass index (BMI). **Methods:** We conducted a retrospective, case-control study among 298 predominantly Hispanic women (136 clinically confirmed cases) who attended the Los Angeles County+University of Southern California Women's and Children's Hospital during 1996–2008. Trimester-specific carbon monoxide (CO), nitrogen dioxide (NO_2), ozone (O_3), and particulate matter with aerodynamic diameter <10 μm and <2.5 μm (PM10, PM2.5) exposure were estimated based on 24-hour exposure level at residential address. Logistic regression models were fitted to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for two standard deviation increase in exposure levels. **Results:** Exposures to CO and PM2.5 in the 1st trimester were significantly associated with Hypertensive Disorders of Pregnancy, and these associations were modified by BMI. In non-obese women (BMI <30), 1st trimester exposures to PM2.5 and CO were significantly associated with increased odds of Hypertensive Disorder of Pregnancy (ORs per 2-standard deviation increase in PM2.5 (7 μg/m3) and CO (1 ppm) exposures were 9.10 [95% CI: 3.33–24.6] and 4.96 [95% CI: 1.85–13.31], respectively). Additionally, there was a significantly positive association between exposure to O_3 in the 2nd trimester and Hypertensive Disorder of Pregnancy (OR per 15 ppb=2.05; 95% CI: 1.22–3.46). **Conclusion:** Among non-obese women, 1st trimester exposure to PM2.5 and carbon monoxide are associated with increased odds of Hypertensive Disorder of Pregnancy.

Table 3. NO_2 Other Morbidity

Authors	Title	Year Published	Journal Published	Pollutant(s) Studied	Causes of Mortality or Morbidity Considered	Geographic scope	Population studied	Study question	Statistically significant relationships?	Analysis method	Controls for factors that could obscure relationship?	Assesses potential lag between exposure and outcome?	Reports uncertainty?	Abstract
Padula, A.M., Tager, I.B., Carmichael, S.L., Hammond, S.K., Yang, W., Lurmann, F., Shaw, G.M.	Ambient Air Pollution and Traffic Exposures and Congenital Heart Defects in the San Joaquin Valley of California	2014	Paediatric and Perinatal Epidemiology	CO, NO2, PM10, PM2.5, O3	Congenital heart defects--heterotaxia, d-Transposition of the great arteries, tetralogy of fallot, double outlet right ventricle (TGA and other)	San Joaquin Valley, CA	All births in San Joaquin valley	Investigates the association between ambient air pollution and congenital heart defects	Yes (with transposition of great arteries and inversely associated with perimembranous ventricular septal defects)	Cases included live births, stillbirths, and pregnancy terminations with congenital heart defects, and controls were non-malformed live-born infants randomly selected from birth hospitals to represent the population. First analyzed the association between pollutants and traffic metrics. Then did multivariate logistic regression analyses to estimate adjusted odds ratios.	In analysis adjusted for maternal race/ethnicity, education, and early prenatal vitamin use. Considered other controls, like maternal age, parity, infant sex, year of birth etc., but did not include them. Investigated effect modification by cigarette smoking. Acknowledge that they may have misclassified exposure, particularly if vulnerable windows for certain heart defects are narrower than they expected. Also potential bias from early fetal loss, possible other confounders	Used average air pollution measurements from the first and second month of pregnancy	Yes	**Background:** Congenital anomalies are a leading cause of infant morbidity and mortality. Studies suggest associations between environmental contaminants and some anomalies, although evidence is limited. **Methods:** We used data from the California Center of the National Birth Defects Prevention Study and the Children's Health and Air Pollution Study to estimate the odds of 27 congenital heart defects with respect to quartiles of seven ambient air pollutant and traffic exposures in California during the first 2 months of pregnancy, 1997-2006 (n = 822 cases and n = 849 controls). **Results:** Particulate matter < 10 microns (PM10) was associated with pulmonary valve stenosis [adjusted odds ratio (aOR)Fourth Quartile = 2.6] [95% confidence intervals (CI) 1.2, 5.7] and perimembranous ventricular septal defects (aORThird Quartile = 2.1) [95% CI 1.1, 3.9] after adjusting for maternal race/ethnicity, education and multivitamin use. PM2.5 was associated with transposition of the great arteries (aORThird Quartile = 2.6) [95% CI 1.1, 6.5] and inversely associated with perimembranous ventricular septal defects (aORFourth Quartile = 0.5) [95% CI 0.2, 0.9]. Secundum atrial septal defects were inversely associated with carbon monoxide (aORFourth Quartile = 0.4) [95% CI 0.2, 0.8] and PM2.5 (aORFourth Quartile = 0.5) [95% CI 0.3, 0.8]. Traffic density was associated with muscular ventricular septal defects (aORFourth Quartile = 3.0) [95% CI 1.2, 7.8] and perimembranous ventricular septal defects (aORThird Quartile = 2.4) [95% CI 1.3, 4.6], and inversely associated with transposition of the great arteries (aORFourth Quartile = 0.3) [95% CI 0.1, 0.8]. **Conclusions:** PM10 and traffic density may contribute to the occurrence of pulmonary valve stenosis and ventricular septal defects, respectively. The results were mixed for other pollutants and had little consistency with previous studies.
Robledo, C.A., Mendola, P., Yeung, E., Mannisto, T., Sundaram, R., Liu, D., Ying, Q., Sherman, S., Grantz, K.L.	Preconception and Early Pregnancy Air Pollution Exposures and Risk of Gestational Diabetes Mellitus	2015	Environmental Research	PM2.5, PM10, NOx, CO, SO2, O3	Gestational diabetes mellitus (ICD-9: 648.8)	United States	Singleton births without preges	Investigates the association between critera air pollutants regulated by the US EPA and the risk of gestational diabetes mellitus	No	First calcualted Spearman rank correlations between each pollutants. Then fitted binary regression models with the log link function to estimate relative risks for IQR increase for each pollutant. Used a first order autoregressive covariance structure to account for within-cluster correlation for women with more than one singleton pregnancy during study period. Made separate models for air pollutants during each exposure window.	Assessed potential confounding by maternal characteristics, including parity, marital status, insurance status, hospital type, prenatal history of smoking and alcohol, study sites. Looked at effect modification by maternal BMI. Also looked at multi-pollutant models to look at confounding by other pollutants.	Included pre-conception exposure (91 days before last menstrual period), average exposure during 1st trimester, weekly averages for gestational weeks 1 through 24	Yes	Background: Air pollution has been linked to gestational diabetes mellitus (GDM) but no studies have evaluated impact of preconception and early pregnancy air pollution exposures on GDM risk. Methods: Electronic medical records provided data on 219,952 singleton deliveries to mothers with (n=11,334) and without GDM (n=208,618). Average maternal exposures to particulate matter (PM) ≤ 2.5μm (PM2.5) and PM2.5 constituents, PM ≤ 10μm (PM10), nitrogen oxides (NOx), carbon monoxide, sulfur dioxide (SO2) and ozone (O3) were estimated for the 3-month preconception window, first trimester, and gestational weeks 1-24 based on modified Community Multiscale Air Quality models for delivery hospital referral regions. Binary regression models with robust standard errors estimated relative risks (RR) for GDM per interquartile range (IQR) increase in pollutant concentrations adjusted for study site, maternal age and race/ethnicity. Results: Preconception maternal exposure to NOX (RR=1.09, 95% CI: 1.04, 1.13) and SO2 (RR=1.05, 1.01, 1.09) were associated with increased risk of subsequent GDM and risk estimates remained elevated for first trimester exposure. Preconception O3 was associated with lower risk of subsequent GDM (RR=0.93, 0.90, 0.96) but risks increased later in pregnancy. Conclusion: Maternal exposures to NOx and SO2 preconception and during the first few weeks of pregnancy were associated with increased GDM risk. O3 appeared to increase GDM risk in association with mid-pregnancy exposure but not in earlier time windows. These common exposures merit further investigation.

Table 3. NO_2 Other Morbidity

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Stingone, J.A., Luben, T.J., Daniels, J.L, Fuentes, M., Richardson, D.B., Aylsworth, A.S,. Herring, A.H., Anderka, M., Botto, L., Correa, A., Gilboa, S.M., Langlois, P.H., Mosley, B., Shaw, G.M>, Siffel, C., Olshan, A.F.	Maternal Exposure to Criteria Air Pollutants and Congenital Heart Defects in Offspring: Results from the National Birth Defects Prevention Study	2014	Environmental Health Perspectives	CO, NO2, O3, PM10, PM2.5, SO2	Simple, isolated congenital heart defects with no extra-cardiac birth defects present		Participants in National Birth D	Investigates the association between maternal exposure to air pollutants during weeks 2-8 of pregnancy and their associations with congenital heart defects	Yes (with hypoplastic left heart syndrome, inversely associated with atrial septal defects, some attenuation of results by multipollutant models)	Construfted two-stage hierarchical regression models to account for correlation between estimates and partially address multiple inference. In first stage, ran uconditional, polytomous logistic regression model of individual CHDs on exposure defined as either all 1-week average exposure or single 7-week average. Looked at sensitivity to changes in the model specification.	Controled for maternal age, race/ethnicity, educational attainment, household income, tobacco smoking in the first month of pregnancy, alcohol consumption during the first trimester, maternal nativity. Also controlled for distance to closest major road, prepregnancy BMI, maternal occupational status. Looked at multipollutant models using a principal component analysis.	Calculated average pollutant concentration for weeks 2-8 of pregnancy and 1-week averages for each week	Yes	Background: Epidemiologic literature suggests that exposure to air pollutants is associated with fetal development. Objectives: We investigated maternal exposures to air pollutants during weeks 2-8 of pregnancy and their associations with congenital heart defects. Methods: Mothers from the National Birth Defects Prevention Study, a nine-state case-control study, were assigned 1-week and 7-week averages of daily maximum concentrations of carbon monoxide, nitrogen dioxide, ozone, and sulfur dioxide and 24-hr measurements of fine and coarse particulate matter using the closest air monitor within 50 km to their residence during early pregnancy. Depending on the pollutant, a maximum of 4,632 live-birth controls and 3,328 live-birth, fetal-death, or electively terminated cases had exposure data. Hierarchical regression models, adjusted for maternal demographics and tobacco and alcohol use, were constructed. Principal component analysis was used to assess these relationships in a multipollutant context. Results: Positive associations were observed between exposure to nitrogen dioxide and coarctation of the aorta and pulmonary valve stenosis. Exposure to fine particulate matter was positively associated with hypoplastic left heart syndrome but inversely associated with atrial septal defects. Examining individual exposure-weeks suggested associations between pollutants and defects that were not observed using the 7-week average. Associations between left ventricular outflow tract obstructions and nitrogen dioxide and between hypoplastic left heart syndrome and particulate matter were supported by findings from the multipollutant analyses, although estimates were attenuated at the highest exposure levels. Conclusions: Using daily maximum pollutant levels and exploring individual exposure-weeks revealed some positive associations between certain pollutants and defects and suggested potential windows of susceptibility during pregnancy.
Volk, H.E., Lurmann, F., Penfold, B., Hertz-Picciotto, I., McConnell, R.	Traffic-Related Air Pollution, Particulate Matter, and Autism	2013	JAMA Psychiatry	NO2, PM2.5, PM10	Autism spectrum disorder	California	Participants in CHARGE study, t	Estimates the association between autism risk and exposure to mixture or traffic-related pollutants, NO2, PM2.5, PM10	Yes	Calculated Spearman correlation coefficients between TRP estimates and regional pollution measures for pregnancy and first year of life. Then, used logistic regression to examine the association between exposure to traffic-related air pollution and autism risk. Fitted models of autism risk as a function of TRP exposure levels from all raod types separately for each time period, with categories of exposure based on quartiles of TRP distribution and continuous variables for other pollutants. When possible, examined both in the same model.	Adjusted models for children's gender and ethnicity, maximum education level of parents, maternal age, maternal smoking during pregnancy. Also adjusted by urban vs. rural. Acknowledge the potential for confounding if proximity to diagnosing physicians or treatment centers was associated with exposure.	Uses long-term exposure, with average exposure during first year of life and during gestational period	Yes	**Context:** Autism is a heterogeneous disorder with genetic and environmental factors likely contributing to its origins. Examination of hazardous pollutants has suggested the importance of air toxics in the etiology of autism, yet little research has examined its association with local levels of air pollution using residence-specific exposure assignments. **Objective:** To examine the relationship between traffic-related air pollution, air quality, and autism. **Design:** This population-based case-control study includes data obtained from children with autism and control children with typical development who were enrolled in the Childhood Autism Risks from Genetics and the Environment study in California. The mother's address from the birth certificate and addresses reported from a residential history questionnaire were used to estimate exposure for each trimester of pregnancy and first year of life. Traffic-related air pollution was assigned to each location using a line-source air-quality dispersion model. Regional air pollutant measures were based on the Environmental Protection Agency's Air Quality System data. Logistic regression models compared estimated and measured pollutant levels for children with autism and for control children with typical development. **Setting:** Case-control study from California. **Participants:** A total of 279 children with autism and a total of 245 control children with typical development. **Main Outcome Measures:** Crude and multivariable adjusted odds ratios (AORs) for autism. **Results:** Children with autism were more likely to live at residences that had the highest quartile of exposure to traffic-related air pollution, during gestation (AOR, 1.98 [95% CI, 1.20-3.31]) and during the first year of life (AOR, 3.10 [95% CI, 1.76-5.57]), compared with control children. Regional exposure measures of nitrogen dioxide and particulate matter less than 2.5 and 10 μm in diameter (PM2.5 and PM10) were also associated with autism during gestation (exposure to nitrogen dioxide: AOR, 1.81 [95% CI, 1.37-3.09]; exposure to PM2.5: AOR, 2.08 [95% CI, 1.93-2.25]; exposure to PM10: AOR, 2.17 [95% CI, 1.49-3.16) and during the first year of life (exposure to nitrogen dioxide: AOR, 2.06 [95% CI, 1.37-3.09]; exposure to PM2.5:

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Wilhelm, M., Ghosh, J.K., Su, J., Cockburn, M., Jerrett, M., Ritz, B.	Traffic-Related Air Toxics and Term Low Birth Weight in Los Angeles County, California	2012	Environmental Health Perspectives	NO, NO2, NOx, PM10, PM2.5	Low Birth Weight	Los Angeles county, California	All singleton live births 1 June 2	Examine the odds of term LBW when mothers are exposed to high levels of traffic-related air pollutants prenatally	Yes (presented for PM2.5 from specific sources)	Calculated correlation coefficients and performed factor analysis to examine clustering among various air pollution exposure metrics. Then examined associations between air pollution exposure and odds of term LBW using single- and multiple-variable logistic regression models.	Adjusted analysis for maternal age, race/ethnicity, education, and parity, and gestational age, gestational age squared. Also tried controlling for sex of infant, prenatal care, payment source for prenatal care, whether mother was born in US, maternal birthplace, and SES measure. Tried to reduce misclassification by looking only at women within a certain distance of monitoring stations.	Uses average exposure during first trimester, second trimester, and through entire pregnancy	Yes	**Background:** Numerous studies have linked criteria air pollutants with adverse birth outcomes, but there is less information on the importance of specific emission sources, such as traffic, and air toxics. **Objectives:** We used three exposure data sources to examine odds of term low birth weight (LBW) in Los Angeles, California, women when exposed to high levels of traffic-related air pollutants during pregnancy. **Methods:** We identified term births during 1 June 2004 to 30 March 2006 to women residing within 5 miles of a South Coast Air Quality Management District (SCAQMD) Multiple Air Toxics Exposure Study (MATES III) monitoring station. Pregnancy period average exposures were estimated for air toxics, including polycyclic aromatic hydrocarbons (PAHs), source-specific particulate matter < 2.5 µm in aerodynamic diameter (PM2.5) based on a chemical mass balance model, criteria air pollutants from government monitoring data, and land use regression (LUR) model estimates of nitric oxide (NO), nitrogen dioxide (NO2) and nitrogen oxides (NOx). Associations between these metrics and odds of term LBW (< 2,500 g) were examined using logistic regression. **Results:** Odds of term LBW increased approximately 5% per interquartile range increase in entire pregnancy exposures to several correlated traffic pollutants: LUR measures of NO, NO2, and NOx, elemental carbon, and PM2.5 from diesel and gasoline combustion and paved road dust (geological PM2.5). **Conclusions:** These analyses provide additional evidence of the potential impact of traffic-related air pollution on fetal growth. Particles from traffic sources should be a focus of future studies.
Trasande, L., Wong, K., Roy, A., Savitz, D.A., Thurston, G.	Exploring Prenatal Outdoor Air Pollution, Birth Outcomes and Neonatal Health Care Utilization in a Nationally Representative Sample	2013	Journal of Exposure Science and Environmental Epidemiology	lead, PM10, NO2, SO2, CO, and PM2.5	Low Birth Weight	United States	Kids Inpatient Database (KID)	Assessed the impact of air pollutants on low birth weight across the U.S.	Yes	Authors used pollutant concentrations from the U.S. EPA Aerometric Information Retrieval System (AIRS) couple with random subsampling of over 2.6 million births in KID for 2000, 2003, and 2006.	Controlled for gestational age, birth month, gender, race, socioeconomic variables	No	No	The impact of air pollutation on fetal growth remains controversial, in part, because studies have been limited to sub-regions of the United Stated with limited variability. No study has examined air pollution impacts on neonatal health care utilization. We performed descriptive, univariate and multivariable analyses on administrative hospital record data from 222,359 births in the 2000, 2003 and 2006 Kids Inpatient Database linked to air pollution data drawn from the US EPA's Aerometric Information Retrieval System. In this study, air pollution exposure during the birth month was estimated based on birth hospital address. Although air pollutants were not individually associated with mean birth weight, a three-pollutant model controlling for hospital characteristics, demographics, and birth month identified 9.3% and 7.2% increases in odds of low birth weight and very low birth weight for each ug/m3 increase in PM2.5 (both P<0.0001). PM2.5 and NO2 were associated with −3.0% odds/p.p.m. and +2.5% odds/p.p.b. of preterm birth, respectively (both P<0.0001). A four-pollutant multivariable model indicated a 0.05 days/p.p.m. NO2 decrease in length of the birth hospitalization (P=0.0061) and a 0.13 days increase/p.p.m. CO (P=0.0416). A $1166 increase in per child costs was estimated for the birth hospitalization per p.p.m. CO (P=0.0002) and $964 per unit increase in O3 (P=0.0448). A reduction from the 75th to the 25th percentile in the highest CO quartile for births predicts annual savings of $134.7 million in direct health care costs. In a national, predominantly urban, sample, air pollutant exposures during the month of birth are associated with increased low birth weight and neonatal health care utilization. Further study of this database, with enhanced control for confounding, improved exposure assessment, examination of exposures across multiple time windows in pregnancy, and in the entire national sample, is supported by these initial investigations.

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Zhu, Y., Zhang, C., Liu, D., Grantz, K.L., Wallace, M., Mendola, P.	Maternal Ambient Air Pollution Exposure Preconception and During Early Gestation and Offspring Congenital Orofacial Defects	2015	Environmental Research	CO, NOx, O3, PM2.5, PM10, SO2	Orofacial defects (isolated/multiple cleft palate and cleft lip with or without cleft palate)	United States	Consortium on Safe Labor	Investigates the association between maternal exposure to various air pollutants with risks of orofacial defects		Performed separate analysis for each outcome and exposure window of interest combination. Estimate generalized estimating equations to calculate robust standard errors accounting for clustering due to multiple pregnancies of the same woman. Performed sensitivity analysis excluding multiple gestation pregnancies and infants born to women with preexisting or gestational diabetes.	Controlled for site/region, maternal age, race/ethnicity, marital status, insurance, prepregnancy body mass index, nulliparity, season of conception, smoking and/or alcohol consumption during pregnancy, multiple birth, preexisting or gestational diabetes mellitus. Performed simulation extrapolation procedures to correct for potential exposure misclassification. I believe they did not do co-pollutant models.	Three months preconception and early gestation (both an average over weeks 3-8 and weekly averages from weeks 1 through 10)	Yes	**Background:** Maternal air pollution exposure has been related to orofacial clefts but the literature is equivocal. Potential chronic preconception effects have not been studied. **Objectives:** Criteria air pollutant exposure during three months preconception and gestational weeks 3-8 was studied in relation to orofacial defects. **Methods:** Among 188,102 live births and fetal deaths from the Consortium on Safe Labor (2002-2008), 63 had isolated cleft palate (CP) and 159 had isolated cleft lip with or without cleft palate (CL ±CP). Exposures were estimated using a modified Community Multiscale Air Quality model. Logistic regression with generalized estimating equations adjusted for site/region and maternal demographic, lifestyle and clinical factors calculated the odds ratio (OR) and 95% CI per interquartile increase in each pollutant. **Results**: Preconception, carbon monoxide (CO; OR=2.24; CI: 1.21, 4.16) and particulate matter (PM) ≤10μm (OR=1.72; CI: 1.12, 2.66) were significantly associated with CP, while sulfur dioxide (SO2) was associated with CL ±CP (OR=1.93; CI: 1.16, 3.21). During gestational weeks 3-8, CO remained a significant risk for CP (OR=2.74; CI: 1.62, 4.62) and nitrogen oxides (NOx; OR=3.64; CI: 1.73, 7.66) and PM ≤2.5μm (PM2.5; OR=1.74; CI: 1.15, 2.64) were also related to the risk. Analyses by individual week revealed that positive associations of NOx and PM2.5 with CP were most prominent from weeks 3-6 and 3-5, respectively. **Conclusions:** Exposure to several criteria air pollutants preconception and during early gestation was associated with elevated odds for CP, while CL ±CP was only associated with preconception SO2 exposure.

Table 1. SO_x Mortality

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Bell, M.L., Dominici, F.	Effect Modification by Community Characteristics on the Short-Term Effects of Ozone Exposure and Mortality in 98 U.S. Communities	2008	American Journal of Epidemiology	O3	All-cause non-accidental	98 U.S. cities	All U.S. residents	Investigates the link between short-term ozone exposure and risk of mortality, looking in particular at effect modification by community characteristics	First estimated relation between ozone in the previous week and mortality within each community in a constrained distributed lag model. Then fit a Bayesian hierarchical regression model to investgiate effect modification by community characteristics, using two-level normal independent sampling estimation with noninformative priors. For comparison, also fit a mixed-effects approach to meta-regression.	Controlled community-specific estimates for seasonality, long-term trend, day of the week, temperature, heat waves, and dew point temperature. Acknowledge potential misclassification by use of community-level socioeconomic etc. characteristics.	Uses exposure in the week before death	Yes	No	Previous research provided evidence of an association between short-term exposure to ozone and mortality risk and of heterogeneity in the risk across communities. The authors investigated whether this heterogeneity can be explained by community-specific characteristics: race, income, education, urbanization, transportation use, particulate matter and ozone levels, number of ozone monitors, weather, and use of air conditioning. Their study included data on 98 US urban communities for 1987 to 2000 from the National Morbidity, Mortality, and Air Pollution Study; US Census; and American Housing Survey. On average across the communities, a 10-ppb increase in the previous week's ozone level was associated with a 0.52% (95% posterior interval: 0.28, 0.77) increase in mortality. The authors found that community-level characteristics modify the relation between ozone and mortality. Higher effect estimates were associated with higher unemployment, fraction of the Black/African-American population, and public transportation use and with lower temperatures or prevalence of central air conditioning. These differences may relate to underlying health status, differences in exposure, or other factors. Results show that some segments of the population may face higher health burdens of ozone pollution.
Eze, I.C., Hemkens, L.G., Bucher, H.C., Hoffmann, B., Schindler, C., Kunzli, N., Schikowski, T., Probst-Hensch, N.M.	Association Between Ambient Air Pollution and Diabetes Mellitus in Europe and North America: Systematic Review and Meta-Analysis	2015	Environmental Health Perspectives	PM2.5, Nox	Type 2 diabetes mellitus	Europe and North American	Electronic literature databases	Reviewed epidemiological evidence on the association between air pollution and diabetes, and synthesized results of studies on type 2 diabetes mellitus (T2DM)	Yes	Evaluated risk of bias and role of potential confounders in all studies. Synthesized reported associations with T2DM in meta-analyses using random-effects models and conducted various sensitivity analyses.	Controlled for air pollution, sex, BMI, age, type of study	Different lag times across different studies	Yes	**Background**: Air pollution is hypothesized to be a risk factor for diabetes. Epidemiological evidence is inconsistent and has not been systematically evaluated. **Objectives:** We systematically reviewed epidemiological evidence on the association between air pollution and diabetes, and synthesized results of studies on type 2 diabetes mellitus (T2DM). **Methods:** We systematically searched electronic literature databases (last search, 29 April 2014) for studies reporting the association between air pollution (particle concentration or traffic exposure) and diabetes (type 1, type 2, or gestational). We systematically evaluated risk of bias and role of potnetial confounders in all studies. We synthesized reported associations with T2DM in meta-analyses using random-effects models and conducted various sensistivity analyses. **Results:** We included 13 studies (8 on T2DM, 2 on type 1, 3 on gestational diabetes), all conducted in Europe or North America. Five studies were longitudinal, 5 cross-sectional, 2 case-control, and 1 ecologic. Risk of bias, air pollution assessment, and confounder control varied across studies. Dose-response effects were not reported. Meta-analyses of 3 studies on PM2.5 and 4 studies on NO2 showed increase risk of T2DM by 8-10% per 10 ug/m3 increase in exposure [PM2.5:1.10 (95% CI: 1.02, 1.18); NO2: 1.08 (95% CI: 1.00, 1.170]. Associations were stronger in females. Sensitivity analyses showed similar results. **Conclusion:** Existing evidence indicates a positive association of air pollution and T2DM risk, albeit there is high risk of bias. High-quality studies assessing dose-response effects are needed. Research should be expanded to developing countries where outdoor and indoor air pollution are high.

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Hart, J.E., Garshick, E., Dockery, D.W., Smith, T.J., Ryan, L., Laden, F.	Long-Term Ambient Multipollutant Exposures and Mortality	2011	American Journal of Respiratory and Critical Care Medicine	PM10, PM2.5, NO2, SO2	All-cause non-accidental, lung cancer (ICD-9: 162, ICD-10: C33-34), cardiovascular disease (ICD-9: 401-440, ICD-10: I10-70), ischemic heart disease (ICD-9: 410-414, ICD-10: I20-I25), respiratory system disease (ICD-9: 480-519, ICD-10: J10-J18, J40-J98), chronic obstructive pulmonary disease and allied conditions (ICD-9: 490-494, 496, ICD-10: J40-J47)	United States	Men employed in 1985 from four trucking companies	Examines the association of ambient residential exposure with all-cause, cardiovascular disease, respiratory disease, and lung cancer mortality, adjusting for occupational exposures.	Estimated Cox proportional hazard regression models. Adjust for age and secular trends using attained age in 1-year increments, with separate baseline hazards by decade of age at entry, calendar year, and decade of hire.	Controlled for age and secular trends, and included race as a potential confounder. Included eight variables for years of work to adjust for potential confounding by occupational exposures. Adjusted for healthy worker survivor effect using time-varying variables for years employed and years off work.	Looks at average exposure in current calendar year and average 1985-2000	Yes	No	Rationale: Population-based studies have demonstrated associations between ambient air pollution exposures and mortality, but few have been able to adjust for occupational exposures. Additionally, two studies have observed higher risks in individuals with occupational dust, gas, or fume exposure. Objectives: We examined the association of ambient residential exposure to particulate matter less than 10 μm in diameter (PM10), particulate matter less than 2.5 μm in diameter (PM2.5), NO2, SO2, and mortality in 53,814 men in the U.S. trucking industry. Methods: Exposures for PM10, NO2, and SO2 at each residential address were assigned using models combining spatial smoothing and geographic covariates. PM2.5 exposures in 2000 were assigned from the nearest available monitor. Single and multipollutant Cox proportional hazard models were used to examine the association of an interquartile range (IQR) change (6 μg/m3 for PM10, 4 μg/m3 for PM2.5, 4ppb for SO2, and 8ppb for NO2) and the risk of all-cause and cause-specific mortality. Measurements and Main Results: An IQR change in ambient residential exposures to PM10 was associated with a 4.3% (95% confidence interval [CI], 1.1–7.7%) increased risk of all-cause mortality. The increase for an IQR change in SO2 was 6.9% (95% CI, 2.3–11.6%), for NO2 was 8.2% (95% CI, 4.5–12.1%), and for PM2.5 was 3.9% (95% CI, 1.0–6.9%). Elevated associations with cause-specific mortality (lung cancer, cardiovascular and respiratory disease) were observed for PM2.5, SO2, and NO2, but not PM10. None of the pollutants were confounded by occupational exposures. In multipollutant models, overall, the associations were attenuated, most strongly for PM10. In sensitivity analyses excluding long-haul drivers, who spend days away from home.
Krewski, D., Jerrett, M., Burnett, R.T., Ma, R., Hughes, E., Shi, Y., Turner, M.C., Pope, A.C., Thurston, G., Calle, E.E., Thun, M.J., Beckerman, B., Deluca, P., Finkelstein, N., Ito, K., Moore, D.K., Newbold, K.B., Ramsay, T., Ross, Z., Shin, H., Tempalski, B.	Extended Follow-up and Spatial Analysis of the American Cancer Society Study Linking Particulate Air Pollution and Mortality	2009	Health Effects Institute	PM2.5, O3, NO2, SO2	All-cause, cardiopulmonary disease, ischemic heart disease, lung cancer, all remaining causes	United States	American Cancer Society Cancer Prevention Study II cohort, enrolled Sep 1982-Feb 1983, >=30 at the time in a household with at least one person 45 years of age or older	Examines the effect of ambient air pollution on mortality	Used standard Cox proportiona lhazards model to calculate hazard ratios. Extended the random effects Cox model to commodate two levels of information for clustering and for ecologic covariates. Performed a nationwide analysis, intra-urban analysis in NYC and LA regions, and analysis of whether critical time windows of exposure might affect mortality.	Included 44 individual-level covariates and seven neighborhood-level covariates, like poverty level, level of educaiton, and unemployment. Looked at effect modification by county, sex, age at enrollment, BMI, education, and PM2.5 concentration. Also looked at threshold of ozone effects.	Constructed long-term average exposure for 1979-1983 and 1999-2000	Yes	Yes	Too long to include here. See http://hero.epa.gov/index.cfm/reference/details/reference_id/191193

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Lipfert, E.W., Baty, J.D., Miller, J.P., Wyzga, R.E.	PM2.5 Constituents and Related Air Quality Variables as Predictors of Survival in a Cohort of U.S. Military Veterans	2006	Inhalation Toxicology	PM2.5, NO2, CO, O3, SO2, others	All-cause	United States	U.S. military veterans, male, 1997-2001	Examines relationships between air quality components and long-term mortality, along with data on vehicular traffic density	Estimate Cox proportional hazards models, with primary independent variables of air pollutants and vehicular traffic density.	Control for individual-level age, race, smoking, BMI, height, blood pressure etc. Look at effect modification by some of those variables. Also control for contextual variables, like climate, education, and income. Estimate single and multipollutant models to look at possible confounding.	Possible use average exposure over 1997-2002, but unclear from abstract	?	Yes	Air quality data on trace metals, other constituents of PM2.5, and criteria air pollutants were used to examine relationships with long-term mortality in a cohort of male U.S. military veterans, along with data on vehicular traffic density (annual vehicle-miles traveled per unit of land area). The analysis used county-level environmental data for the period 1997-2002 and cohort mortality for 1997-2001. The proportional hazards model included individual data on age, race, smoking, body mass index, height, blood pressure, and selected interactions; contextual variables also controlled for climate, education, and income. In single-pollutant models, traffic density appears to be the most important predictor of survival, but potential contributions are also seen for NO2, NO3-, elemental carbon, nickel, and vanadium. The effects of the other main constituents of PM2.5, of crustal particles, and of peak levels of CO, O3, or SO2 appear to be less important. Traffic density is also consistently the most important environmental predictor in multiple-pollutant models, with combined relative risks up to about 1.2. However, from these findings it is not possible to discern which aspects of traffic (pollution, noise, stress) may be the most relevant to public health or whether an area-based predictor such as traffic density may have an inherent advantage over localized measures of ambient air quality. It is also possible that traffic density could be a marker for unmeasured pollutants or for geographic gradients per se. Pending resolution of these issues, including replication in other cohorts, it will be difficult to formulate additional cost-effective pollution control strategies that are likely to benefit public health.
Miller, K.A., Siscovick, D.S., Sheppard, L., Shepherd, K., Sullivan, J.H., Anderson, G.L., Kaufman, J.D.	Long-Term Exposure to Air Pollution and Incidence of Cardiovascular Events in Women	2007	The New England Journal of Medicine	PM10, SO2, NO2, CO, O3	Cardiovascular events, myocardial infarction, coronary revascularization, stroke, and death from either coronary heart disease or cerebrovascular disease	United States	Participants in the Women's Health Initiative, enrolled postmenopausal women between 50 and 79 from 1994-1998, with no history of cardiovascular disease	Looks at the effect of long-term exposure to air pollution on the incidence of cardiovascular disease among women		Used Cox proportional hazards regressions to estimate hazard ratios for the time to the first cardiovascular event. Stratified with use of separate baseline hazards according to current treatment for diabetes, age, and BMI. Created exposure variables to estimate between-city and within-city effects. Averaged exposures for all women in a metropolitan area into a weighted citywide exposure. Then, to look at within-city effects, fit indicator variables for each metropolitan area or subtracted the weighted citywide mean exposure.	In all models, controlled for age, BMI, smoking status, the number of cigarettes smoked per day, the number of years of smoking, systolic blood pressure, education level, household income, race or ethnic group, and presence or absence of diabetes, hypertension, hypercholestrolemia. Also evaluated possible confounding by presence or absense of environmental tobacco smoke, occupation, physical activity, diet, alcohol consumption, waist circumference, medical history etc. Looked at effect modification by many of these controls. Considered multipollutant models to assess confounding.	Used long-term average PM2.5 concentration, measured in 2000	Yes	Background: Fine particulate air pollution has been linked to cardiovascular disease, but previous studies have assessed only mortality and differences in exposure between cities. We examined the association of long-term exposure to particulate matter of less than 2.5 µm in aerodynamic diameter (PM2.5) with cardiovascular events. Methods: We studied 65,893 postmenopausal women without previous cardiovascular disease in 36 U.S. metropolitan areas from 1994 to 1998, with a median follow-up of 6 years. We assessed the women's exposure to air pollutants using the monitor located nearest to each woman's residence. Hazard ratios were estimated for the first cardiovascular event, adjusting for age, race or ethnic group, smoking status, educational level, household income, body-mass index, and presence or absence of diabetes, hypertension, or hypercholesterolemia. Results: A total of 1816 women had one or more fatal or nonfatal cardiovascular events, as confirmed by a review of medical records, including death from coronary heart disease or cerebrovascular disease, coronary revascularization, myocardial infarction, and stroke. In 2000, levels of PM2.5 exposure varied from 3.4 to 28.3 µg per cubic meter (mean, 13.5). Each increase of 10 µg per cubic meter was associated with a 24% increase in the risk of a cardiovascular event (hazard ratio, 1.24; 95% confidence interval [CI], 1.09 to 1.41) and a 76% increase in the risk of death from cardiovascular disease (hazard ratio, 1.76; 95% CI, 1.25 to 2.47). For cardiovascular events, the between-city effect appeared to be smaller than the within-city effect. The risk of cerebrovascular events was also associated with increased levels of PM2.5 (hazard ratio, 1.35; 95% CI, 1.08 to 1.68). Conclusions: Long-term exposure to fine particulate air

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Moolgavkar et al.	Time-Series Analyses of Air Pollution and Mortality in the United States: A Subsampling Approach	2013	Environmental Health Perspectives	PM10, O3, CO, NO2, SO2	All-cause non-accident	108 United States cities	All deaths, 1987-2000, from NMMAPS	Estimates maximum likelihoods of the common national effects of criteria pollutants on mortality	Use subsampling, where they randomly choose 4 cities without replacement from the 108 cities, and estimate the common pollutant effect for each sample. Ran 5,000 bootstrap cycles. Fit an over-dispersed Poisson model to the randomly chosen 4 cities. Investigate the shape of the concentration-response relationship	Control for temperature and relative humidity in each of the 4 cities in each sample. Also control for day of the week, temporal trends, mean temperature on the previous day, and mean dew-point temperature--should control for city-specific confounders, day of week effects, and time trends	Use a 1-day lag for pollutant exposure, i.e. 24-hr average pollutant concentration	Yes	Yes	Background: Hierarchical Bayesian methods have been used in previous papers to estimate national mean effects of air pollutants on daily deaths in time-series analyses. Objectives: We obtained maximum likelihood estimates of the common national effects of the criteria pollutants on mortality based on time-series data from ≤ 108 metropolitan areas in the United States. Methods: We used a subsampling bootstrap procedure to obtain the maximum likelihood estimates and confidence bounds for common national effects of the criteria pollutants, as measured by the percentage increase in daily mortality associated with a unit increase in daily 24-hr mean pollutant concentration on the previous day, while controlling for weather and temporal trends. We considered five pollutants [PM10, ozone (O3), carbon monoxide (CO), nitrogen dioxide (NO2), and sulfur dioxide (SO2)] in single- and multipollutant analyses. Flexible ambient concentration–response models for the pollutant effects were considered as well. We performed limited sensitivity analyses with different degrees of freedom for time trends. Results: In single-pollutant models, we observed significant associations of daily deaths with all pollutants. The O3 coefficient was highly sensitive to the degree of smoothing of time trends. Among the gases, SO2 and NO2 were most strongly associated with mortality. The flexible ambient concentration–response curve for O3 showed evidence of nonlinearity and a threshold at about 30 ppb. Conclusions: Differences between the results of our analyses and those reported from using the Bayesian approach suggest that estimates of the quantitative impact of pollutants depend on the choice of statistical approach, although results are not directly comparable because they are based on different
Moolgavkar, S.H.	Air Pollution and Daily Mortality in Two U.S. Counties: Season-Specific Analyses and Exposure-Response Relationships	2003	Inhalation Toxicology	PM10, CO, NO2, SO2, O3	All-cause non-accidental, and deaths due to vascular disease	Cook County, Illinois, and Los Angeles County, California	All deaths, 1987-1995	Analyzes the time series of daily total nonaccidental deaths and deaths due to vascular disease	Did full-year and season-specific analyses for each city.	Looked at both single- and multi-pollutant models to account for confounding, and stratified analysis by season.	?	?	Yes	I used generalized additive models to analyze the time series of daily total nonaccidental deaths and deaths due to vascular disease over the period 1987-1995 in two major metropolitan areas, Cook County, Illinois, and Los Angeles County, California, in the United States. In both counties I had monitoring information on PM(10), CO, SO(2), NO(2), and O(3). In Los Angeles, monitoring information on PM(2.5) was available as well. In addition to full-year analyses, I performed season-specific analyses. I present the results of both single- and multipollutant analyses. Although components of air pollution were associated with total nonaccidental and vascular disease mortality in both counties, the results indicate considerable heterogeneity of these associations in the two locations and also from season to season. In Los Angeles County, the gases, particularly CO and SO(2) but not ozone, were more strongly associated with mortality than was particulate matter, which exhibited only weak and inconsistent associations with both mortality endpoints. Both PM(10) and the gases were associated with total and vascular disease mortality in Cook County. The association of the gases with both mortality endpoints appeared to be stronger and more robust than that of PM(10). Exposure-response analyses using flexible smoothers showed significant departures from linearity, particularly for PM effects.

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Moolgavkar, S.H., McClellan, R.O., Dewanji, A., Turim, J., Luebeck, E.G., Edwards, E.	Time-Series Analyses of Air Pollution and Mortality in the United States: A Subsampling Approach	2013	Environmental Health Perspectives	PM10, O3, CO, NO2, SO2	All-cause non-accident	108 United States cities	All deaths, 1987-2000, from NMMAPS	Estimates maximum likelihoods of the common national effects of criteria pollutants on mortality	Use subsampling, where they randomly choose 4 cities without replacement from the 108 cities, and estimate the common pollutant effect for each sample. Ran 5,000 bootstrap cycles. Fit an over-dispersed Poisson model to the randomly chosen 4 cities. Investigate the shape of the concentration-response relationship	Control for temperature and relative humidity in each of the 4 cities in each sample. Also control for day of the week, temporal trends, mean temperature on the previous day, and mean dew-point temperature--should control for city-specific confounders, day of week effects, and time trends	Use a 1-day lag for pollutant exposure, i.e. 24-hr average pollutant concentration	Yes	No	Background: Hierarchical Bayesian methods have been used in previous papers to estimate national mean effects of air pollutants on daily deaths in time-series analyses. Objectives: We obtained maximum likelihood estimates of the common national effects of the criteria pollutants on mortality based on time-series data from ≤ 108 metropolitan areas in the United States. Methods: We used a subsampling bootstrap procedure to obtain the maximum likelihood estimates and confidence bounds for common national effects of the criteria pollutants, as measured by the percentage increase in daily mortality associated with a unit increase in daily 24-hr mean pollutant concentration on the previous day, while controlling for weather and temporal trends. We considered five pollutants [PM10, ozone (O3), carbon monoxide (CO), nitrogen dioxide (NO2), and sulfur dioxide (SO2)] in single- and multipollutant analyses. Flexible ambient concentration–response models for the pollutant effects were considered as well. We performed limited sensitivity analyses with different degrees of freedom for time trends. Results: In single-pollutant models, we observed significant associations of daily deaths with all pollutants. The O3 coefficient was highly sensitive to the degree of smoothing of time trends. Among the gases, SO2 and NO2 were most strongly associated with mortality. The flexible ambient concentration–response curve for O3 showed evidence of nonlinearity and a threshold at about 30 ppb. Conclusions: Differences between the results of our analyses and those reported from using the Bayesian approach suggest that estimates of the quantitative impact of pollutants depend on the choice of statistical approach, although results are not directly comparable because they are based on different
Smith, K.R., Jerrett, M., Anderson, H.R., Burnett, R.T., Stone, V., Derwent, R., Atkinson, R.W., Cohen, A., Shonkoff, S.B., Krewski, D., Pope, C.A., Thun, M.J., Thurston, G.	Public Health Benefits of Strategies to Reduce Greenhouse-Gas Emissions: Health Implications of Short-Lived Greenhouse Pollutants	2009	Lancet	PM2.5, O3, SO2	All-cause, cardiopulmonary	United States	American Cancer Society Cancer Prevention Study II cohort, enrolled Sep 1982-Feb 1983, >=30 at the time in a household with at least one person 45 years of age or older	Looks at the association between long-term ozone exposure and cardiovascular, cardiopulmonary, and respiratory mortality	Used multilevel random-effects Cox proportional hazards models, stratifying by age, sex, and race in the baseline hazard. Estimated mortality effects with models for independent pollutants and various combinations of co-pollutants.	They look at effect modification by age, sex, and race, and they control for 20 individual characteristics that might confound the relationship between air pollution and mortality. Looked at confounding by copollutants.	Calculated ozone measurements from the second and third quarters (warm season), and used long-term averages (what period?)	Yes	Yes	Summary In this report we review the health effects of three short-lived greenhouse pollutants--black carbon, ozone, and sulphates. We undertook new meta-analyses of existing time-series studies and an analysis of a cohort of 352[punctuation space]000 people in 66 US cities during 18 years of follow-up. This cohort study provides estimates of mortality effects from long-term exposure to elemental carbon, an indicator of black carbon mass, and evidence that ozone exerts an independent risk of mortality. Associations among these pollutants make drawing conclusions about their individual health effects difficult at present, but sulphate seems to have the most robust effects in multiple-pollutant models. Generally, the toxicology of the pure compounds and their epidemiology diverge because atmospheric black carbon, ozone, and sulphate are associated and could interact with related toxic species. Although sulphate is a cooling agent, black carbon and ozone could together exert nearly half as much global warming as carbon dioxide. The complexity of these health and climate effects needs to be recognised in mitigation policies.

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Woodruff, T.J., Darrow, L.A., Parker, J.D.	Air Pollution and Postneonatal Infant Mortality in the United States, 1999-2002	2008	Environmental Health Perspectives	CO, SO2, O3, PM2.5, PM10	All-cause, respiratory mortality (ICD-10: J000-99, P27.1, R95, R99)	United States	All singleton births who die within the first year of life but not within 28 days, 1999-2002 with data	Evaluates the role of chronic exposure to gaseous air pollutants and different particle size on postneonatal respiratory and SIDS infant mortality	Used logistic regression that incorporated generalized estimating equations to estimate the odds ratios. Assumed na exchangeable correlation structure. Modeled all air pollution exposures using a continuous, linaer form. Checked the appropriateness of this model using analysis based on quartiles of exposure. Used single-pollutant models for each cause of death, and then checked against copollutant models.	Controlled for maternal race/ethnicity, marital status, educatino, primiparity. Included county-level poverty and per capita income levels. Included year and month of birth dummy variables to account for time trend and seasonal effects, and controlled for region of the county to account for potential confounding by population and PM composition variation. Looked at confounding by trying copollutant models and comparing results.	Calculated average concentration of each pollutant over the first 2 months of life	Yes	Yes	OBJECTIVE: Our goal was to evaluate the relationship between cause-specific postneonatal infant mortality and chronic early-life exposure to particulate matter and gaseous air pollutants across the United States. METHODS: We linked county-specific monitoring data for particles with aerodiameter of < or = 2.5 microm (PM2.5) and < or = 10 microm (PM10), ozone, sulfur dioxide, and carbon monoxide to birth and death records for infants born from 1999 to 2002 in U.S. counties with > 250,000 residents. For each infant, we calculated the average concentration of each pollutant over the first 2 months of life. We used logistic generalized estimating equations to estimate odds ratios of postneonatal mortality for all causes, respiratory causes, sudden infant death syndrome (SIDS), and all other causes for each pollutant, controlling for individual maternal factors (race, marital status, education, age, and primiparity), percentage of county population below poverty, region, birth month, birth year, and other pollutants. This analysis includes about 3.5 million births, with 6,639 postneonatal infant deaths. RESULTS: After adjustment for demographic and other factors and for other pollutants, we found adjusted odds ratios of 1.16 [95% confidence interval (CI), 1.06-1.27] for a 10-mug/m3 increase in PM10 for respiratory causes and 1.20 (95% CI, 1.09-1.32) for a 10-ppb increase in ozone and deaths from SIDS. We did not find relationships with other pollutants and for other causes of death (control category). CONCLUSIONS: This study supports particulate matter air pollution being a risk factor for respiratory-related postneonatal mortality and suggests that ozone may be associated with SIDS in the United States.

Table 2. SO_x Respiratory Morbidity

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Akinbami, L.J., Lynch, C.D., Parker, J.D., Woodruff, T.J.	The Association Between Childhood Asthma Prevalence and Monitored Air Pollutants in Metropolitan Areas, United States, 2001-2004	2010	Environmental Research	O3, PM10, PM2.5, SO2, NO2	Current asthma and asthma attacks	United States	Children aged 3-17 who w	Looks at the association between chronic exposure to oudoor air pollutants and asthma outcomes		Used logistic regression to assess the association between asthma outcomes and each pollutant in separate models as continuous measures and as quartiles.	Controlled for age, sex, race/ethnicity, adult smoker in the household, single parent household, highest level of parental education, poverty status, and region of residence. To control for nonresponse on income,analyzed multiply imputed income files. Looked at multipollutant models and got similar results.	Average exposure previous 12 months	Yes	BACKGROUND: Air pollution exposure has been linked to adverse respiratory health outcomes among children, primarily in studies of acute exposures that are often in limited geographic areas. We sought to assess the association between chronic outdoor air pollution exposure, as measured by 12-month averages by county, and asthma among children in metropolitan areas across the nation. METHODS: Eligible children included those aged 3-17 years residing in US metropolitan areas who were sampled in the 2001-2004 National Health Interview Survey (N=34,073). 12-month average air pollutant levels for sulfur dioxide, nitrogen dioxide, ozone and particulate matter were compiled by county for 2000-2004. Eligible children were linked to pollutant levels for the previous 12 months for their county of residence. Adjusted odds ratios of having current asthma or an asthma attack in the past 12 months were estimated in single pollutant logistic regression models. RESULTS: Children in counties with ozone and, to a less consistent degree, particulate matter levels in the highest quartile were more likely to have current asthma and/or a recent asthma attack than children residing in counties with the lowest pollution levels; the adjusted odds for current asthma for the highest quartile of estimated ozone exposure was 1.56 (95% confidence interval [CI]: 1.15, 2.10) and for recent asthma attack 1.38 (95% CI: 0.99, 1.91). No associations were found with sulfur dioxide or nitrogen dioxide levels. CONCLUSION: Although the current US standard for ozone is based on short-term exposure, this cross-sectional study suggests that chronic (12-month) exposure to ozone and particles is related to asthma outcomes among children in metropolitan areas throughout the US.
Eze, I.C., Hemkens, L.G., Bucher, H.C., Hoffmann, B., Schindler, C., Kunzli, N., Schikowski, T., Probst-Hensch, N.M.	Association Between Ambient Air Pollution and Diabetes Mellitus in Europe and North America: Systematic Review and Meta-Analysis	2015	Environmental Health Perspectives	PM2.5, Nox	Type 2 diabetes mellitus	Europe and North American	Electronic literature databases	Reviewed epidemiological evidence on the association between air pollution and diabetes, and synthesized results of studies on type 2 diabetes mellitus (T2DM)	Yes	Evaluated risk of bias and role of potential confounders in all studies. Synthesized reported associations with T2DM in meta-analyses using random-effects models and conducted various sensitivity analyses.	Controlled for air pollution, sex, BMI, age, type of study	Different lag times across different studies	Yes	**Background**: Air pollution is hypothesized to be a risk factor for diabetes. Epidemiological evidence is inconsistent and has not been systematically evaluated. **Objectives:** We systematically reviewed epidemiological evidence on the association between air pollution and diabetes, and synthesized results of studies on type 2 diabetes mellitus (T2DM). **Methods:** We systematically searched electronic literature databases (last search, 29 April 2014) for studies reporting the association between air pollution (particle concentration or traffic exposure) and diabetes (type 1, type 2, or gestational). We systematically evaluated risk of bias and role of potnetial confounders in all studies. We synthesized reported associations with T2DM in meta-analyses using random-effects models and conducted various sensistivity analyses. **Results:** We included 13 studies (8 on T2DM, 2 on type 1, 3 on gestational diabetes), all conducted in Europe or North America. Five studies were longitudinal, 5 cross-sectional, 2 case-control, and 1 ecologic. Risk of bias, air pollution assessment, and confounder control varied across studies. Dose-response effects were not reported. Meta-analyses of 3 studies on PM2.5 and 4 studies on NO2 showed increase risk of T2DM by 8-10% per 10 ug/m3 increase in exposure [PM2.5:1.10 (95% CI: 1.02, 1.18); NO2: 1.08 (95% CI: 1.00, 1.170]. Associations were stronger in females. Sensitivity analyses showed similar results. **Conclusion:** Existing evidence indicates a positive association of air pollution and T2DM risk, albeit there is high risk of bias. High-quality studies assessing dose-response effects are needed. Research should be expanded to developing countries where outdoor and indoor air pollution are high.

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Gauderman, W.J., Urman, R., Avol, E., Berhane, K., McConnell, R., Rappaport, E., Chang, M.S., Lurmann, F., Gilliland, F.	Association of Improved Air Quality with Lung Development in Children	2015	N Engl J Med	NO2, O3, PM2.5, PM10, PM10-PM2.5	Lung function impairment (FEV1 and FVC) in children with and without asthma	Southern California (Long Beach, Mira Loma, Riverside, San Dimas, and Upland)	A total of 2120 children between the ages of 11 and 15 recruited from three separate Children's Health Study cohorts, including 669 in cohort C, 588 in cohort D, and 863 in cohort E. The two earlier cohorts (cohorts C and D) enrolled fourth-grade students in 1992–1993 and 1995–1996, respectively, from elementary schools in 12 southern California communities. The third cohort (cohort E) enrolled kindergarten and first-grade students in 2002–2003 from 13 communities, 9 of which overlapped with the 12 cohort C and D communities.	The goal of the analyses was to examine the association between long-term improvements in ambient air quality and lung-function development in children from 11 to 15 years of age, measured as the increases in FEV1 and FVC during that period (referred to as 4-year growth in FEV1 and FVC).	Yes	All available pulmonary-function measurements were used to estimate lung-function growth curves, including measurements at ages ranging from approximately 9 to 19 years in cohorts C and D and 10 to 16 years in cohort E. A previously developed linear-spline model, with knots placed at ages 12, 14, and 16 years, was used to capture the nonlinear pattern of growth during adolescence (see the Supplementary Appendix for details). In addition to examining 4-year growth from 11 to 15 years of age, we analyzed the cross-sectional pulmonary-function measurements obtained for 1585 children at the end of this period (mean age, 15 years) to determine whether changes in air quality over time were associated with clinically important deficits in attained FEV1 and FVC. Using data from all three cohorts, we developed a linear prediction model for FEV1 that included adjustments for age, sex, race and ethnic background, height, height squared, BMI, BMI squared, and the presence or absence of respiratory illness. For each child, we determined whether the ratio of observed to predicted FEV1 and FVC fell below each of three cutoffs for defining low lung function: 90%, 85%, and 80%. Logistic regression was used to test for temporal trends in the proportion of children with low lung function across cohorts after adjustment for community. A P value of less than 0.05 was considered to indicate statistical significance, under the assumption of a two-sided alternative hypothesis.	The model included adjustments for sex, race, Hispanic ethnic background, height, height squared, body-mass index (BMI, the weight in kilograms divided by the square of the height in meters), BMI squared, and presence or absence of respiratory-tract illness on the day of the pulmonary-function test.	Yes (indirectly)	Yes (qualitatively - discusses sensitivity analyses and study limitations)	BACKGROUND—Air-pollution levels have been trending downward progressively over the past several decades in southern California, as a result of the implementation of air quality– control policies. We assessed whether long-term reductions in pollution were associated with improvements in respiratory health among children. METHODS—As part of the Children's Health Study, we measured lung function annually in 2120 children from three separate cohorts corresponding to three separate calendar periods: 1994–1998, 1997–2001, and 2007–2011. Mean ages of the children within each cohort were 11 years at the beginning of the period and 15 years at the end. Linear-regression models were used to examine the relationship between declining pollution levels over time and lung-function development from 11 to 15 years of age, measured as the increases in forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) during that period (referred to as 4-year growth in FEV1 and FVC). RESULTS—Over the 13 years spanned by the three cohorts, improvements in 4-year growth of both FEV1 and FVC were associated with declining levels of nitrogen dioxide (P<0.001 for FEV1 and FVC) and of particulate matter with an aerodynamic diameter of less than 2.5 μm (P = 0.008 for FEV1 and P<0.001 for FVC) and less than 10 μm (P<0.001 for FEV1 and FVC). These associations persisted after adjustment for several potential confounders. Significant improvements in lung-function development were observed in both boys and girls and in children with asthma and children without asthma. The proportions of children with clinically low FEV1 (defined as <80% of the predicted value) at 15 years of age declined significantly, from 7.9% to 6.3% to 3.6% across the three periods, as the air quality improved (P = 0.001). CONCLUSIONS—We found that long-term improvements in air quality were associated with statistically and clinically significant positive effects on lung-function growth in children. (Funded by the Health Effects Institute and others.)
Klea Katsouyanni, Jonathan M. Samet, H. Ross Anderson, Richard Atkinson, Alain Le Tertre, Sylvia Medina, Evangelia Samoli, and Giota Touloumi, Richard T. Burnett, Daniel Krewski, Timothy Ramsay, Francesca Dominici, Roger D. Peng, Joel Schwartz, and Antonella Zanobetti	Air Pollution and Health: A European and North American Approach (APHENA)	2009	Health Effects Institute	PM10, O3, SO2, NO2, CO	Mortality (all-cause, respiratory, cardiovascular): morbidity (respiratory, cardiovascular hospital admissions)	90 U.S. cities, 32 European cities, and 12 Canadian cities	Ages 65-99	The study evaluated the effects of air pollutant exposures on morbidity and mortality in the U.S., Canada, and Europe.	Yes	Time series analysis	Yes	Lags of 0 and 1 day	Yes	This report provides the methodology and findings from the project: Air Pollution and Health: a European and North American Approach (APHENA*). The principal purpose of the project was to provide an understanding of the degree of consistency among findings of multicity time-series studies on the effects of air pollution on mortality and hospitalization in several North American and European cities. The project included parallel and combined analyses of existing data. The investigators sought to understand how methodological differences might contribute to variation in effect estimates from different studies, to characterize the extent of heterogeneity in effect estimates, and to evaluate determinants of heterogeneity. The APHENA project was based on data collected by three groups of investigators for three earlier studies: (1) Air Pollution and Health: A European Approach (APHEA), which comprised two multicity projects in Europe. (Phase 1 [APHEA1] involving 15 cities, and Phase 2 [APHEA2] involving 32 cities); (2) the National Morbidity, Mortality, and Air Pollution Study (NMMAPS), conducted in the 90 largest U.S. cities; and (3) multicity research on the health effects of air pollution in 12 Canadian cities.

Table 2. SO_x Respiratory Morbidity

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Koken, P.J.M., Piver, W.T., Ye, F., Elixhauser, A., Olsen, L.M., Portier, C.J.	Temperature, Air Pollution, and Hospitalization for Cardiovascular Diseases Among Elderly People in Denver	2003	Environmental Health Perspectives	NO2, SO2, O3, CO, PM10	Hospital admissions for acute myocardial infarction (ICD-9-CML 410.00-410.92), coronary atherosclerosis (ICD-9-CM: 414.00-414.05), pulmonary heart disease (ICD-9-CM: 416.0-416.9), cardiac dysrhythmias (ICD-9-CM: 427.0-427.9), congestive heart failure (ICD-9-CM: 428.0)	Denver County, CO	All hospital admissions for	Examines the epidemiologic link between air pollution and cardiovascular diseases in the elderly		Used general linear models, assuming a Poisson error structure. Assumed that the daily number of hospital admissions for each disease and daily levels of each environmental variable within any given year were independent of daily disease counts and environmental levels for the previous years. Included offset or normalizing factor to account for population changes. Estimated parameters with generalized estimating equations to account for the possibility of overdispersion and serial correlation.	Limiting study to July and August should eliminate any confounding by seasonal patterns. Controlled for sex, day of the week, and year of study. Also controlled for max temperature and dew point temperature. Acknowledges potential for exposure misclassification.	Explores lag times of 1-4 days before exposure for each of the environmental variables	Yes	Daily measures of maximum temperature, particulate matter less than or equal to 10 micro m in aerodynamic diameter (PM10), and gaseous pollution (ozone, nitrogen dioxide, sulfur dioxide, and carbon monoxide) were collected in Denver, Colorado, in July and August between 1993 and 1997. We then compared these exposures with concurrent data on the number of daily hospital admissions for cardiovascular diseases in men and women > 65 years of age. Generalized linear models, assuming a Poisson error structure for the selected cardiovascular disease hospital admissions, were constructed to evaluate the associations with air pollution and temperature. After adjusting the admission data for yearly trends, day-of-week effects, ambient maximum temperature, and dew point temperature, we studied the associations of the pollutants in single-pollutant models with lag times of 0-4 days. The results suggest that O3 is associated with an increase in the risk of hospitalization for acute myocardial infarction, coronary atherosclerosis, and pulmonary heart disease. SO2 appears to be related to increased hospital stays for cardiac dysrhythmias, and CO is significantly associated with congestive heart failure. No association was found between particulate matter or NO2 and any of the health outcomes. Males tend to have higher numbers of hospital admissions than do females for all of the selected cardiovascular diseases, except for congestive heart failure. Higher temperatures appear to be an important factor in increasing the frequency of hospitalization for acute myocardial infarction and congestive heart failure, and are associated with a decrease in the frequency of visits for coronary atherosclerosis and pulmonary heart disease.
Mortimer,K.M., L.M. Neas, D.W. Dockery, S. Redlinez, I.B. Tager	The effect of air pollution on inner-city children with asthma	2002	Eur Respir J	O3, SO2, NO2, PM10	Peak expiratory flow rate (PEFR) and asthma symptoms (cough, chest tightness, wheeze).	Participants are from one of the following 8 urban areas: Bronx and East Harlem, NY; Baltimore, MD; Washington, DC; Detroit, MI; Cleveland, OH; Chicago, IL; and St. Louis, MO.	Children aged 4-9 yrs old with asthma from the National Cooperative Inner-City Asthma Study (NCICAS).	Study evaluated air pollution-related health effects in a large cohort of inner-city children with asthma.	Yes	The per cent change in PEFR was analysed using linear mixed effect models (SAS Proc Mixed), while the incidence of symptoms and incidence of a 10% decline in median PEFR were modelled with generalized estimating equations, using a logistic link. Change-in-estimate criteria and likelihood ratio tests were used to determine the choice of covariates, with an alpha level of 0.05. AIC was used to evaluate the best correlation structure and to determine if a covariate should be entered as a fixed or random effect. Models with the AIC closest to zero were considered to best fit the data. Standard errors were insensitive to the use of several covariance structures, therefore results from models assuming the most simple structure (independence) were reported. Lagged air pollution effects were evaluated using moving averages, unrestricted distributed lags, and polynomial distributed lags. Within-model lag-specific estimates were combined to create a cumulative effect over a specified interval and estimates were then compared across models.	Yes	Yes	Yes	ABSTRACT: The effect of daily ambient air pollution was examined within a cohort of 846 asthmatic children residing in eight urban areas of the USA, using data from the National Cooperative Inner-City Asthma Study. Daily air pollution concentrations were extracted from the Aerometric Information Retrieval System database from the Environment Protection Agency in the USA. Mixed linear models and generalized estimating equation models were used to evaluate the effects of several air pollutants (ozone, sulphur dioxide (SO2), nitrogen dioxide (NO2) and particles with a 50% cut-off aerodynamic diameter of 10 mm (PM10) on peak expiratory flow rate (PEFR) and symptoms in 846 children with a history of asthma (ages 4–9 yrs). None of the pollutants were associated with evening PEFR or symptom reports. Only ozone was associated with declines in morning % PEFR (0.59% decline (95% confidence interval (CI) 0.13–1.05%) per interquartile range (IQR) increase in 5-day average ozone). In single pollutant models, each pollutant was associated with an increased incidence of morning symptoms: (odds ratio (OR)=1.16 (95% CI 1.02–1.30) per IQR increase in 4-day average ozone, OR=1.32 (95% CI 1.03–1.70) per IQR increase in 2-day average SO2, OR=1.48 (95% CI 1.02–2.16) per IQR increase in 6-day average NO2 and OR=1.26 (95% CI 1.0–1.59) per IQR increase in 2-day average PM10. This longitudinal analysis supports previous time-series findings that at levels below current USA air-quality standards, summer-air pollution is significantly related to symptoms and decreased pulmonary function among children with asthma.
Nishimura, K.K., Joshua M. Galanter, Lindsey A. Roth, Sam S. Oh, Neeta Thakur, Elizabeth A. Nguyen, Shannon Thyne, Harold J. Farber, Denise Serebrisky, Rajesh Kumar, Emerita Brigino-Buenaventura, Adam Davis, Michael A. LeNoir, Kelley Meade, William Rodriguez-Cintron, Pedro C. Avila, Luisa N. Borrell, Kirsten Bibbins-Domingo, Jose R. Rodriguez-	Early-Life Air Pollution and Asthma Risk in Minority Children: The GALA II and SAGE II Studies	2013	Am J Respir Crit Care Med	O3, NO2, SO2, PM10, PM2.5	Physician-diagnosed asthma plus two or more symptoms of coughing, wheezing, or shortness of breath	Participants from Chicago, IL; Bronx, NY; Houston, TX; San Francisco Bay Area, CA) and Puerto Rico	Latino (n = 3,343) and African American (n = 977) children (ages 8-21 years old) with and without asthma from five urban regions in the mainland United States and Puerto Rico who are participants in the Genes–environments and Admixture in Latino Americans (GALA II) and the Study of African Americans, Asthma, Genes and Environments (SAGE II) studies.	Study seeks to assess the relationship between traffic-related air pollution and childhood asthma, in high-risk racial/ethnic minorities (African Americans and Puerto Ricans)	Yes	To account for regional characteristics, the authors used a two-stage analysis, allowing us to measure the between-region heterogeneity and to obtain a representative estimate across all regions. In the first stage, associations for each pollutant were determined separately for each study and region. Unadjusted logistic regression models and models adjusted for age, sex, ethnicity, and composite socioeconomic status (SES) were used to calculate the association between pollutant exposures during the first 3 years of life and subsequent asthma diagnosis as a dichotomous outcome. We also performed a sensitivity analysis examining additional potential covariates for maternal in utero smoking, environmental tobacco smoke in the household between 0 and 2 years old, and maternal language of preference (as an indicator of acculturation). These variables were included in the final site-specific adjusted models if the sample size was large enough and their inclusion improved the fit of the model as indicated by the Akaike Information Criterion (AIC). In the second stage, the regression coefficients for each region were combined, using a random-effects meta-analysis with a restricted maximum-likelihood estimator to generate a summary OR for each pollutant. The authors performed three stratified analyses: with or without family history of asthma, male or female sex, and high or low total IgE (above/	Yes: age, sex, ethnicity, and composite SES (calculated for each participant by assigning a low, medium, or high score for income, level of education, and insurance type, and then by taking the sum of these three values). The investigators also performed a sensitivity analysis examining additional potential covariates for maternal in utero smoking, environmental tobacco smoke in the household between 0 and 2 years old, and maternal language of preference (as an indicator of acculturation).	Yes (through study design)	Yes (reports confidence intervals around Ors and discusses study limitations)	Rationale: Air pollution is a known asthma trigger and has been associated with short-term asthma symptoms, airway inflammation, decreased lung function, and reduced response to asthma rescuemedications. Objectives: To assess a causal relationship between air pollution and childhood asthma using data that address temporality by estimating air pollution exposures before the development of asthma and to establish the generalizability of the association by studying diverse racial/ethnic populations in different geographic regions. Methods: This study included Latino (n = 3,343) and African American (n = 977) participants with and without asthma from five urban regions in the mainland United States and Puerto Rico. Residential history and data from local ambient airmonitoring stationswere used to estimate average annual exposure to five air pollutants: ozone, nitrogen dioxide (NO2), sulfur dioxide, particulatematter not greater than 10 mm in diameter, and particulatematter not greater than 2.5 mmindiameter. Within each region, we performed logistic regression to determine the relationship between early-life exposure to air pollutants and subsequent asthma diagnosis. A random-effects model was used to combine the region specific effects and generate summary odds ratios for each pollutant. Measurements and Main Results: After adjustment for confounders, a 5-ppb increase in average NO2 during the first year of life was associated with an odds ratio of 1.17 for physician-diagnosed asthma (95% confidence interval, 1.04–1.31). Conclusions: Early-life NO2 exposure is associated with childhood asthma in Latinos and African Americans. These results add to a growing body of evidence that traffic-related pollutants may be causally related to childhood asthma.

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George T. O'Connor; Lucas Neas; Benjamin Vaughn; Meyer Kattan; Herman Mitchell; Ellen F. Crain; Richard Evans, III; Rebecca Gruchalla; Wayne Morgan; James Stout; G. Kenneth Adams; and Morton Lippmann	Acute respiratory health effects of air pollution on children with asthma in US inner cities	2008	U.S. Environmental Protection Agency Papers	PM2.5, NO2, SO2, CO, and O3	Acute respiratory morbidity	Low-income Census tracts in Boston, the Bronx, Chicago, Dallas, New York, Seattle, and Tucson	Low-income children	The association between changes in ambient air pollutants and asthma morbidity in inner city children.	Yes	Mixed-effects models; both single and three pollutant models	No	Yes; 1-, 3-, and 5-day lags	Yes	Background: Children with asthma in inner-city communities may be particularly vulnerable to adverse effects of air pollution because of their airways disease and exposure to relatively high levels of motor vehicle emissions. Objective: To investigate the association between fluctuations in outdoor air pollution and asthma morbidity among inner-city children with asthma. Methods: We analyzed data from 861 children with persistent asthma in 7 US urban communities who performed 2-week periods of twice-daily pulmonary function testing every 6 months for 2 years. Asthma symptom data were collected every 2 months. Daily pollution measurements were obtained from the Aerometric Information Retrieval System. The relationship of lung function and symptoms to fluctuations in pollutant concentrations was examined by using mixed models. Results: Almost all pollutant concentrations measured were below the National Ambient Air Quality Standards. In singlepollutant models, higher 5-day average concentrations of NO2, sulfur dioxide, and particles smaller than 2.5 mm were associated with significantly lower pulmonary function. Higher pollutant levels were independently associated with reduced lung function in a 3-pollutant model. Higher concentrations of NO2 and particles smaller than 2.5 mm were associated with asthma-related missed school days, and higher NO2 concentrations were associated with asthma symptoms. Conclusion: Among inner-city children with asthma, short-term increases in air pollutant concentrations below the National Ambient Air Quality Standards were associated with adverse respiratory health effects. The associations with NO2 suggest that motor vehicle emissions may be causing excess morbidity in this population.

Table 3. SO_x Other Morbidity

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Ensor, K.B., Raun, L.H., Persse, D.	A Case-Crossover Analysis of Out-of-Hospital Cardiac Arrest and Air Pollution	2013	Circulation	PM2.5, O3, NO2, SO2, CO	Out of hospital cardiac arrest (ER visits)	Houston, TX	All non-dead-on-arrival adults >	Studies the association between air pollution and risk of out-of-hospital cardiac arrest.	Yes	Used a time-stratified case-crossover design coupled with conditional logistic regression. Uses ambient air pollution concentrations at times when the study individual is not experiencing the OHCA health event as reference for each case. Use conditional logistic regression to estimate the association of pollution and increased relative risk of health event. Did sensitivity analysis with single lag models to look at hour and day time scales. Implemented constrained distributed lag models to estimate the cumulative effect over 2-hour average or 2-day average increments.	Case-crossover design should control for individual-level confounders. When there was a significant association between individual pollutants and OHCA, looked at potential confounding between pollutants by estimating correlations and including pollutants as covariates in the model. Looked at effect modification by age, sex, race, and season. Acknowledge the possibility of exposure time misclassification and selection bias from not including individuals dead on arrival.	Assessed lags on hourly and daily time scale, for 1-8 lag hours and 1-5 day lags	Yes	**Background:** Evidence of an association between the exposure to air pollution and overall cardiovascular morbidity and mortality is increasingly found in the literature. However, results from studies of the association between acute air pollution exposure and risk of out-of-hospital cardiac arrest (OHCA) are inconsistent for fine particulate matter, and, although pathophysiological evidence indicates a plausible link between OHCA and ozone, none has been reported. Approximately 300 000 persons in the United States experience an OHCA each year, of which >90% die. Understanding the association provides important information to protect public health. **Methods and Results:** The association between OHCA and air pollution concentrations hours and days before onset was assessed by using a time-stratified case-crossover design using 11 677 emergency medical service–logged OHCA events between 2004 and 2011 in Houston, Texas. Air pollution concentrations were obtained from an extensive area monitor network. An average increase of 6 µg/m3 in fine particulate matter 2 days before onset was associated with an increased risk of OHCA (1.046; 95% confidence interval, 1.012–1.082). A 20-ppb ozone increase for the 8-hour average daily maximum was associated with an increased risk of OHCA on the day of the event (1.039; 95% confidence interval, 1.005–1.073). Each 20-ppb increase in ozone in the previous 1 to 3 hours was associated with an increased risk of OHCA (1.044; 95% confidence interval, 1.004–1.085). Relative risk estimates were higher for men, blacks, or those aged >65 years. **Conclusions:** The findings confirm the link between OHCA and fine particulate matter and introduce evidence of a similar link with ozone.
Eze, I.C., Hemkens, L.G., Bucher, H.C., Hoffmann, B., Schindler, C., Kunzli, N., Schikowski, T., Probst-Hensch, N.M.	Association Between Ambient Air Pollution and Diabetes Mellitus in Europe and North America: Systematic Review and Meta-Analysis	2015	Environmental Health Perspectives	PM2.5, Nox	Type 2 diabetes mellitus (T2DM)	Europe and North American	Electronic literature databases	Reviewed epidemiological evidence on the association between air pollution and diabetes, and synthesized results of studies on type 2 diabetes mellitus	Yes	Evaluated risk of bias and role of potential confounders in all studies. Synthesized reported associations with T2DM in meta-analyses using random-effects models and conducted various sensitivity analyses.	Controlled for air pollution, sex, BMI, age, type of study	Different lag times across different studies	Yes	**Background**: Air pollution is hypothesized to be a risk factor for diabetes. Epidemiological evidence is inconsistent and has not been systematically evaluated. **Objectives:** We systematically reviewed epidemiological evidence on the association between air pollution and diabetes, and synthesized results of studies on type 2 diabetes mellitus (T2DM). **Methods:** We systematically searched electronic literature databases (last search, 29 April 2014) for studies reporting the association between air pollution (particle concentration or traffic exposure) and diabetes (type 1, type 2, or gestational). We systematically evaluated risk of bias and role of potnetial confounders in all studies. We synthesized reported associations with T2DM in meta-analyses using random-effects models and conducted various sensistivity analyses. **Results:** We included 13 studies (8 on T2DM, 2 on type 1, 3 on gestational diabetes), all conducted in Europe or North America. Five studies were longitudinal, 5 cross-sectional, 2 case-control, and 1 ecologic. Risk of bias, air pollution assessment, and confounder control varied across studies. Dose-response effects were not reported. Meta-analyses of 3 studies on PM2.5 and 4 studies on NO2 showed increase risk of T2DM by 8-10% per 10 ug/m3 increase in exposure [PM2.5:1.10 (95% CI: 1.02, 1.18); NO2: 1.08 (95% CI: 1.00, 1.170]. Associations were stronger in females. Sensitivity analyses showed similar results. **Conclusion:** Existing evidence indicates a positive association of air pollution and T2DM risk, albeit there is high risk of bias. High-quality studies assessing dose-response effects are needed. Research should be expanded to developing countries where outdoor and indoor air pollution are high.

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Gilboa, S.M., Mendola, P., Olshan, A.F., Langlois, P.H., Savitz, D.A., Loomis, D., Herring, A.H., Fixler, D.E.	Relation Between Ambient Air Quality and Selected Birth Defects, Seven County Study, Texas, 1997-2000	2005	American Journal of Epidemiology	PM10, O3, CO, NO2, SO2	Birth defects, classified as conotruncal defects, endocardial cushion and mitral valve defects, pulmonary artery and valve defects, aortic artery and valve defects, ventricular septal defects, atrial and atrial septal defects, cleft lip w/ or w/o cleft palate, cleft palate	7 counties in Texas	Livebirths and fetal deaths of ir	Explores associations between ambient air quality and the incidence of a selection of birth defects		For the six mutually exclusive defect groupings, used polytomous logistic regression models with a seven-level outcome variable. Conducted "step-down" analysis to control the type 1 error rate without sacrificing statistical power. First tested the hypothesis of no association between each pollutant and any of the six isolated birth defect groups as a group, then stepped down to conduct pollutant-defect-specific hypothesis tests of no association. Modeled air pollution both using a continuous exposure metric and with quartiles.	Considered confounding by alcohol consumption during pregnancy, attendant of delivery, gravidity, marital status, maternal age, maternal education, maternal illness, race/ethnicity, parity, place of delivery, plurality, prenatal care, season of conception, and tobacco use during pregnancy. Did both single-pollutant and multi-pollutant analysis to assess confounding. Looked at effect modification by infant sex ,plurality, maternal education, maternal race, and season of conception.	Looks at average pollutant concentrations during weeks 3-8 of pregnancy	Yes	A population-based case-control study investigated the association between maternal exposure to air pollutants, carbon monoxide, nitrogen dioxide, ozone, sulfur dioxide, and particulate matter <10 µm in aerodynamic diameter during weeks 3–8 of pregnancy and the risk of selected cardiac birth defects and oral clefts in livebirths and fetal deaths between 1997 and 2000 in seven Texas counties. Controls were frequency matched to cases on year of birth, vital status, and maternal county of residence at delivery. Stationary monitoring data were used to estimate air pollution exposure. Logistic regression models adjusted for covariates available in the vital record. When the highest quartile of exposure was compared with the lowest, the authors observed positive associations between carbon monoxide and tetralogy of Fallot (odds ratio = 2.04, 95% confidence interval: 1.26, 3.29), particulate matter <10 µm in aerodynamic diameter and isolated atrial septal defects (odds ratio = 2.27, 95% confidence interval: 1.43, 3.60), and sulfur dioxide and isolated ventricular septal defects (odds ratio = 2.16, 95% confidence interval: 1.51, 3.09). There were inverse associations between carbon monoxide and isolated atrial septal defects and between ozone and isolated ventricular septal defects. Evidence that air pollution exposure influences the risk of oral clefts was limited. Suggestive results support a previously reported finding of an association between ozone exposure and pulmonary artery and valve defects.
Hart, J.E., Kallberg, H., Laden, F., Costenbader, K.H., Yanosky, J.D., Klareskog, Alfredsson, L., Karlson, E.W.	Ambient Air Pollution Exposures and Risk of Rheumatoid Arthritis in the Nurses' Health Study	2014	Arthritis Care Research	PM10, PM2.5, SO2, NO2	Rheumatoid arthritis	United States	Nurses' Health Study participar	Considers the possible association between air pollution and risks of rheumatoid arthritis		Used time-varying Cox proportional hazards models with each air pollutant in a separate model. Person-time accrued from baseine until diagnosis of RA, loss to follow-up, date of death, or end of follow-up. Stratified all models by age in months and calendar year.	Controlled for age, race, age at menarche, parity, total months of lactation, current menopausal status, menopausal hormone use, oral contraceptive use, physical activity, and BMI. Controlled for smoking and individual level SES using education levels. Also included census tract-level median income and house value. Looked at effect modification by age in months and calendar year. Also looked at effect modification by SES and smoking status, as well as by census region.	Looked at time-varying annual exposure the 6th- and 10th-year prior to each questionnaire cycle. Also looked at time-varying cumulative average exposure during the follow-up period	Yes	Objective: Environmental factors may play a role in the development of rheumatoid arthritis (RA), and we have previously observed increased RA risk among women living closer to major roads (a source of air pollution). We examined whether long-term exposures to specific air pollutants were associated with RA risk among women in the Nurses' Health Study. Methods: The Nurses' Health Study (NHS) is a large cohort of U.S. female nurses followed prospectively every two years since 1976. We studied 111,425 NHS participants with information on air pollution exposures as well as data concerning other lifestyle and behavioral exposures and disease outcomes. Outdoor levels of different size fractions of particulate matter (PM10 and PM2.5) and gaseous pollutants (SO2 and NO2) were predicted for all available residential addresses using monitoring data from the USEPA. We examined the association of time-varying exposures, 6 and 10 years before each questionnaire cycle, and cumulative average exposure with the risks of RA, seronegative (rheumatoid factor [RF] and anti–citrullinated peptide antibodies [ACPA]) RA, and seropositive RA. Results: Over the 3,019,424 years of follow-up, 858 incident RA cases were validated by medical record review by two board-certified rheumatologists. Overall, we found no evidence of increased risks of RA, seronegative or seropositive RA, with exposure to the different pollutants, and little evidence of effect modification by socioeconomic status or smoking status, geographic region, or calendar period. Conclusion: In this group of socioeconomically-advantaged middle-aged and elderly women, adult exposures to air pollution were not associated with an increased RA risk.
Koken, P.J.M., Piver, W.T., Ye, F., Elixhauser, A., Olsen, L.M., Portier, C.J.	Temperature, Air Pollution, and Hospitalization for Cardiovascular Diseases Among Elderly People in Denver	2003	Environmental Health Perspectives	NO2, SO2, O3, CO, PM10	Hospital admissions for acute myocardial infarction (ICD-9-CML 410.00-410.92), coronary atherosclerosis (ICD-9-CM: 414.00-414.05), pulmonary heart disease (ICD-9-CM: 416.0-416.9), cardiac dysrhythmias (ICD-9-CM: 427.0-427.9), congestive heart failure (ICD-9-CM: 428.0)	Denver County, CO	All hospital admissions for men	Examines the epidemiologic link between air pollution and cardiovascular diseases in the elderly		Used general linear models, assuming a Poisson error structure. Assumed that the daily number of hospital admissions for each disease and daily levels of each environmental variable within any given year were independent of daily disease counts and environmental levels for the previous years. Included offset or normalizing factor to account for population changes. Estimated parameters with generalized estimating equations to account for the possibility of overdispersion and serial correlation.	Limiting study to July and August should eliminate any confounding by seasonal patterns. Controlled for sex, day of the week, and year of study. Also controlled for max temperature and dew point temperature. Acknowledges potential for exposure misclassification.	Explores lag times of 1-4 days before exposure for each of the environmental variables	Yes	Daily measures of maximum temperature, particulate matter less than or equal to 10 micro m in aerodynamic diameter (PM10), and gaseous pollution (ozone, nitrogen dioxide, sulfur dioxide, and carbon monoxide) were collected in Denver, Colorado, in July and August between 1993 and 1997. We then compared these exposures with concurrent data on the number of daily hospital admissions for cardiovascular diseases in men and women > 65 years of age. Generalized linear models, assuming a Poisson error structure for the selected cardiovascular disease hospital admissions, were constructed to evaluate the associations with air pollution and temperature. After adjusting the admission data for yearly trends, day-of-week effects, ambient maximum temperature, and dew point temperature, we studied the associations of the pollutants in single-pollutant models with lag times of 0-4 days. The results suggest that O3 is associated with an increase in the risk of hospitalization for acute myocardial infarction, coronary atherosclerosis, and pulmonary heart disease. SO2 appears to be related to increased hospital stays for cardiac dysrhythmias, and CO is significantly associated with congestive heart failure. No association was found between particulate matter or NO2 and any of the health outcomes. Males tend to have higher numbers of hospital admissions than do females for all of the selected cardiovascular diseases, except for congestive heart failure. Higher temperatures appear to be an important factor in increasing the frequency of hospitalization for acute myocardial infarction and congestive heart failure, and are associated with a decrease in the frequency of visits for coronary atherosclerosis and pulmonary heart disease.

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Miller, K.A., Siscovick, D.S., Sheppard, L., Shepherd, K., Sullivan, J.H., Anderson, G.L., Kaufman, J.D.	Long-Term Exposure to Air Pollution and Incidence of Cardiovascular Events in Women	2007	The New England Journal of Medicine	PM10, SO2, NO2, CO, O3	Cardiovascular events, myocardial infarction, coronary revascularization, stroke, and death from either coronary heart disease or cerebrovascular disease	United States	Participants in the Women's He	Looks at the effect of long-term exposure to air pollution on the incidence of cardiovascular disease among women		Used Cox proportional hazards regressions to estimate hazard ratios for the time to the first cardiovascular event. Stratified with use of separate baseline hazards according to current treatment for diabetes, age, and BMI. Created exposure variables to estimate between-city and within-city effects. Averaged exposures for all women in a metropolitan area into a weighted citywide exposure. Then, to look at within-city effects, fit indicator variables for each metropolitan area or subtracted the weighted citywide mean exposure.	In all models, controlled for age, BMI, smoking status, the number of cigarettes smoked per day, the number of years of smoking, systolic blood pressure, education level, household income, race or ethnic group, and presence or absence of diabetes, hypertension, hypercholestrolemia. Also evaluated possible confounding by presence or absense of environmental tobacco smoke, occupation, physical activity, diet, alcohol consumption, waist circumference, medical history etc. Looked at effect modification by many of these controls. Considered multipollutant models to assess confounding.	Used long-term average PM2.5 concentration, measured in 2000	Yes	Background: Fine particulate air pollution has been linked to cardiovascular disease, but previous studies have assessed only mortality and differences in exposure between cities. We examined the association of long-term exposure to particulate matter of less than 2.5 µm in aerodynamic diameter (PM2.5) with cardiovascular events. Methods: We studied 65,893 postmenopausal women without previous cardiovascular disease in 36 U.S. metropolitan areas from 1994 to 1998, with a median follow-up of 6 years. We assessed the women's exposure to air pollutants using the monitor located nearest to each woman's residence. Hazard ratios were estimated for the first cardiovascular event, adjusting for age, race or ethnic group, smoking status, educational level, household income, body-mass index, and presence or absence of diabetes, hypertension, or hypercholesterolemia. Results: A total of 1816 women had one or more fatal or nonfatal cardiovascular events, as confirmed by a review of medical records, including death from coronary heart disease or cerebrovascular disease, coronary revascularization, myocardial infarction, and stroke. In 2000, levels of PM2.5 exposure varied from 3.4 to 28.3 µg per cubic meter (mean, 13.5). Each increase of 10 µg per cubic meter was associated with a 24% increase in the risk of a cardiovascular event (hazard ratio, 1.24; 95% confidence interval [CI], 1.09 to 1.41) and a 76% increase in the risk of death from cardiovascular disease (hazard ratio, 1.76; 95% CI, 1.25 to 2.47). For cardiovascular events, the between-city effect appeared to be smaller than the within-city effect. The risk of cerebrovascular events was also associated with increased levels of PM2.5 (hazard ratio, 1.35; 95% CI, 1.08 to 1.68). Conclusions: Long-term exposure to fine particulate air pollution is associated with the incidence of cardiovascular disease and death among postmenopausal women. Exposure differences within cities are associated with the risk of cardiovascular disease.
Morello-Frosch, R., Jesdale, B.M., Sadd, J.L., Pastor, M.	Ambient Air Pollution Exposure and Full-term Birth Weight in California	2010	Environmental Health	PM2.5, PM10, CO, NO2, SO2, O3	Average birth weight and low birth weight	California	Singleton live births with gestational age between 37-44, from California residents, 1996-2006	Analyzes the effect of air pollution on average birth weight and risk of low birth weight in California		Used linear multivariable models to estimate the impact of air pollutants on birth weight as a continuous measure, and logistic regression models to estimate air pollution effects on birth weight as dichotomous outcome. Examined trimester-specific models as well as full-pregnancy models.	Controlled for maternal age, educational attainment, maternal race/ethnicity, maternal birthplace, calendar year, season of delivery, marital status, partiy, Kotelchuk index of prenatal care, and presence of other pregnancy risk factors, like anemia, diabetes, chronic or pregnancy-associated hypertension, and/or herpes. Also included neighborhood socio-economic status variables. Also stratified by maternal race/ethnicity and neighborhood-level poverty rate to look at effect modification. Also ran copollutant models to assess potential confounding effects.			Background:Studies have identified relationships between air pollution and birth weight, but have been inconsistent in identifying individual pollutants inversely associated with birth weight or elucidating susceptibility of the fetus by trimester of exposure. We examined effects of prenatal ambient pollution exposure on average birth weight and risk of low birth weight in full-term births. Methods: We estimated average ambient air pollutant concentrations throughout pregnancy in the neighborhoods of women who delivered term singleton live births between 1996 and 2006 in California. We adjusted effect estimates of air pollutants on birth weight for infant characteristics, maternal characteristics, neighborhood socioeconomic factors, and year and season of birth. Results: 3,545,177 singleton births had monitoring for at least one air pollutant within a 10 km radius of the tract or ZIP Code of the mother's residence. In multivariate models, pollutants were associated with decreased birth weight; -5.4 grams (95% confidence interval -6.8 g, -4.1 g) per ppm carbon monoxide, -9.0 g (-9.6 g, -8.4 g) per pphm nitrogen dioxide, -5.7 g (-6.6 g, -4.9 g) per pphm ozone, -7.7 g (-7.9 g, -6.6 g) per 10 µg/m3 particulate matter under 10 µm, -12.8 g (-14.3 g, -11.3 g) per 10 µg/m3 particulate matter under 2.5 µm, and -9.3 g (-10.7 g, -7.9 g) per 10 µg/m3 of coarse particulate matter. With the exception of carbon monoxide, estimates were largely unchanged after controlling for co-pollutants. Effect estimates for the third trimester largely reflect the results seen from full pregnancy exposure estimates; greater variation in results is seen in effect estimates specific to the first and second trimesters. Conclusions: This study indicates that maternal exposure to ambient air pollution results in modestly lower infant birth weight. A small decline in birth weight is unlikely to have clinical relevance for individual infants, and there is debate about whether a small shift in the population distribution of birth weight has broader health implications. However, the ubiquity of air pollution exposures, the responsiveness of pollutant levels to regulation, and the fact that the highest pollution levels in California are lower than those regularly experienced in other countries suggest

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Robledo, C.A., Mendola, P., Yeung, E., Mannisto, T., Sundaram, R., Liu, D., Ying, Q., Sherman, S., Grantz, K.L.	Preconception and Early Pregnancy Air Pollution Exposures and Risk of Gestational Diabetes Mellitus	2015	Environmental Research	PM2.5, PM10, NOx, CO, SO2, O3	Gestational diabetes mellitus (ICD-9: 648.8)	United States	Singleton births without preges	Investigates the association between critera air pollutants regulated by the US EPA and the risk of gestational diabetes mellitus	No	First calcualted Spearman rank correlations between each pollutants. Then fitted binary regression models with the log link function to estimate relative risks for IQR increase for each pollutant. Used a first order autoregressive covariance structure to account for within-cluster correlation for women with more than one singleton pregnancy during study period. Made separate models for air pollutants during each exposure window.	Assessed potential confounding by maternal characteristics, including parity, marital status, insurance status, hospital type, prenatal history of smoking and alcohol, study sites. Looked at effect modification by maternal BMI. Also looked at multi-pollutant models to look at confounding by other pollutants.	Included pre-conception exposure (91 days before last menstrual period), average exposure during 1st trimester, weekly averages for gestational weeks 1 through 24	Yes	Background: Air pollution has been linked to gestational diabetes mellitus (GDM) but no studies have evaluated impact of preconception and early pregnancy air pollution exposures on GDM risk. Methods: Electronic medical records provided data on 219,952 singleton deliveries to mothers with (n=11,334) and without GDM (n=208,618). Average maternal exposures to particulate matter (PM) ≤ 2.5μm (PM2.5) and PM2.5 constituents, PM ≤ 10μm (PM10), nitrogen oxides (NOx), carbon monoxide, sulfur dioxide (SO2) and ozone (O3) were estimated for the 3-month preconception window, first trimester, and gestational weeks 1-24 based on modified Community Multiscale Air Quality models for delivery hospital referral regions. Binary regression models with robust standard errors estimated relative risks (RR) for GDM per interquartile range (IQR) increase in pollutant concentrations adjusted for study site, maternal age and race/ethnicity. Results: Preconception maternal exposure to NOX (RR=1.09, 95% CI: 1.04, 1.13) and SO2 (RR=1.05, 1.01, 1.09) were associated with increased risk of subsequent GDM and risk estimates remained elevated for first trimester exposure. Preconception O3 was associated with lower risk of subsequent GDM (RR=0.93, 0.90, 0.96) but risks increased later in pregnancy. Conclusion: Maternal exposures to NOx and SO2 preconception and during the first few weeks of pregnancy were associated with increased GDM risk. O3 appeared to increase GDM risk in association with mid-pregnancy exposure but not in earlier time windows. These common exposures merit further investigation.
Stingone, J.A., Luben, T.J., Daniels, J.L, Fuentes, M., Richardson, D.B., Aylsworth, A.S,. Herring, A.H., Anderka, M., Botto, L., Correa, A., Gilboa, S.M., Langlois, P.H., Mosley, B., Shaw, G.M>, Siffel, C., Olshan, A.F.	Maternal Exposure to Criteria Air Pollutants and Congenital Heart Defects in Offspring: Results from the National Birth Defects Prevention Study	2014	Environmental Health Perspectives	CO, NO2, O3, PM10, PM2.5, SO2	Simple, isolated congenital heart defects with no extra-cardiac birth defects present		Participants in National Birth D	Investigates the association between maternal exposure to air pollutants during weeks 2-8 of pregnancy and their associations with congenital heart defects	Yes (with hypoplastic left heart syndrome, inversely associated with atrial septal defects, some attenuation of results by multipollutant models)	Construfted two-stage hierarchical regression models to account for correlation between estimates and partially address multiple inference. In first stage, ran uconditional, polytomous logistic regression model of individual CHDs on exposure defined as either all 1-week average exposure or single 7-week average. Looked at sensitivity to changes in the model specification.	Controled for maternal age, race/ethnicity, educational attainment, household income, tobacco smoking in the first month of pregnancy, alcohol consumption during the first trimester, maternal nativity. Also controlled for distance to closest major road, prepregnancy BMI, maternal occupational status. Looked at multipollutant models using a principal component analysis.	Calculated average pollutant concentration for weeks 2-8 of pregnancy and 1-week averages for each week	Yes	Background: Epidemiologic literature suggests that exposure to air pollutants is associated with fetal development. Objectives: We investigated maternal exposures to air pollutants during weeks 2-8 of pregnancy and their associations with congenital heart defects. Methods: Mothers from the National Birth Defects Prevention Study, a nine-state case-control study, were assigned 1-week and 7-week averages of daily maximum concentrations of carbon monoxide, nitrogen dioxide, ozone, and sulfur dioxide and 24-hr measurements of fine and coarse particulate matter using the closest air monitor within 50 km to their residence during early pregnancy. Depending on the pollutant, a maximum of 4,632 live-birth controls and 3,328 live-birth, fetal-death, or electively terminated cases had exposure data. Hierarchical regression models, adjusted for maternal demographics and tobacco and alcohol use, were constructed. Principal component analysis was used to assess these relationships in a multipollutant context. Results: Positive associations were observed between exposure to nitrogen dioxide and coarctation of the aorta and pulmonary valve stenosis. Exposure to fine particulate matter was positively associated with hypoplastic left heart syndrome but inversely associated with atrial septal defects. Examining individual exposure-weeks suggested associations between pollutants and defects that were not observed using the 7-week average. Associations between left ventricular outflow tract obstructions and nitrogen dioxide and between hypoplastic left heart syndrome and particulate matter were supported by findings from the multipollutant analyses, although estimates were attenuated at the highest exposure levels. Conclusions: Using daily maximum pollutant levels and exploring individual exposure-weeks revealed some positive associations between certain pollutants and defects and suggested potential windows of susceptibility during pregnancy.

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Trasande, L., Wong, K., Roy, A., Savitz, D.A., Thurston, G.	Exploring Prenatal Outdoor Air Pollution, Birth Outcomes and Neonatal Health Care Utilization in a Nationally Representative Sample	2013	Journal of Exposure Science and Environmental Epidemiology	lead, PM10, NO2, SO2, CO, and PM2.5	Low Birth Weight	United States	Kids Inpatient Database (KID)	Assessed the impact of air pollutants on low birth weight across the U.S.	Yes	Authors used pollutant concentrations from the U.S. EPA Aerometric Information Retrieval System (AIRS) couple with random subsampling of over 2.6 million births in KID for 2000, 2003, and 2006.	Controlled for gestational age, birth month, gender, race, socioeconomic variables	No	No	The impact of air pollutation on fetal growth remains controversial, in part, because studies have been limited to sub-regions of the United Stated with limited variability. No study has examined air pollution impacts on neonatal health care utilization. We performed descriptive, univariate and multivariable analyses on administrative hospital record data from 222,359 births in the 2000, 2003 and 2006 Kids Inpatient Database linked to air pollution data drawn from the US EPA's Aerometric Information Retrieval System. In this study, air pollution exposure during the birth month was estimated based on birth hospital address. Although air pollutants were not individually associated with mean birth weight, a three-pollutant model controlling for hospital characteristics, demographics, and birth month identified 9.3% and 7.2% increases in odds of low birth weight and very low birth weight for each ug/m3 increase in PM2.5 (both P<0.0001). PM2.5 and NO2 were associated with −3.0% odds/p.p.m. and +2.5% odds/p.p.b. of preterm birth, respectively (both P<0.0001). A four-pollutant multivariable model indicated a 0.05 days/p.p.m. NO2 decrease in length of the birth hospitalization (P=0.0061) and a 0.13 days increase/p.p.m. CO (P=0.0416). A $1166 increase in per child costs was estimated for the birth hospitalization per p.p.m. CO (P=0.0002) and $964 per unit increase in O3 (P=0.0448). A reduction from the 75th to the 25th percentile in the highest CO quartile for births predicts annual savings of $134.7 million in direct health care costs. In a national, predominantly urban, sample, air pollutant exposures during the month of birth are associated with increased low birth weight and neonatal health care utilization. Further study of this database, with enhanced control for confounding, improved exposure assessment, examination of exposures across multiple time windows in pregnancy, and in the entire national sample, is supported by these initial investigations.
Wellenius, G.A., Schwartz, J., Mittleman, M.A.	Air Pollution and Hospital Admissions for Ischemic and Hemorrhagic Stroke Among Medicare Beneficiaries	2005	Stroke	PM10, CO, NO2, SO2	Ischemic or hemorrhagic stroke	9 cities in the United States	Hospital admissions for Medica	Studies the association between ambient air particles and stroke incidence.		Used a 2-stage hierarchical model. In the first stage, use a time-stratified case-crossover study design to separately estimate the effect of air pollution in each city. Chose control periods that fell on the same day of the week during the same month as case. Performed conditional logistic regression, stratifying on each day. In the second stage, used standard random-effects meta-analysis to combine city-specific estimates	Lag structure and case-crossover design with case-control matching is apparently effective at controlling for seasonality, time trends, and chronic and slowly varying potential confounders. Controlled for meteorological covariates, with apparent temperature.	Looked at pollutant concentrations 0 to 2 days before admission	Yes	Background and Purpose: The association between short-term elevations in ambient air particles and increased cardiovascular morbidity and mortality is well documented. Ambient particles may similarly increase the risk of stroke. Methods: We evaluated the association between daily levels of respirable particulate matter (aerodynamic diameter ≤10 μm, PM10) and hospital admission for ischemic and hemorrhagic stroke among Medicare recipients (age ≥65 years) in 9 US cities using a 2-stage hierarchical model. In the first stage, we applied the time-stratified case-crossover design to estimate the effect of PM10 in each city. We used a 3-day unconstrained, distributed lag model to simultaneously estimate the effect of PM10 0 to 2 days before the admission day and controlled for meteorological covariates in all of the models. In the second stage, we used random-effects metaanalytic techniques to combine the city-specific effect estimates. Results: Ischemic (n=155 503) and hemorrhagic (19 314) stroke admissions were examined separately. For ischemic stroke, an interquartile range increase in PM10 was associated with a 1.03% (95% CI, 0.04% to 2.04%) increase in admissions on the same day only. Similar results were observed with CO, NO2, and SO2. For hemorrhagic stroke, no association was observed with any pollutant 0 to 2 days before admission. Conclusions: These results suggest that elevations in ambient particles may transiently increase the risk of ischemic, but not hemorrhagic, stroke. Studies with more accurate assessment of timing of stroke onset are necessary to confirm or refute these findings.

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Zhu, Y., Zhang, C., Liu, D., Grantz, K.L., Wallace, M., Mendola, P.	Maternal Ambient Air Pollution Exposure Preconception and During Early Gestation and Offspring Congenital Orofacial Defects	2015	Environmental Research	CO, NOx, O3, PM2.5, PM10, SO2	Orofacial defects (isolated/multiple cleft palate and cleft lip with or without cleft palate)	United States	Consortium on Safe Labor	Investigates the association between maternal exposure to various air pollutants with risks of orofacial defects		Performed separate analysis for each outcome and exposure window of interest combination. Estimate generalized estimating equations to calculate robust standard errors accounting for clustering due to multiple pregnancies of the same woman. Performed sensitivity analysis excluding multiple gestation pregnancies and infants born to women with preexisting or gestational diabetes.	Controlled for site/region, maternal age, race/ethnicity, marital status, insurance, prepregnancy body mass index, nulliparity, season of conception, smoking and/or alcohol consumption during pregnancy, multiple birth, preexisting or gestational diabetes mellitus. Performed simulation extrapolation procedures to correct for potential exposure misclassification. I believe they did not do co-pollutant models.	Three months preconception and early gestation (both an average over weeks 3-8 and weekly averages from weeks 1 through 10)	Yes	**Background:** Maternal air pollution exposure has been related to orofacial clefts but the literature is equivocal. Potential chronic preconception effects have not been studied. **Objectives:** Criteria air pollutant exposure during three months preconception and gestational weeks 3-8 was studied in relation to orofacial defects. **Methods:** Among 188,102 live births and fetal deaths from the Consortium on Safe Labor (2002-2008), 63 had isolated cleft palate (CP) and 159 had isolated cleft lip with or without cleft palate (CL ±CP). Exposures were estimated using a modified Community Multiscale Air Quality model. Logistic regression with generalized estimating equations adjusted for site/region and maternal demographic, lifestyle and clinical factors calculated the odds ratio (OR) and 95% CI per interquartile increase in each pollutant. **Results**: Preconception, carbon monoxide (CO; OR=2.24; CI: 1.21, 4.16) and particulate matter (PM) ≤10μm (OR=1.72; CI: 1.12, 2.66) were significantly associated with CP, while sulfur dioxide (SO2) was associated with CL ±CP (OR=1.93; CI: 1.16, 3.21). During gestational weeks 3-8, CO remained a significant risk for CP (OR=2.74; CI: 1.62, 4.62) and nitrogen oxides (NOx; OR=3.64; CI: 1.73, 7.66) and PM ≤2.5μm (PM2.5; OR=1.74; CI: 1.15, 2.64) were also related to the risk. Analyses by individual week revealed that positive associations of NOx and PM2.5 with CP were most prominent from weeks 3-6 and 3-5, respectively. **Conclusions:** Exposure to several criteria air pollutants preconception and during early gestation was associated with elevated odds for CP, while CL ±CP was only associated with preconception SO2 exposure.

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Bell, M.L. and Dominici, F.	Effect Modification by Community Characteristics on the Short-term Effects of Ozone Exposure and Mortality in 98 US Communities	2008	Am J Epidemiol.	O3	Total, non-injury mortality	98 US cities	all ages	Can heterogeneity in ozone mortaltiy effect estimates be explained by community specific characteristics	yes	Bayesian hierarchical distributed lag model	yes - see abstract	yse	yes	Previous research provided evidence of an association between short-term exposure to ozone and mortality risk and of heterogeneity in the risk across communities. The authors investigated whether this heterogeneity can be explained by community-specific characteristics: race, income, education, urbanization, transportation use, particulate matter and ozone levels, number of ozone monitors, weather, and use of air conditioning. Their study included data on 98 US urban communities for 1987 to 2000 from the National Morbidity, Mortality, and Air Pollution Study; US Census; and American Housing Survey. On average across the communities, a 10-ppb increase in the previous week's ozone level was associated with a 0.52% (95% posterior interval: 0.28, 0.77) increase in mortality. The authors found that community-level characteristics modify the relation between ozone and mortality. Higher effect estimates were associated with higher unemployment, fraction of the Black/African-American population, and public transportation use and with lower temperatures or prevalence of central air conditioning. These differences may relate to underlying health status, differences in exposure, or other factors. Results show that some segments of the population may face higher health burdens of ozone pollution
Bell, M.L., McDermott, A., Zeger, S., Samet, J., Dominici, F.	Ozone and Short-term Mortality in 95 US Urban Communities, 1987-2000	2004	JAMA	O3	Total, non-injury mortality	95 U.S. cities	all mortality	Investigates whether short=-term (daily and weekly) exosure to ambient ozone is associated with mortality in the U.S.	yes	2-stage statistical model distributed lag Poisson regression models and hierarchical models to generate US estimates	yes, including PM, weather, seasonality and long-term trends	yes	yes	Context Ozone has been associated with various adverse health effects, including increased rates of hospital admissions and exacerbation of respiratory illnesses. Although numerous time-series studies have estimated associations between day-today variation in ozone levels and mortality counts, results have been inconclusive. Objective To investigate whether short-term (daily and weekly) exposure to ambient ozone is associated with mortality in the United States. Design and Setting Using analytical methods and databases developed for the National Morbidity, Mortality, and Air Pollution Study, we estimated a national average relative rate of mortality associated with short-term exposure to ambient ozone for 95 large US urban communities from 1987-2000. We used distributed-lag models for estimating community-specific relative rates of mortality adjusted for time-varying confounders (particulate matter, weather, seasonality, and long-term trends) and hierarchical models for combining relative rates across communities to estimate a national average relative rate, taking into account spatial heterogeneity. Main Outcome Measure Daily counts of total non–injury-related mortality and cardiovascular and respiratory mortality in 95 large US communities during a 14-year period. Results A 10-ppb increase in the previous week's ozone was associated with a 0.52% increase in daily mortality (95% posterior interval [PI], 0.27%-0.77%) and a 0.64% increase in cardiovascular and respiratory mortality (95% PI, 0.31%-0.98%). Effect estimates for aggregate ozone during the previous week were larger than for models
Bell, M.L., Dominici, F. and, Samet, J.,	A Meta-Analysis of Time-Series Studies of Ozone and Mortality With Comparison to the National Morbidity, Mortality, and Air Pollution Study	2005	Epidemiology	O3	Total, non-injury mortality	95 U.S. cities	all mortality	Compares Bell et al 2004 results with results of large scale meta anlaysis of 144 estimates across 39 studies conducted in the U.S.	yes	2-stage Bayesian hierarchical model for meta analysis.	yes - weather seasonality, long-term trends	yes	yes	Background: Although many time-series studies of ozone and mortality have identified positive associations, others have yielded null or inconclusive results, making the results of these studies difficult to interpret. Methods: 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 with pooled estimates from the National Morbidity, Mortality, and Air Pollution Study (NMMAPS), a time-series study of 95 large U.S. urban centers from 1987 to 2000. Results: 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. In both analyses, results were insensitive to adjustment for particulate matter and model specifications. In the meta-analysis, a 10-ppb increase in daily ozone at single-day or 2-day average of lags 0, 1, or 2 days was associated with an 0.87% increase in total mortality (95% posterior interval = 0.55% to 1.18%), whereas the lag 0 NMMAPS estimate is 0.25% (0.12% to 0.39%). Several findings indicate possible publication bias: meta-analysis results were consistently larger than those from NMMAPS; meta-analysis pooled estimates at lags 0 or 1 were larger when only a single lag was reported than when estimates for multiple lags were reported; and heterogeneity of city-specific estimates in the meta-analysis were larger than with NMMAPS.

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Bell, M.L., Kim, J.Y., Dominici, F.	Potential Confounding of Particulate Matter on the Short-Term Association Between Ozone and Mortality in Multisite Time-Series Studies	2007	Environmental Health Perspectives	PM10, PM2.5, O3	All-cause non-accidental	98 U.S. cities	All mortality	Evaluates whether results from ozone and mortality time-series studies are robust to sensitivity analysis regarding potential cnofounding by PM	Applied time-series analysis estimating the relationship between the log of expected daily mortality rate in each community and average of same and previous day's 24-hr ozone levels. After generating community-specific estimates, combined them to create national estimate using Bayesian hierarchical modeling. Experimented with other lag structures and ozone metrics.	Included variables controlling for day of week, natural cubic splines of temperature, dew point temperature, adjusted previous day's temperature, adjusted previous day's dew point temperature, and a variable representing time to adjust for long-term trends and seasonality. Explored confounding by PM with several approaches. Looked for effect modification by season and by geographic region.	Used average of same and previous day's 24-hr ozone levels	Yes	No	BACKGROUND: A critical question regarding the association between short-term exposure to ozone and mortality is the extent to which this relationship is confounded by ambient exposure to particles.OBJECTIVES: We investigated whether particulate matter < 10 and < 2.5 mu m in aerodynamic diameter (PM10 and PM2.5) is a confounder of the ozone and mortality association using data for 98 U.S. urban communities from 1987 to 2000.METHODS: We a) estimated correlations between daily ozone and daily PM concentrations stratified by ozone or PM levels; b) included PM as a covariate in time-series models; and c) included PM as a covariate as in a), but within a subset approach considering only days with ozone below a specified value. RESULTS: Analysis was hindered by data availability. In the 93 communities with PM10 data, only 25.0% of study days had data on both ozone and PM10. In the 91 communities with PM2.5 data, only 9.2% of days in the study period had data on ozone and PM2.5. Neither PM measure was highly correlated with ozone at any level of ozone or PM. National and community-specific effect estimates of the short-term effects of ozone on mortality were robust to inclusion of PM10 or PM(2.)5 in time-series models. The robustness remains even at low ozone levels (< 10 ppb) using a subset approach.CONCLUSIONS: Results provide evidence that neither PM10 nor PM(2.)5 is a likely confounder of observed ozone and mortality relationships. Further investigation is needed to investigate potential confounding of the short-term effects of ozone on mortality by PM chemical composition.
Eze, I.C., Hemkens, L.G., Bucher, H.C., Hoffmann, B., Schindler, C., Kunzli, N., Schikowski, T., Probst-Hensch, N.M.	Association Between Ambient Air Pollution and Diabetes Mellitus in Europe and North America: Systematic Review and Meta-Analysis	2015	Environmental Health Perspectives	PM2.5, Nox	Type 2 diabetes mellitus	Europe and North American	Electronic literature databases	Reviewed epidemiological evidence on the association between air pollution and diabetes, and synthesized results of studies on type 2 diabetes mellitus (T2DM)	Yes	Evaluated risk of bias and role of potential confounders in all studies. Synthesized reported associations with T2DM in meta-analyses using random-effects models and conducted various sensitivity analyses.	Controlled for air pollution, sex, BMI, age, type of study	Different lag times across different studies	Yes	**Background**: Air pollution is hypothesized to be a risk factor for diabetes. Epidemiological evidence is inconsistent and has not been systematically evaluated. **Objectives:** We systematically reviewed epidemiological evidence on the association between air pollution and diabetes, and synthesized results of studies on type 2 diabetes mellitus (T2DM). **Methods:** We systematically searched electronic literature databases (last search, 29 April 2014) for studies reporting the association between air pollution (particle concentration or traffic exposure) and diabetes (type 1, type 2, or gestational). We systematically evaluated risk of bias and role of potnetial confounders in all studies. We synthesized reported associations with T2DM in meta-analyses using random-effects models and conducted various sensitivity analyses. **Results:** We included 13 studies (8 on T2DM, 2 on type 1, 3 on gestational diabetes), all conducted in Europe or North America. Five studies were longitudinal, 5 cross-sectional, 2 case-control, and 1 ecologic. Risk of bias, air pollution assessment, and confounder control varied across studies. Dose-response effects were not reported. Meta-analyses of 3 studies on PM2.5 and 4 studies on NO2 showed increase risk of T2DM by 8-10% per 10 ug/m3 increase in exposure [PM2.5:1.10 (95% CI: 1.02, 1.18); NO2: 1.08 (95% CI: 1.00, 1.170]. Associations were stronger in females. Sensitivity analyses showed similar results. **Conclusion:** Existing evidence indicates a positive association of air pollution and T2DM risk, albeit there is high risk of bias. High-quality studies assessing dose-response effects are needed. Research should be expanded to developing countries where outdoor and indoor air pollution are high.
Franklin, M., Schwartz, J.	The Impact of Secondary Particles on the Association Between Ambient Ozone and Mortality	2008	Environmental Health Perspectives	O3	All-cause non-accidental	18 U.S. communities	All deaths, 2000-2005	Addresses whether the ozone-mortality relationship is entirely due to the adverse of ozone, or may be the result of confounding by secondary pollutants	Matched community-specific daily mortality counts with daily ozone and other pollutant concentrations. Then performed time-series analysis using Poisson regression. Used separate models to examine the effect of ozone alone and ozone adjusted for each of the secondary particle pollutants. Only looked in the warm season. Examined confounding by other pollutants by including them in the model one-by-one. Combined the effect estimates from community-specific Poisson regression models using random-effects meta-analysis to get an overall estimate.	Controlled for confounding effects of temperature and dew point temperature using 3-day running mean. Did sensitivity analysis allowing different specifications of the effect of temperature. Also controlled for day of the week and time, with a cubic regression spline for each 5-month warm season. Much of text is dedicated to looking at confounding by other pollutants.	Considered lag0, lag1, two-day moving average	Yes	No	BACKGROUND: Although several previous studies have found a positive association between ambient ozone and mortality, the observed effect may be confounded by other secondary pollutants that are produced concurrently with ozone. OBJECTIVES: We addressed the question of whether the ozone-mortality relationship is entirely a reflection of the adverse effect of ozone, or whether it is, at least in part, an effect of other secondary pollutants. METHODS: Separate time-series models were fit to 3-6 years of data between 2000 and 2005 from 18 U.S. communities. The association between nonaccidental mortality was examined with ozone alone and with ozone after adjustment for fine particle mass, sulfate, organic carbon, or nitrate concentrations. The effect estimates from each of these models were pooled using a random-effects meta-analysis to obtain an across-community average. RESULTS: We found a 0.89% [95% confidence interval (CI), 0.45-1.33%] increase in nonaccidental mortality with a 10-ppb increase in same-day 24-hr summertime ozone across the 18 communities. After adjustment for PM(2.5) (particulate matter with aerodynamic diameter. CONCLUSIONS: Our results demonstrate that the association between ozone and mortality is confounded by particle sulfate, suggesting that some secondary particle pollutants could be responsible for part of the observed ozone effect.

Table 1. O_x Mortality

Authors	Title	Year Published	Journal Published	Pollutant(s) Studied	Causes of Mortality or Morbidity Considered	Geographic scope	Population studied	Study question	Statistically significant relationships?	Analysis method	Controls for factors that could obscure relationship?	Assesses potential lag between exposure and outcome?	Reports uncertainty?	Abstract
Hao, Y., Balluz, L., Strosnider, H., Wen, X.J., Li, C., Qualters, J.R.	Ozone, Fine Particulate Matter and Chronic Lower Respiratory Disease Mortality in the United States	2015	American Journal of Respiratory and Critical Care Medicine	O3, PM2.5	Mortality from Chronic lower respiratory disease (ICD-9:?, ICD-10: J40-J47) *I do not have access to the full text, so I have assigned this code to the best of my ability	Contiguous United States	2007-2008 CLRD deaths	Examines the effect of long-term exposure to O3 and PM2.5 on chronic lower respiratory disease mortality	No	Derived county-level average daily exposure levels for 2001-2008 and then fit Bayesian hierarchical spatial Poisson models. They use random effects at state and county levels to account for spatial heterogeneity and spatial dependence	Adjusts for five county-level covariates (percent adults over 65, poverty, lifetime smoking, obesity, and temperature). I can't access the text to look for other controls for things that might obscure the true relationship.	Uses long-term exposure data calculated as average daily exposure for 2001 to 2008	Yes	Abstract RATIONALE: Short-term effects of air pollution exposure on respiratory disease mortality are well established. However, few studies have examined the effects of long-term exposure and, among those that have, results are inconsistent. OBJECTIVE: To evaluate long-term association between ambient ozone, fine particulate matter (PM2.5, particles with aerodynamic diameter of 2.5 micrometers or less) and chronic lower respiratory disease (CLRD) mortality in the contiguous United States. METHODS: We fit Bayesian hierarchical spatial Poisson models, adjusting for five county-level covariates (percent adults aged ≥65 years, poverty, lifetime smoking, obesity, and temperature), with random effects at state and county levels to account for spatial heterogeneity and spatial dependence. MEASUREMENTS AND MAIN RESULTS: We derived county-level average daily exposure levels for ambient ozone and PM2.5 for 2001-2008 from the U.S. Environmental Protection Agency's down-scaled estimates and obtained 2007-2008 CLRD deaths from the National Center for Health Statistics. Exposure to ambient ozone was associated with increased rate of CLRD deaths, with a rate ratio of 1.05 (95% credible interval, 1.01-1.09) per 5-ppb increase in ozone; the association between ambient PM2.5 and CLRD mortality was positive but statistically insignificant (rate ratio 1.068, 95% credible interval, 0.995-1.146). CONCLUSIONS: This is the first national study that links air pollution exposure data with CLRD mortality for 3109 contiguous U.S. counties. Ambient ozone may be associated with increased rate of death from CLRD in the contiguous United States.
Jerrett, M., Burnett, R.T., Beckerman, B.S., Turner, M.C., Krewski, D., Thurston, G., Martin, R.V., van Donkelaar, A., Hughes, E., Shi, Y., Gapstur, S.M., Thun, M.J., Pope, C.A.	Spatial Analysis of Air Pollution and Mortality in California	2013	Respiratory and Critical Care Medicine	PM2.5, O3, NO2	Mortality from Cardiovascular disease (ICD-9: 390-429, ICD-10:I01-I59), ischemic heart disease (ICD-9: 410-414, ICD-10:I20-I25), stroke (ICD-9: 430-438, ICD-10: I60-I69), respiratory disease, lung cancer (ICD-9: 162, ICD-10: C34), all-cause *Paper does not include specific ICD codes, so I have assigned them to the best of my ability.	California	California adults from American Cancer Society Cancer Prevention II Study	Assesses the associations of PM2.5, O3, and NO2 with the risk of mortality in California adults	Yes (with ischemic heart disease mortality and all causes combined)	Assigned exposure for PM2.5 to subjects' addresses using an advanced remote sensing model coupled with atmospheric modeling, applied to monthly average monitoring data from 112 sites. Assessed the association between air pollution and mortality (CVD, IHD, stroke, respiratory disease, lung cancer, all other, all causes) using standard and multilevel Cox proportional hazards models.	Controlled for individual-level variables for lifestyle, diet, demographics, ocupation, and education and ecological variables at the county level. Also control for residence in a metropolitan area. Acknowledges the potential for bias from intercorrelation among the various pollutants.	Used long-term averaged exposure rates. Exposures appear to be averaged over different year ranges for different pollutants. For PM2.5, seems to be over 1998 to 2002	Yes	Rationale: Although substantial scientific evidence suggests that chronic exposure to ambient air pollution contributes to premature mortality, uncertainties exist in the size and consistency of this association. Uncertainty may arise from inaccurate exposure assessment. Objectives: To assess the associations of three types of air pollutants (fine particulate matter, ozone [O3], and nitrogen dioxide [NO2]) with the risk of mortality in a large cohort of California adults using individualized exposure assessments. Methods: For fine particulate matter and NO2, we used land use regression models to derive predicted individualized exposure at the home address. For O3, we estimated exposure with an inverse distance weighting interpolation. Standard and multilevel Cox survival models were used to assess the association between air pollution and mortality. Measurements and Main Results: Data for 73,711 subjects who resided in California were abstracted from the American Cancer Society Cancer Prevention II Study cohort, with baseline ascertainment of individual characteristics in 1982 and follow-up of vital status through to 2000. Exposure data were derived from government monitors. Exposure to fine particulate matter, O3, and NO2 was positively associated with ischemic heart disease mortality. NO2 (a marker for traffic pollution) and fine particulate matter were also associated with mortality from all causes combined. Only NO2 had significant positive association with lung cancer mortality. Conclusions: Using the first individualized exposure assignments in this important cohort, we found positive associations of fine particulate matter, O3, and NO2 with mortality. The positive associations of NO2 suggest that traffic pollution relates to premature death.

Table 1. O_3 Mortality

Authors	Title	Year Published	Journal Published	Pollutant(s) Studied	Causes of Mortality or Morbidity Considered	Geographic scope	Population studied	Study question	Statistically significant relationships?	Analysis method	Controls for factors that could obscure relationship?	Assesses potential lag between exposure and outcome?	Reports uncertainty?	Abstract
Huang, Y., Dominici, F. and Bell, M.L.	Bayesian hierarchical distributed lag models for summer ozone exposure and cardio-respiratory mortality	2005	Environmetrics	O3	cardiovascular and respiratory mortality	19 large US cities	all ages	Investigates relatioship between short term ozone exposure and cardiovascular and respiratory mortality in large US cities	yes	Bayesian hierarchical distributed lag model	yes - long-term ternds, other pollutants, heat waves	yes	yes	In this article we develop Bayesian hierarchical distributed lag models for estimating associations between daily variations in summer ozone levels and daily variations in cardiovascular and respiratory (CVDRESP) mortality counts for 19 large U.S. cities included in the National Morbidity, Mortality and Air Pollution Study (NMMAPS) for the summers of 1987–1994. In the first stage, we define a semi-parametric distributed lag Poisson regression model to estimate city-specific relative rates of CVDRESP mortality associated with short-term exposure to summer ozone. In the second stage, we specify a class of distributions for the true city-specific relative rates to estimate an overall effect by taking into account the variability within and across cities.We perform the calculations with respect to several random effects distributions (normal, t-student, and mixture of normal), thus relaxing the common assumption of a two-stage normal–normal hierarchical model.We assess the sensitivity of the results to: (i) lag structure for ozone exposure; (ii) degree of adjustment for long-term trends; (iii) inclusion of other pollutants in the model; (iv) heat waves; (v) random effects distributions; and (vi) prior hyperparameters. On average across cities, we found that a 10ppb increase in summer ozone level over the previous week is associated with a 1.25 per cent increase in CVDRESP mortality (95 per cent posterior regions: 0.47, 2.03). The relative rate estimates are also positive and statistically significant at lags 0, 1 and 2. We found that associations between summer ozone and CVDRESP mortality are sensitive to the confounding adjustment for PM10, but are robust to: (i) the adjustment for long-term trends, other gaseous pollutants (NO_2, SO_2 and CO); (ii) the istributional assumptions at the second stage of the hierarchical model; and (iii) the prior distributions on all unknown parameters. Bayesian hierarchical distributed lag models and their application to the NMMAPS data allow us to estimate of an acute health effect associated with exposure to ambient air pollution in the last few days
Jerrett, M., Burnett, R.T., Pope, C.A., Ito, K., Thurston, G., Krewski, D. Shi, Y., Calle, E., Thun, M.	Long-Term Ozone Exposure and Mortality	2009	New England Journal of Medicine	O3, PM2.5	Mortality from Cardiopulmonary causes, cardiovascular cases, ischemic heart disease, respiratory causes	48 contiguous states of District of Columbia	American Cancer Society Cance	Examines the potential contribution of exposure to ozone to the risk of death from cardiopulmonary causes and, specifically, to death from respiratory causes	Estimated standard and multilevel random-effects Cox proportional hazard models to assess the risk of death in relation to exposure to pollution. Matched subjects according to age (in years), sex, and race. Estimated models both for just PM2.5 and just O3 and then with both pollutants. Then modified basic Cox models to include an adjustment for community-level random effects, which allowed them to take into account residual variation in mortality among communities.	Included 20 control variables, including individual-level controls and ecological covariates for census tracts, including median household income, proportion of people living in households of a certain income, education proportions, proportion homes with air conditioning, etc. Looked for threshold for association between exposure to ozone and risk. Acknowledge potential exposure misclassification because of people moving.	Calculated average exposures for April-June and July-September, and then calculated average of those two for each year	Yes	No	Background: Although many studies have linked elevations in tropospheric ozone to adverse health outcomes, the effect of long-term exposure to ozone on air pollution–related mortality remains uncertain. We examined the potential contribution of exposure to ozone to the risk of death from cardiopulmonary causes and specifically to death from respiratory causes. Methods: Data from the study cohort of the American Cancer Society Cancer Prevention Study II were correlated with air-pollution data from 96 metropolitan statistical areas in the United States. Data were analyzed from 448,850 subjects, with 118,777 deaths in an 18-year follow-up period. Data on daily maximum ozone concentrations were obtained from April 1 to September 30 for the years 1977 through 2000. Data on concentrations of fine particulate matter (particles that are 2.5 μm in aerodynamic diameter [PM2.5]) were obtained for the years 1999 and 2000. Associations between ozone concentrations and the risk of death were evaluated with the use of standard and multilevel Cox regression models. Results: In single-pollutant models, increased concentrations of either PM2.5 or ozone were significantly associated with an increased risk of death from cardiopulmonary causes. In two-pollutant models, PM2.5 was associated with the risk of death from cardiovascular causes, whereas ozone was associated with the risk of death from respiratory causes. The estimated relative risk of death from respiratory causes that was associated with an increment in ozone concentration of 10 ppb was 1.040 (95% confidence interval, 1.010 to 1.067). The association of ozone with the risk of death from respiratory causes was insensitive to adjustment for confounders and to the type of statistical model used. Conclusions: In this large study, we were not able to detect an effect of ozone on the risk of death from cardiovascular causes when the concentration of PM2.5 was taken into account. We did, however, demonstrate a significant increase in the risk of death from respiratory causes in association with an increase in ozone concentration.

Table 1. O_x Mortality

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Jhun, I., Fann, N., Zanobetti, A., Hubbell, B.	Effect Modification of Ozone-Related Mortality Risks by Temperature in 97 U.S. Cities	2014	Environment International	O3	All-cause non-accidental	97 communities in U.S.	All deaths of residents, age 0-9	Explores whether temperature modifies the association between short-term ozone exposure and mortality	Used a two-stage statistical approach. In the first stage, perform a time-series analysis using a Poisson regression model to estimate community-specific mortality risk from exposure to same-day ozone. Use a generalized linear regression model with a quasi-Poisson link function to account for overdispersion. In second stage of analysis, combined city-specific estimates using a random effects meta-analysis technique. Conducted sensitivity analysis on choice of exposure metrics for ozone and temperature.	Controlled for long-term patterns and seasonality using natural splines with 3 degrees of freedom for each warm season. Controlled for day of week and for potential confounding by weather using dew point and temperature. Assessed effect modification by temperature using three temperature categories. Looked at effect modification by AC use.	Used same-day ozone concentrations	Yes	No	Many time-series studies have characterized the relationship between short-term ozone exposure and adverse health outcomes, controlling for temperature as a confounder. Temperature may also modify ozone effects, though this has been largely under-investigated. In this study, we explored whether temperature modifies the effect of short-term ozone exposure on mortality. We used the database developed for the National Morbidity and Mortality Air Pollution Study to estimate ozone mortality risks in 97 US cities in May through September, 1987-2000. We treated temperature as a confounder as well as an effect modifier by estimating risks at low, moderate, and high temperature categories. When temperature was treated as a confounder, a 10-ppb increase in daily 24-h ozone was associated with a 0.47% (95% CI: 0.19%-0.76%) increase in mortality. When we assessed effect modification by temperature, the interaction between ozone and temperature was not statistically significant. However, there was a U-shaped pattern in mortality risk, which was greater at the low (<25th percentile) and high (>75th percentile) temperature levels than moderate temperature levels. At the high temperature category, a 10% increase in AC prevalence mitigated mortality risk associated with 10-ppb of ozone exposure by -0.18% (95% CI: -0.35%, -0.02%). Furthermore, ozone mortality risk in the high temperature category increased as we restricted our analyses to hotter days. On days where temperatures exceeded the 75th, 90th, and 95th percentile temperatures, a 10-ppb increase in ozone was associated with a 0.65% (95% CI: 0.20%-1.09%), 0.83% (95% CI: 0.17%-1.48%), and 1.35% (95% CI: 0.44%-2.27%) increase in mortality, respectively. These results suggested that high temperatures may exacerbate physiological responses to short-term ozone exposure.
Ito, K., DeLeon, S.F., and Lippmann, M.	Associations Between Ozone and Daily Mortality: Analysis and Meta-Analysis	2004	Epidemiology	O3	Total, non-injury mortality	43 studies from major U.S. and world ciites; additonal analysis of 7 US cities - mostly east coast and midwest	all mortality	Investigates the relationship between mortality and short term ozone exposure,	yes	DerSimonian and Laird approachto meta analysis; Poisson GLM for 7 citites analysis	yes	yes	yes	Background: There is ample evidence that short-term ozone exposure is associated with transient decrements in lung functions and increased respiratory symptoms, but the short-term mortality effect of such exposures has not been established. Methods: We conducted a review and meta-analysis of short-term ozone mortality studies, identified unresolved issues, and conducted an additional time-series analysis for 7 U.S. cities (Chicago, Detroit, Houston, Minneapolis–St. Paul, New York City, Philadelphia, and St. Louis). Results: Our review found a combined estimate of 0.39% (95% confidence interval 0.26–0.51%) per 10-ppb increase in 1-hour daily maximum ozone for the all-age nonaccidental cause/single pollutant model (43 studies). Adjusting for the funnel plot asymmetry resulted in a slightly reduced estimate (0.35%; 0.23– 0.47%). In a subset for which particulate matter (PM) data were available (15 studies), the corresponding estimates were 0.40% (0.27–0.53%) for ozone alone and 0.37% (0.20–0.54%) with PM in model. The estimates for warm seasons were generally larger than those for cold seasons. Our additional time-series analysis found that including PM in the model did not substantially reduce the ozone risk estimates. However, the difference in the weather adjustment model could result in a 2-fold difference in risk estimates (eg, 0.24% to 0.49% in multicity combined estimates across alternative weather models for the ozone-only all-year case). Conclusions: Overall, the results suggest short-term associations between ozone and daily mortality in the majority of the cities, although the estimates appear to be heterogeneous across cities.

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Klea Katsouyanni, Jonathan M. Samet, H. Ross Anderson, Richard Atkinson, Alain Le Tertre, Sylvia Medina, Evangelia Samoli, and Giota Touloumi, Richard T. Burnett, Daniel Krewski, Timothy Ramsay, Francesca Dominici, Roger D. Peng, Joel Schwartz, and Antonella Zanobetti	Air Pollution and Health: A European and North American Approach (APHENA)	2009	Health Effects Institute	PM10, O3, SO2, NO2, CO	Mortality (all-cause, respiratory, cardiovascular): morbidity (respiratory, cardiovascular hospital admissions)	90 U.S. cities, 32 European cities, and 12 Canadian cities	Ages 65-99	The study evaluated the effects of air pollutant exposures on morbidity and mortality in the U.S., Canada, and Europe.	Yes	Time series analysis	Yes	Lags of 0 and 1 day	Yes	This report provides the methodology and findings from the project: Air Pollution and Health: a European and North American Approach (APHENA*). The principal purpose of the project was to provide an understanding of the degree of consistency among findings of multicity time-series studies on the effects of air pollution on mortality and hospitalization in several North American and European cities. The project included parallel and combined analyses of existing data. The investigators sought to understand how methodological differences might contribute to variation in effect estimates from different studies, to characterize the extent of heterogeneity in effect estimates, and to evaluate determinants of heterogeneity. The APHENA project was based on data collected by three groups of investigators for three earlier studies: (1) Air Pollution and Health: A European Approach (APHEA), which comprised two multicity projects in Europe. (Phase 1 [APHEA1] involving 15 cities, and Phase 2 [APHEA2] involving 32 cities); (2) the National Morbidity, Mortality, and Air Pollution Study (NMMAPS), conducted in the 90 largest U.S. cities; and (3) multicity research on the health effects of air pollution in 12 Canadian cities.
Krewski, D., Jerrett, M., Burnett, R.T., Ma, R., Hughes, E., Shi, Y., Turner, M.C., Pope, A.C., Thurston, G., Calle, E.E., Thun, M.J., Beckerman, B., Deluca, P., Finkelstein, N., Ito, K., Moore, D.K., Newbold, K.B., Ramsay, T., Ross, Z., Shin, H., Tempalski, B.	Extended Follow-up and Spatial Analysis of the American Cancer Society Study Linking Particulate Air Pollution and Mortality	2009	Health Effects Institute	PM2.5, O3, NO2, SO2	All-cause, cardiopulmonary disease, ischemic heart disease, lung cancer, all remaining causes	United States	American Cancer Society Cance	Examines the effect of ambient air pollution on mortality	Used standard Cox proportiona lhazards model to calculate hazard ratios. Extended the random effects Cox model to commodate two levels of information for clustering and for ecologic covariates. Performed a nationwide analysis, intra-urban analysis in NYC and LA regions, and analysis of whether critical time windows of exposure might affect mortality.	Included 44 individual-level covariates and seven neighborhood-level covariates, like poverty level, level of educaiton, and unemployment. Looked at effect modification by temperature and region of county, sex, age at enrollment, BMI, education, and PM2.5 concentration. Also looked at threshold of ozone effects.	Constructed long-term average exposure for 1979-1983 and 1999-2000	Yes	Yes	Too long to include here. See http://hero.epa.gov/index.cfm/reference/details/reference_id/191193
Lipfert, E.W., Baty, J.D., Miller, J.P., Wyzga, R.E.	PM2.5 Constituents and Related Air Quality Variables as Predictors of Survival in a Cohort of U.S. Military Veterans	2006	Inhalation Toxicology	PM2.5, NO2, CO, O3, SO2, others	All-cause	United States	U.S. military veterans, male, 19	Examines relationships between air quality components and long-term mortality, along with data on vehicular traffic density	Estimate Cox proportional hazards models, with primary independent variables of air pollutants and vehicular traffic density.	Control for individual-level age, race, smoking, BMI, height, blood pressure etc. Look at effect modification by some of those variables. Also control for contextual variables, like climate, education, and income. Estimate single and multipollutant models to look at possible confounding.	Possible use average exposure over 1997-2002, but unclear from abstract		Yes	Air quality data on trace metals, other constituents of PM2.5, and criteria air pollutants were used to examine relationships with long-term mortality in a cohort of male U.S. military veterans, along with data on vehicular traffic density (annual vehicle-miles traveled per unit of land area). The analysis used county-level environmental data for the period 1997-2002 and cohort mortality for 1997-2001. The proportional hazards model included individual data on age, race, smoking, body mass index, height, blood pressure, and selected interactions; contextual variables also controlled for climate, education, and income. In single-pollutant models, traffic density appears to be the most important predictor of survival, but potential contributions are also seen for NO2, NO3-, elemental carbon, nickel, and vanadium. The effects of the other main constituents of PM2.5, of crustal particles, and of peak levels of CO, O3, or SO2 appear to be less important. Traffic density is also consistently the most important environmental predictor in multiple-pollutant models, with combined relative risks up to about 1.2. However, from these findings it is not possible to discern which aspects of traffic (pollution, noise, stress) may be the most relevant to public health or whether an area-based predictor such as traffic density may have an inherent advantage over localized measures of ambient air quality. It is also possible that traffic density could be a marker for unmeasured pollutants or for geographic gradients per se. Pending resolution of these issues, including replication in other cohorts, it will be difficult to formulate additional cost-effective pollution control strategies that are likely to benefit public health.

Table 1. O_x Mortality

Authors	Title	Year Published	Journal Published	Pollutant(s) Studied	Causes of Mortality or Morbidity Considered	Geographic scope	Population studied	Study question	Statistically significant relationships?	Analysis method	Controls for factors that could obscure relationship?	Assesses potential lag between exposure and outcome?	Reports uncertainty?	Abstract
Medina-Ramon, M., Schwartz, J.	Who is More Vulnerable to Die From Ozone Air Pollution?	2008	Epidemiology	O3	All-cause non-accidental	48 US cities	All deaths, 1989-2000	Investigates the relationship between mortality and ozone exposure, and possible modification by socio-demographics and underlying conditions	Use a case-only approach to identify modifiers of the effect of ozone on mortality. In the first stage, fit city-specific logistic regression models. Models include the hypothesized modifier (i.e. socio-demographic characteristic or a chronic condition) as dependent variable and mean ozone level of last three days as predictor. Next, used random-effects meta-analysis to calculate combined estimates for baseline mortality risk and additional mortality associated with eahc potential modifier.	Looks at modification of the ozone-mortality effect by socio-demographic characteristics and the presence of other underlying conditions. Models include sine and cosine term to capture any interactions between season and characteristic being investigated. Acknowledges possible misclassification of cause of death, and possible confounding from lack of control for PM.	Use mean ozone level of last three days	Yes	No	
Levy, J.I., Chemerynski, S.M., and Sarnat, J.A.	Ozone Exposure and Mortality: An Empiric Bayes Metaregression Analysis	2005	Epidemiology	O3	Total, non-injury mortality	multiple US studies	all ages	Investigated ozone effect on mortality and whether it varies as a function of hypothesized confounders or effect modifiers	yes	Empiric Bayes metagression analysis	yes	yes	yes	Background: Results from time-series epidemiologic studies evaluating the relationship between ambient ozone concentrations and premature mortality vary in their conclusions about the magnitude of this relationship, if any, making it difficult to estimate public health benefits of air pollution control measures. We conducted an empiric Bayes metaregression to estimate the ozone effect on mortality, and to assess whether this effect varies as a function of hypothesized confounders or effect modifiers. Methods: We gathered 71 time-series studies relating ozone to all-cause mortality, and we selected 48 estimates from 28 studies for the metaregression. Metaregression covariates included the relationship between ozone concentrations and concentrations of other air pollutants, proxies for personal exposure–ambient concentration relationships, and the statistical methods used in the studies. For our metaregression, we applied a hierarchical linear model with known level-1 variances. Results: We estimated a grand mean of a 0.21% increase (95% confidence interval 0.16–0.26%) in mortality per 10- g/m3 increase of 1-hour maximum ozone (0.41% increase per 10 ppb) without controlling for other air pollutants. In the metaregression, air-conditioning prevalence and lag time were the strongest predictors of between-study variability. Air pollution covariates yielded inconsistent findings in regression models, although correlation analyses indicated a potential influence of summertime PM2.5. Conclusions: These findings, coupled with a greater relative risk of ozone in the summer versus the winter, demonstrate that geographic and seasonal heterogeneity in ozone relative risk should be anticipated, but that the observed relationship between ozone and mortality should be considered for future regulatory impact analyses.
Miller, K.A., Siscovick, D.S., Sheppard, L., Shepherd, K., Sullivan, J.H., Anderson, G.L., Kaufman, J.D.	Long-Term Exposure to Air Pollution and Incidence of Cardiovascular Events in Women	2007	The New England Journal of Medicine	PM10, SO2, NO2, CO, O3	Cardiovascular events, myocardial infarction, coronary revascularization, stroke, and death from either coronary heart disease or cerebrovascular disease	United States	Participants in the Women's He	Looks at the effect of long-term exposure to air pollution on the incidence of cardiovascular disease among women	Used Cox proportional hazards regressions to estimate hazard ratios for the time to the first cardiovascular event. Stratified with use of separate baseline hazards according to current treatment for diabetes, age, and BMI. Created exposure variables to estimate between-city and within-city effects. Averaged exposures for all women in a metropolitan area into a weighted citywide exposure. Then, to look at within-city effects, fit indicator variables for each metropolitan area or subtracted the weighted citywide mean exposure.	In all models, controlled for age, BMI, smoking status, the number of cigarettes smoked per day, the number of years of smoking, systolic blood pressure, education level, household income, race or ethnic group, and presence or absence of diabetes, hypertension, hypercholestrolemia. Also evaluated possible confounding by presence or absense of environmental tobacco smoke, occupation, physical activity, diet, alcohol consumption, waist circumference, medical history etc. Looked at effect modification by many of these controls. Considered multipollutant models to assess confounding.	Used long-term average PM2.5 concentration, measured in 2000	Yes		Background: Fine particulate air pollution has been linked to cardiovascular disease, but previous studies have assessed only mortality and differences in exposure between cities. We examined the association of long-term exposure to particulate matter of less than 2.5 μm in aerodynamic diameter (PM2.5) with cardiovascular events. Methods: We studied 65,893 postmenopausal women without previous cardiovascular disease in 36 U.S. metropolitan areas from 1994 to 1998, with a median follow-up of 6 years. We assessed the women's exposure to air pollutants using the monitor located nearest to each woman's residence. Hazard ratios were estimated for the first cardiovascular event, adjusting for age, race or ethnic group, smoking status, educational level, household income, body-mass index, and presence or absence of diabetes, hypertension, or hypercholesterolemia. Results: A total of 1816 women had one or more fatal or nonfatal cardiovascular events, as confirmed by a review of medical records, including death from coronary heart disease or cerebrovascular disease, coronary revascularization, myocardial infarction, and stroke. In 2000, levels of PM2.5 exposure varied from 3.4 to 28.3 μg per cubic meter (mean, 13.5). Each increase of 10 μg per cubic meter was associated with a 24% increase in the risk of a cardiovascular event (hazard ratio, 1.24; 95% confidence interval [CI], 1.09 to 1.41) and a 76% increase in the risk of death from cardiovascular disease (hazard ratio, 1.76; 95% CI, 1.25 to 2.47). For cardiovascular events, the between-city effect appeared to be smaller than the within-city effect. The risk of cerebrovascular events was also associated with increased levels of PM2.5 (hazard ratio, 1.35; 95% CI, 1.08 to 1.68). Conclusions: Long-term exposure to fine particulate air pollution is associated with the incidence of cardiovascular disease and death among postmenopausal women. Exposure differences within cities are associated with the risk of cardiovascular disease.

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Authors	Title	Year Published	Journal Published	Pollutant(s) Studied	Causes of Mortality or Morbidity Considered	Geographic scope	Population studied	Study question	Statistically significant relationships?	Analysis method	Controls for factors that could obscure relationship?	Assesses potential lag between exposure and outcome?	Reports uncertainty?	Abstract
Moolgavkar et al.	Time-Series Analyses of Air Pollution and Mortality in the United States: A Subsampling Approach	2013	Environmental Health Perspectives	PM10, O3, CO, NO2, SO2	All-cause non-accident	108 United States cities	All deaths, 1987-2000, from NMMAPS	Estimates maximum likelihoods of the common national effects of criteria pollutants on mortality	Use subsampling, where they randomly choose 4 cities without replacement from the 108 cities, and estimate the common pollutant effect for each sample. Ran 5,000 bootstrap cycles. Fit an over-dispersed Poisson model to the randomly chosen 4 cities. Investigate the shape of the concentration-response relationship	Control for temperature and relative humidity in each of the 4 cities in each sample. Also control for day of the week, temporal trends, mean temperature on the previous day, and mean dew-point temperature--should control for city-specific confounders, day of week effects, and time trends	Use a 1-day lag for pollutant exposure, i.e. 24-hr average pollutant concentration	Yes	Yes	Background: Hierarchical Bayesian methods have been used in previous papers to estimate national mean effects of air pollutants on daily deaths in time-series analyses. Objectives: We obtained maximum likelihood estimates of the common national effects of the criteria pollutants on mortality based on time-series data from ≤ 108 metropolitan areas in the United States. Methods: We used a subsampling bootstrap procedure to obtain the maximum likelihood estimates and confidence bounds for common national effects of the criteria pollutants, as measured by the percentage increase in daily mortality associated with a unit increase in daily 24-hr mean pollutant concentration on the previous day, while controlling for weather and temporal trends. We considered five pollutants [PM10, ozone (O3), carbon monoxide (CO), nitrogen dioxide (NO2), and sulfur dioxide (SO2)] in single- and multipollutant analyses. Flexible ambient concentration–response models for the pollutant effects were considered as well. We performed limited sensitivity analyses with different degrees of freedom for time trends. Results: In single-pollutant models, we observed significant associations of daily deaths with all pollutants. The O3 coefficient was highly sensitive to the degree of smoothing of time trends. Among the gases, SO2 and NO2 were most strongly associated with mortality. The flexible ambient concentration–response curve for O3 showed evidence of nonlinearity and a threshold at about 30 ppb. Conclusions: Differences between the results of our analyses and those reported from using the Bayesian approach suggest that estimates of the quantitative impact of pollutants depend on the choice of statistical approach, although results are not directly comparable because they are based on different data. In addition, the estimate of the O3-mortality coefficient depends on the amount of smoothing of time trends.
Moolgavkar, S.H.	Air Pollution and Daily Mortality in Two U.S. Counties: Season-Specific Analyses and Exposure-Response Relationships	2003	Inhalation Toxicology	PM10, CO, NO2, SO2, O3	All-cause non-accidental, and deaths due to vascular disease	Cook County, Illinois, and Los Angeles County, California	All deaths, 1987-1995	Analyzes the time series of daily total nonaccidental deaths and deaths due to vascular disease	Did full-year and season-specific analyses for each city.	Looked at both single- and multi-pollutant models to account for confounding, and stratified analysis by season.			Yes	I used generalized additive models to analyze the time series of daily total nonaccidental deaths and deaths due to vascular disease over the period 1987-1995 in two major metropolitan areas, Cook County, Illinois, and Los Angeles County, California, in the United States. In both counties I had monitoring information on PM(10), CO, SO(2), NO(2), and O(3). In Los Angeles, monitoring information on PM(2.5) was available as well. In addition to full-year analyses, I performed season-specific analyses. I present the results of both single- and multipollutant analyses. Although components of air pollution were associated with total nonaccidental and vascular disease mortality in both counties, the results indicate considerable heterogeneity of these associations in the two locations and also from season to season. In Los Angeles County, the gases, particularly CO and SO(2) but not ozone, were more strongly associated with mortality than was particulate matter, which exhibited only weak and inconsistent associations with both mortality endpoints. Both PM(10) and the gases were associated with total and vascular disease mortality in Cook County. The association of the gases with both mortality endpoints appeared to be stronger and more robust than that of PM(10). Exposure-response analyses using flexible smoothers showed significant departures from linearity, particularly for PM effects.

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Moolgavkar, S.H., McClellan, R.O., Dewanji, A., Turim, J., Luebeck, E.G., Edwards, E.	Time-Series Analyses of Air Pollution and Mortality in the United States: A Subsampling Approach	2013	Environmental Health Perspectives	PM10, O3, CO, NO2, SO2	All-cause non-accident	108 United States cities	All deaths, 1987-2000, from NMMAPS	Estimates maximum likelihoods of the common national effects of criteria pollutants on mortality	Use subsampling, where they randomly choose 4 cities without replacement from the 108 cities, and estimate the common pollutant effect for each sample. Ran 5,000 bootstrap cycles. Fit an over-dispersed Poisson model to the randomly chosen 4 cities. Investigate the shape of the concentration-response relationship	Control for temperature and relative humidity in each of the 4 cities in each sample. Also control for day of the week, temporal trends, mean temperature on the previous day, and mean dew-point temperature--should control for city-specific confounders, day of week effects, and time trends	Use a 1-day lag for pollutant exposure, i.e. 24-hr average pollutant concentration	Yes	No	Background: Hierarchical Bayesian methods have been used in previous papers to estimate national mean effects of air pollutants on daily deaths in time-series analyses. Objectives: We obtained maximum likelihood estimates of the common national effects of the criteria pollutants on mortality based on time-series data from ≤ 108 metropolitan areas in the United States. Methods: We used a subsampling bootstrap procedure to obtain the maximum likelihood estimates and confidence bounds for common national effects of the criteria pollutants, as measured by the percentage increase in daily mortality associated with a unit increase in daily 24-hr mean pollutant concentration on the previous day, while controlling for weather and temporal trends. We considered five pollutants [PM10, ozone (O3), carbon monoxide (CO), nitrogen dioxide (NO2), and sulfur dioxide (SO2)] in single- and multipollutant analyses. Flexible ambient concentration–response models for the pollutant effects were considered as well. We performed limited sensitivity analyses with different degrees of freedom for time trends. Results: In single-pollutant models, we observed significant associations of daily deaths with all pollutants. The O3 coefficient was highly sensitive to the degree of smoothing of time trends. Among the gases, SO2 and NO2 were most strongly associated with mortality. The flexible ambient concentration–response curve for O3 showed evidence of nonlinearity and a threshold at about 30 ppb. Conclusions: Differences between the results of our analyses and those reported from using the Bayesian approach suggest that estimates of the quantitative impact of pollutants depend on the choice of statistical approach, although results are not directly comparable because they are based on different data. In addition, the estimate of the O3-mortality coefficient depends on the amount of smoothing of time trends.
Peng, R.D., Samoli, E., Pham, L., Dominici, F., Touloumi, G., Ramsay, T., Burnett, R.T, Krewski, D., Le Tertre, A., Cohen, A., Atkinson, R.W., Anderson, H.R., Katsouyanni, K., Samet, J.M.	Acute Effects of Ambient Ozone on Mortality in Europe and North America: Results from the APHENA Study	2013	Air Quality, Atmosphere and Health	O3	All-cause non-accidental, cardiovascular, respiratory	86 U.S. cities, 23 European cities, 12 Canadian cities	All deaths, with US records from	Assesses the association between daily concentrations of O3 and all-cause, cardiovascular, and respiratory mortality	Fit regression models in each city separately to control for seasonal effects, weather, and other potential confounders. Did sensitivity analysis varying the dfs used to control for seasonality. Then used the estimated effect parameters from individual city analysis in a second-stage model to provide center-specific estimates (US, Canada, Europe) and overall estimates. For each city, described year-round O3-mortality with log-linear Poisson regression models allowing for overdispersion. In second stage, assumed city-specific effects to be normally distributed around overall effect. Estimated pooled regression coefficients using a Bayesian hierarchical model of city-specific effects on potential city-level effect modifiers.	Included dummy variables for day of the week and bank holiday effects. Smooth function of time should serve as a proxy for any time-dependent outcome predictors or confounders with long-term trends and seasonal patterns. Did threshold analysis for each of Europe, US, Canada. Looked at potential effect modifiers, including average air pollution level and mix in each city, health status of population, the geographical area, and the climatic conditions. Also controlled for temperature, and looked at effect modification by presence of other pollutants.	Used the average of the same and previous day's air pollution. Also assessed the effect of lag 1 air pollution, and tried unconstrained distributed lag models for 0, 1, and 2-day lags.	Yes	Yes	The “Air Pollution and Health: A Combined European and North American Approach” (APHENA) project is a collaborative analysis of multi-city time-series data on the association between air pollution and adverse health outcomes. The main objective of APHENA was to examine the coherence of findings of time-series studies relating short-term fluctuations in air pollution levels to mortality and morbidity in 125 cities in Europe, the US, and Canada. Multi-city time-series analysis was conducted using a two-stage approach. We used Poisson regression models controlling for overdispersion with either penalized or natural splines to adjust for seasonality. Hierarchical models were used to obtain an overall estimate of excess mortality associated with ozone and to assess potential effect modification. Potential effect modifiers were city-level characteristics related to exposure to other ambient air pollutants, weather, socioeconomic status, and the vulnerability of the population. Regionally pooled risk estimates from Europe and the US were similar; those from Canada were substantially higher. The pooled estimated excess relative risk associated with a 10 μg/m3 increase in 1 h daily maximum O3 was 0.26 % (95 % CI, 0.15 %, 0.37 %). Across regions, there was little consistent indication of effect modification by age or other effect modifiers considered in the analysis. The findings from APHENA on the effects of O3 on mortality in the general population were comparable with previously reported results and relatively robust to the method of data analysis. Overall, there was no indication of strong effect modification by age or ecologic variables considered in the analysis.

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Ritz, B., Wilhelm, M., Zhao, Y.	Air Pollution and Infant Death in Southern California, 1989-2000	2006	Pediatrics	CO, PM10, NO2, O3	All-cause	Residents within 10 miles of a South Coast Air Quality Management monitoring station	Infant deaths from electronic files assembled by the California Department of Health Services	Evaluates the influence of outdoor air pollution on infant death in the South Coast Air Basin of California, an area characterized by some of the worst air quality in the United States.	The risk of respiratory death increased from 20% to 36% per 1-ppm increase in average carbon monoxide levels 2 weeks before death in early infancy (age: 28 days to 3 months). We also estimated 7% to 12% risk increases for respiratory deaths per 10-ug/m3 increase in particulate matter <10 um in aerodynamic diameter exposure experienced 2 weeks before death for infants 4 to 12 monts of age. Risp of respiratory death more than doubled for infants 7 to 12 months of age who were exposure to high average levels of particulates in the previous 6 months. Furthermore, the risk of dying as a result of sudden infant death syndrome increased 15% to 19% per 1-part per hundred million incerase in average nitrogen dioxide levels 2 months before death. Low birth weight and preterm infants seemed to be more susceptible to air pollution-related death resulting from these causes; however, we lacked statistical power to confirm this heterogeneity with formal testing.	Exposure averages for each air pollutant were calculated for 2-week, 1-month, 2-month, and 6-month periods before death for case subjects, relying on CO, NO2, O3, and PM10 measurements collected at a maximum of 31 stations during 1989-2000. Therefore, the start and end dates of each control subject's exposure period were based on the case subject's age at death. Air pollution concentration averages measured at assigned monitoring stations were based on hourly measurements for gaseous pollutants and 24-hour average measurements taken every 6 days for PM10. Used conditional logisitc regression analysis to derive estimates of air pollution effects on infant deaths for age-matched risk sets. They modeled air pollutants as continuous and categorical measures, relying on percentiles of pollutant distributions for this population.	Controls for maternal age, race/ethnicity, education, level of prenatal care, infant gender, parity, birth country, and death season	Yes	No	**Objective:** We evaluated the influence of outdoor air pollution on infant death in the South Coast Air Basin of California, an area characterized by some of the worst air quality in the United States. **Methods:** Linking birth and death certificates for infants who died between 1989 and 2000, we identified all infant deaths, matched 10 living control subjects to each case subject, and assigned the nearest air monitoring station to each birth address. For all subjects, we calculated average carbon monoxide, nitrogen dioxide, ozone, and particulate matter <10 um in aerodynamic diameter exposures experienced during the 2-week, 1-month, 2-month, and 6-month periods before a case subject's death. **Results:** The risk of respiratory death increased from 20% to 36% per 1-ppm increase in average carbon monoxide levels 2 weeks before death in early infancy (age: 28 days to 3 months). We also estimated 7% to 12% risk increases for respiratory deaths per 10-ug/m3 increase in particulate matter <10 um in aerodynamic diameter exposure experienced 2 weeks before death for infants 4 to 12 monts of age. Risp of respiratory death more than doubled for infants 7 to 12 months of age who were exposure to high average levels of particulates in the previous 6 months. Furthermore, the risk of dying as a result of sudden infant death syndrome increased 15% to 19% per 1-part per hundred million incerase in average nitrogen dioxide levels 2 months before death. Low birth weight and preterm infants seemed to be more susceptible to air pollution-related death resulting from these causes; however, we lacked statistical power to confirm this heterogeneity with formal testing. **Conclusions:** Our results add to the growing body of literature implicating air pollution in infant death from respiratory causes and sudden infant death syndrome and provide additional information for future risk assessment.
Smith, K.R., Jerrett, M., Anderson, H.R., Burnett, R.T., Stone, V., Derwent, R., Atkinson, R.W., Cohen, A., Shonkoff, S.B., Krewski, D., Pope, C.A., Thun, M.J., Thurston, G.	Public Health Benefits of Strategies to Reduce Greenhouse-Gas Emissions: Health Implications of Short-Lived Greenhouse Pollutants	2009	Lancet	PM2.5, O3, SO2	All-cause, cardiopulmonary	United States	American Cancer Society Cance	Looks at the association between long-term ozone exposure and cardiovascular, cardiopulmonary, and respiratory mortality	Used multilevel random-effects Cox proportional hazards models, stratifying by age, sex, and race in the baseline hazard. Estimated mortality effects with models for independent pollutants and various combinations of co-pollutants.	They look at effect modification by age, sex, and race, and they control for 20 individual characteristics that might confound the relationship between air pollution and mortality. Looked at confounding by copollutants.	Calculated ozone measurements from the second and third quarters (warm season), and used long-term averages (what period?)	Yes	Yes	Summary In this report we review the health effects of three short-lived greenhouse pollutants--black carbon, ozone, and sulphates. We undertook new meta-analyses of existing time-series studies and an analysis of a cohort of 352[punctuation space]000 people in 66 US cities during 18 years of follow-up. This cohort study provides estimates of mortality effects from long-term exposure to elemental carbon, an indicator of black carbon mass, and evidence that ozone exerts an independent risk of mortality. Associations among these pollutants make drawing conclusions about their individual health effects difficult at present, but sulphate seems to have the most robust effects in multiple-pollutant models. Generally, the toxicology of the pure compounds and their epidemiology diverge because atmospheric black carbon, ozone, and sulphate are associated and could interact with related toxic species. Although sulphate is a cooling agent, black carbon and ozone could together exert nearly half as much global warming as carbon dioxide. The complexity of these health and climate effects needs to be recognised in mitigation policies.
Woodruff, T.J., Darrow, L.A., Parker, J.D.	Air Pollution and Postneonatal Infant Mortality in the United States, 1999-2002	2008	Environmental Health Perspectives	CO, SO2, O3, PM2.5, PM10	All-cause, respiratory mortality (ICD-10: J000-99, P27.1, R95, R99)	United States	All singleton births who die wit	Evaluates the role of chronic exposure to gaseous air pollutants and different particle size on postneonatal respiratory and SIDS infant mortality	Used logistic regression that incorporated generalized estimating equations to estimate the odds ratios. Assumed na exchangeable correlation structure. Modeled all air pollution exposures using a continuous, linaer form. Checked the appropriateness of this model using analysis based on quartiles of exposure. Used single-pollutant models for each cause of death, and then checked against copollutant models.	Controlled for maternal race/ethnicity, marital status, educatino, primiparity. Included county-level poverty and per capita income levels. Included year and month of birth dummy variables to account for time trend and seasonal effects, and controlled for region of the county to account for potential confounding by population and PM composition variation. Looked at confounding by trying copollutant models and comparing results.	Calculated average concentration of each pollutant over the first 2 months of life	Yes	Yes	OBJECTIVE: Our goal was to evaluate the relationship between cause-specific postneonatal infant mortality and chronic early-life exposure to particulate matter and gaseous air pollutants across the United States. METHODS: We linked county-specific monitoring data for particles with aerodiameter of < or = 2.5 microm (PM2.5) and < or = 10 microm (PM10), ozone, sulfur dioxide, and carbon monoxide to birth and death records for infants born from 1999 to 2002 in U.S. counties with > 250,000 residents. For each infant, we calculated the average concentration of each pollutant over the first 2 months of life. We used logistic generalized estimating equations to estimate odds ratios of postneonatal mortality for all causes, respiratory causes, sudden infant death syndrome (SIDS), and all other causes for each pollutant, controlling for individual maternal factors (race, marital status, education, age, and primiparity), percentage of county population below poverty, region, birth month, birth year, and other pollutants. This analysis includes about 3.5 million births, with 6,639 postneonatal infant deaths. RESULTS: After adjustment for demographic and other factors and for other pollutants, we found adjusted odds ratios of 1.16 [95% confidence interval (CI), 1.06-1.27] for a 10-mug/m3 increase in PM10 for respiratory causes and 1.20 (95% CI, 1.09-1.32) for a 10-ppb increase in ozone and deaths from SIDS. We did not find relationships with other pollutants and for other causes of death (control category). CONCLUSIONS: This study supports particulate matter air pollution being a risk factor for respiratory-related postneonatal mortality and suggests that ozone may be associated with SIDS in the United States.

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Zanobetti, A., Schwartz, J.	Is There Adaptation in the Ozone Mortality Relationship: A Multi-City Case-Crossover Analysis	2008	Environmental Health	O3	All-cause	48 U.S. cities	All deaths	Examines the effect of ozone on mortality by season, by month, and by age groups, particularly focusing on whether there is an adaptation effect	Ran a case-crossover model, comparing each subject's exposure experience in a time period just prior to a case event with that subject's exposure at other times. Use a time-stratified approach, choosing control days every third day in the same month and year as the case. Test for adaptation by first examining the effect of ozone by season, and then by month in the warm season, which is the period when adaptation has been reported for other outcomes. Then combine city-specific results using meta-regression technique.	Case-crossover design should control for all time-invariatn subject characteristics. Also control for same day apparent temperature and indicator variables for day of the week. Also look at effect modification by age categories during May-September.	Use ozone concentration on the day of death, 8-h max	Yes	No	BACKGROUND: Ozone has been associated with daily mortality, mainly in the summer period. Despite the ample literature on adaptation of inflammatory and pulmonary responses to ozone, and the link, in cohort studies, between lung function and mortality risk there has been little done to date to examine the question of adaptation in the acute mortality risk associated with ambient ozone. METHODS: We applied a case-crossover design in 48 US cities to examine the ozone effect by season, by month and by age groups, particularly focusing on whether there was an adaptation effect. RESULTS: We found that the same day ozone effect was highest in summer with a 0.5% (95% CI: 0.38, 0.62) increase in total mortality for 10 ppb increase in 8-hr ozone, whilst the effect decrease to null in autumn and winter. We found higher effects in the months May- July with a 0.46% (95% CI: 0.24, 0.68) increase in total mortality for 10 ppb increase in ozone in June, and a 0.65% (95% CI: 0.47, 0.82) increase in mortality during July. The effect decreased in August and became null in September. We found similar effects from the age group 51-60 up to age 80 and a lower effect in 80 years and older. CONCLUSION: The mortality effects of ozone appear diminished later in the ozone season, reaching the null effect previously reported in winter by September. More work should address this issue and examine the biological mechanism of adaptation.
Zanobetti, A., Schwartz, J.	Mortality Displacement in the Association of Ozone with Mortality: An Analysis of 48 Cities in the United States	2008	American Journal of Respiratory and Critical Care Medicine	O3	All-cause, cardiovascular stroke, respiratory	48 U.S. cities	All deaths	Analyzes the effect of ozone on mortality, and the extent to which this is due to short-term mortality displacement	Used a generalized linear model with a quasi Poisson link function to account for overdispersion. Limited analysis to June-August, since the ozone effect is most substantial during the warm season. First used just same day exposure and then used unconstrained distributed lag, using a penalized quasi likelihood to estimate the coefficient of smooth distributed lag. In second stage of analysis, combined city-specific results using meta-regression.	Controlled for 2-df splines to control for longer term trends in each summer, and included day-of-the-week indicator variables. Also controlled for apparent temperature. Looked at effect modification by city characteristics, and evaluated mortality displacement. Acknowledge the concern that they did not control for SO2 and other photochemical oxidants, which could be confounders	First looked at 8-h max ozone on day of death and then using unconstrained distributed lag model up to the previous 20 days	Yes	No	Rationale: Although the association between mortality and particles is well established, fewer studies have been reported with ozone. The harvesting hypothesis posits that the deaths associated with an exposure are occurring in people who are dying already, and the effect of exposure is merely to move the death from one day to an earlier day, and has no other effects that would influence deaths. Objectives: The aim of this study was to analyze the effect of ozone on mortality, and the extent to which this is due to short-term mortality displacement in 48 U.S. cities between 1989 and 2000. Methods: Time series of mortality and ozone were investigated with a generalized linear model during the June–August months, controlling for season, day of the week, and apparent temperature. We examined an unconstrained and a smooth distributed lag with 21 lags of ozone, and effect modification for city-specific characteristics. Measurements and Main Results: We found a 0.3% (95% confidence interval, 0.2–0.4) increase in total mortality for a 10-ppb increase in 8-hour ozone at lag 0 during summer months. The effect increased to 0.5% (95% confidence interval, 0.05–0.96) when looking at the unconstrained distributed lag. The shape of the distributed lag indicates that all the effect is in the first week. Conclusions: We did not find mortality displacement due to ozone; rather, the effect size estimate when looking at 21 days of ozone was larger than when using a single day's ozone concentration. Therefore, these results indicate that risk assessments using the single day of ozone exposure are likely to underestimate, rather than overestimate, the public health impact.
Zanobetti, A., Schwartz, J.	Ozone and Survival in Four Cohorts with Potentially Predisposing Diseases	2011	American Journal of Respiratory and Critical Care Medicine	O3	All-cause mortality	105 U.S. cities	Medicare beneficiaries (>=65) c	Investigates whether ozone is associated with survival in four cohorts of persons with specific diseases, namely chronic obstructive pulmonary disease, diabetes, congestive heart failure, and myocardial infarction	To avoid cross-sectional confounding, fit separate survival analyses in each city and each cohort. Defined exposure as warm season (or transitional season) ozone, which was treated as time-varying.	Controlled for long-term time trends with a linear term for year of follow-up. Also adjusted for season, weather, and individual risk factors.	Uses yearly average of the 8-hour mean daily ozone concentrations for the summer (May to September) and transitional season (Spring and Autumn)	Yes	Yes	RATIONALE: Time series studies have reported associations between ozone and daily deaths. Only one cohort study has reported the effect of long-term exposures on deaths, and little is known about effects of chronic ozone exposure on survival in susceptible populations. OBJECTIVE: We investigated whether ozone was associated with survival in four cohorts of persons with specific diseases in 105 US cities, treating ozone as a time varying exposure. METHODS: We used Medicare data (1985-2006), and constructed cohorts of persons hospitalized with chronic conditions that might predispose to ozone effects: chronic obstructive pulmonary disease (COPD), diabetes, congestive heart failure (CHF), and myocardial infarction (MI). Yearly warm-season average ozone was merged to the individual follow up in each city. We applied Cox's proportional hazard model for each cohort within each city, adjusting for individual risk factors, temperature and city specific long term trends. RESULTS: We found significant associations with a hazard ratio for mortality of 1.06 (95% Confidence Interval (CI): 1.03, 1.08) per 5 ppb increase in summer average ozone for persons with CHF, of 1.09 (95% CI: 1.06, 1.12) with MI, of 1.07 (95% CI: 1.04, 1.09) with COPD, and of 1.07 (95% CI: 1.05, 1.10) for diabetics. We also found that the effect varied by region, but that this was mostly explained by mean temperature, which is likely a surrogate of air conditioning use, and hence exposure. CONCLUSIONS: This is the first study that follows persons with specific chronic conditions, and shows that long-term ozone exposure is associated with increased risk of death in these groups.

Table 2. O_3 Respiratory Morbidity

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Akinbami, L.J., Lynch, C.D., Parker, J.D., Woodruff, T.J.	The Association Between Childhood Asthma Prevalence and Monitored Air Pollutants in Metropolitan Areas, United States, 2001-2004	2010	Environmental Research	O3, PM10, PM2.5, SO2, NO2	Current asthma and asthma attacks	United States	Children aged 3-17 who were	Looks at the association between chronic exposure to oudoor air pollutants and asthma outcomes		Used logistic regression to assess the association between asthma outcomes and each pollutant in separate models as continuous measures and as quartiles.	Controlled for age, sex, race/ethnicity, adult smoker in the household, single parent household, highest level of parental education, poverty status, and region of residence. To control for nonresponse on income,analyzed multiply imputed income files. Looked at multipollutant models and got similar results.	Average exposure previous 12 months	Yes	BACKGROUND: Air pollution exposure has been linked to adverse respiratory health outcomes among children, primarily in studies of acute exposures that are often in limited geographic areas. We sought to assess the association between chronic outdoor air pollution exposure, as measured by 12-month averages by county, and asthma among children in metropolitan areas across the nation. METHODS: Eligible children included those aged 3-17 years residing in US metropolitan areas who were sampled in the 2001-2004 National Health Interview Survey (N=34,073). 12-month average air pollutant levels for sulfur dioxide, nitrogen dioxide, ozone and particulate matter were compiled by county for 2000-2004. Eligible children were linked to pollutant levels for the previous 12 months for their county of residence. Adjusted odds ratios of having current asthma or an asthma attack in the past 12 months were estimated in single pollutant logistic regression models. RESULTS: Children in counties with ozone and, to a less consistent degree, particulate matter levels in the highest quartile were more likely to have current asthma and/or a recent asthma attack than children residing in counties with the lowest pollution levels; the adjusted odds for current asthma for the highest quartile of estimated ozone exposure was 1.56 (95% confidence interval [CI]: 1.15, 2.10) and for recent asthma attack 1.38 (95% CI: 0.99, 1.91). No associations were found with sulfur dioxide or nitrogen dioxide levels. CONCLUSION: Although the current US standard for ozone is based on short-term exposure, this cross-sectional study suggests that chronic (12-month) exposure to ozone and particles is related to asthma outcomes among children in metropolitan areas throughout the US.
Delamater, P.L., Finley, A.O., Banerjee, S.	An Analysis of Asthma Hospitalizations, Air Pollution, and Weather Conditions in Los Angeles County, California	2012	Science of the Total Environment	CO, NO2, O3, PM10, PM2.5	Extrinsic, intrinsic, other asthma (ICD-9-CM: 493.0x, 493.1x, 493.8x)	Los Angeles County, CA	Daily hospital admissions	Examines the relationship between asthma morbidity, air pollution, and weather conditions at a county-level scale.		Generated monthly rates of asthma hospitalizations and then mean daily hospitalization rate for each month. Removed yearly trend and seasonal trends. Then experimented with a number of diferent model specifications, using Bayesian regression models with temporal random effects.	Controls for time trends and seasonality, but perhaps not other controls typically used.	Uses monthly average pollutant exposure	Yes	There is now a large body of literature supporting a linkage between exposure to air pollutants and asthma morbidity. However, the extent and significance of this relationship varies considerably between pollutants, location, scale of analysis, and analysis methods. Our primary goal is to evaluate the relationship between asthma hospitalizations, levels of ambient air pollution, and weather conditions in Los Angeles (LA) County, California, an area with a historical record of heavy air pollution. County-wide measures of carbon monoxide (CO), nitrogen dioxide (NO(2)), ozone(O(3)), particulate matter<10 μm (PM(10)), particulate matter<2.5 μm (PM(2.5)), maximum temperature, and relative humidity were collected for all months from 2001 to 2008. We then related these variables to monthly asthma hospitalization rates using Bayesian regression models with temporal random effects. We evaluated model performance using a goodness of fit criterion and predictive ability. Asthma hospitalization rates in LA County decreased between 2001 and 2008. Traffic-related pollutants, CO and NO(2), were significant and positively correlated with asthma hospitalizations. PM(2.5) also had a positive, significant association with asthma hospitalizations. PM(10), relative humidity, and maximum temperature produced mixed results, whereas O(3) was non-significant in all models. Inclusion of temporal random effects satisfies statistical model assumptions, improves model fit, and yields increased predictive accuracy and precision compared to their non-temporal counterparts. Generally, pollution levels and asthma hospitalizations decreased during the 9 year study period. Our findings also indicate that after accounting for seasonality in the data, asthma hospitalization rate has a significant positive relationship with ambient levels of CO, NO(2), and PM(2.5).
Delfino, R.J., Wu, J., Tjoa, T., Gullesserian, S.K., Nickerson, B., Gillen, D.L.	Asthma Morbidity and Ambient Air Pollution: Effect Modification by Residential Traffic-Related Air Pollution	2014	Epidemiology	PM2.5, NO2, NOx, CO, O3	"Hospital encounters" (ER visits and hospital admissions) from asthma	Orange County, CA	Subjects aged 0-18 with hospital encounters with a primary diagnosis of asthma between 2000 and 2008	Assesses the association between ambient air pollution and asthma-related hospital admissions and ER visits and investigates whether this association is modified by exposure to residential traffic-related air pollutants (NO2, NOx, CO)		Estimated long-term traffic-related NO2, NOx, CO, PM2.5 for each residence. Then evaluated associations of asthma-related hospital morbidity with air pollution exposure using a case-crossover design with conditional logistic regression. Exposures are sampled from each subject's time-varying distribution of exposure, so each person is his or her own control. Use semisymmetric bidirectional referent selection design	Case-crossover design controls for time-invariant subject characteristics, and using sufficiently narrow reference windows for controls avoids bias from seasonal confounding. To reduce serial correlation and avoid confounding from temporally adjacent exposures, did not select referent days within 7 days of exposure. Controlled for overlap bias between two sample hospitals, and controlled for within-subject correlation. Controlled for mean temperature and relative humidity over same lag period as pollutants. Tested effect modification by 6-month seasonal average residential air pollution. Addressed confounding in this analysis by doing secondary analysis to assess influence of race/ethnicity or health insurance status on differences in association with traffic-related air pollution strata	Estimates average traffic pollutant exposure for 6-month seasonal periods, and looks at PM2.5 exposure over 7 days before hospitalization, and tested other lags	Yes	**Background:** Ambient air pollution has been associated with asthma-related hospital admissions and emergency department visits (hospital encounters). We hypothesized that higher individual exposure to residential traffic-related air pollutants would enhance these associations. **Methods:** We studied 11,390 asthma-related hospital encounters among 7492 subjects 0-18 years of age living in Orange County, California. Ambient exposures were measured at regional air monitoring stations. Seasonal average traffic-related exposures (PM2.5, ultrafine particles, NOx, and CO) were estimated near subjects' geocoded residences for 6-month warm and cool seasonal periods, using dispersion models based on local traffic within 500 m radii. Associations were tested in case-crossover conditional logistic regression models adjusted for temperature and humidity. We assessed effect modification by seasonal residential traffic-related air pollution exposures above and below median dispersion-modeled exposures. Secondary analyses considered effect modification by traffic exposures within race/ethnicity and insurance group strata. **Results:** Asthma morbidity was positively associated with daily ambient O3 and PM2.5 in warm seasons and with CO, NOx, and PM2.5 in cool seasons. Associations with CO, NOx, and PM2.5 were stronger among subjects living at residences with above-median traffic-related exposures, especially in cool seasons. Secondary analyses showed no consistent differences in association, and 95% confidence intervals were wide, indicating a lack of precision for estimating these highly stratified associations. **Conclusions:** Associations of asthma with ambient air pollution were enhanced among subjects living in homes with high traffic-related air pollution. This may be because of increased susceptibility (greater asthma severity) or increased vulnerability (meteorologic amplification of local vs. correlated ambient exposures).

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						Europe and North American	Electronic literature databases	Reviewed epidemiological evidence on the association between air pollution and diabetes, and synthesized results of studies on type 2 diabetes mellitus (T2DM)	Yes	Evaluated risk of bias and role of potential confounders in all studies. Synthesized reported associations with T2DM in meta-analyses using random-effects models and conducted various sensitivity analyses.	Controlled for air pollution, sex, BMI, age, type of study	Different lag times across different studies	Yes	**Background**: Air pollution is hypothesized to be a risk factor for diabetes. Epidemiological evidence is inconsistent and has not been systematically evaluated. **Objectives:** We systematically reviewed epidemiological evidence on the association between air pollution and diabetes, and synthesized results of studies on type 2 diabetes mellitus (T2DM). **Methods:** We systematically searched electronic literature databases (last search, 29 April 2014) for studies reporting the association between air pollution (particle concentration or traffic exposure) and diabetes (type 1, type 2, or gestational). We systematically evaluated risk of bias and role of potnetial confounders in all studies. We synthesized reported associations with T2DM in meta-analyses using random-effects models and conducted various sensistivity analyses. **Results:** We included 13 studies (8 on T2DM, 2 on type 1, 3 on gestational diabetes), all conducted in Europe or North America. Five studies were longitudinal, 5 cross-sectional, 2 case-control, and 1 ecologic. Risk of bias, air pollution assessment, and confounder control varied across studies. Dose-response effects were not reported. Meta-analyses of 3 studies on PM2.5 and 4 studies on NO2 showed increase risk of T2DM by 8-10% per 10 ug/m3 increase in exposure [PM2.5:1.10 (95% CI: 1.02, 1.18); NO2: 1.08 (95% CI: 1.00, 1.170]. Associations were stronger in females. Sensitivity analyses showed similar results. **Conclusion:** Existing evidence indicates a positive association of air pollution and T2DM risk, albeit there is high risk of bias. High-quality studies assessing dose-response effects are needed. Research should be expanded to developing countries where outdoor and indoor air pollution are high.
Eze, I.C., Hemkens, L.G., Bucher, H.C., Hoffmann, B., Schindler, C., Kunzli, N., Schikowski, T., Probst-Hensch, N.M.	Association Between Ambient Air Pollution and Diabetes Mellitus in Europe and North America: Systematic Review and Meta-Analysis	2015	Environmental Health Perspectives	PM2.5, Nox	Type 2 diabetes mellitus									
Gauderman, W.J., Urman, R., Avol, E., Berhane, K., McConnell, R., Rappaport, E., Chang, M.S., Lurmann, F., Gilliland, F.	Association of Improved Air Quality with Lung Development in Children	2015	N Engl J Med	NO2, O3, PM2.5, PM10, PM10-PM2.5	Lung function impairment (FEV1 and FVC) in children with and without asthma	Southern California (Long Beach, Mira Loma, Riverside, San Dimas, and Upland)	A total of 2120 children between the ages of 11 and 15 recruited from three separate Children's Health Study cohorts, including 669 in cohort C, 588 in cohort D, and 863 in cohort E. The two earlier cohorts (cohorts C and D) enrolled fourth-grade students in 1992–1993 and 1995–1996, respectively, from elementary schools in 12 southern California communities. The third cohort (cohort E) enrolled kindergarten and first-grade students in 2002–2003 from 13 communities, 9 of which overlapped with the 12 cohort C and D communities.	The goal of the analyses was to examine the association between long-term improvements in ambient air quality and lung-function development in children from 11 to 15 years of age, measured as the increases in FEV1 and FVC during that period (referred to as 4-year growth in FEV1 and FVC).	Yes	All available pulmonary-function measurements were used to estimate lung-function growth curves, including measurements at ages ranging from approximately 9 to 19 years in cohorts C and D and 10 to 16 years in cohort E. A previously developed linear-spline model, with knots placed at ages 12, 14, and 16 years, was used to capture the nonlinear pattern of growth during adolescence (see the Supplementary Appendix for details). In addition to examining 4-year growth from 11 to 15 years of age, we analyzed the cross-sectional pulmonary-function measurements obtained for 1585 children at the end of this period (mean age, 15 years) to determine whether changes in air quality over time were associated with clinically important deficits in attained FEV1 and FVC. Using data from all three cohorts, we developed a linear prediction model for FEV1 that included adjustments for age, sex, race and ethnic background, height, height squared, BMI, BMI squared, and the presence or absence of respiratory illness. For each child, we determined whether the ratio of observed to predicted FEV1 and FVC fell below each of three cutoffs for defining low lung function: 90%, 85%, and 80%. Logistic regression was used to test for temporal trends in the proportion of children with low lung function across cohorts after adjustment for community. A P value of less than 0.05 was considered to indicate statistical significance, under the assumption of a two-sided alternative hypothesis.	The model included adjustments for sex, race, Hispanic ethnic background, height, height squared, body-mass index (BMI, the weight in kilograms divided by the square of the height in meters), BMI squared, and presence or absence of respiratory-tract illness on the day of the pulmonary-function test.	Yes (indirectly)	Yes (qualitatively - discusses sensitivity analyses and study limitations)	BACKGROUND—Air-pollution levels have been trending downward progressively over the past several decades in southern California, as a result of the implementation of air quality– control policies. We assessed whether long-term reductions in pollution were associated with improvements in respiratory health among children. METHODS—As part of the Children's Health Study, we measured lung function annually in 2120 children from three separate cohorts corresponding to three separate calendar periods: 1994–1998, 1997–2001, and 2007–2011. Mean ages of the children within each cohort were 11 years at the beginning of the period and 15 years at the end. Linear-regression models were used to examine the relationship between declining pollution levels over time and lung-function development from 11 to 15 years of age, measured as the increases in forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) during that period (referred to as 4-year growth in FEV1 and FVC). RESULTS—Over the 13 years spanned by the three cohorts, improvements in 4-year growth of both FEV1 and FVC were associated with declining levels of nitrogen dioxide (P<0.001 for FEV1 and FVC) and of particulate matter with an aerodynamic diameter of less than 2.5 μm (P = 0.008 for FEV1 and P<0.001 for FVC) and less than 10 μm (P<0.001 for FEV1 and FVC). These associations persisted after adjustment for several potential confounders. Significant improvements in lung-function development were observed in both boys and girls and in children with asthma and children without asthma. The proportions of children with clinically low FEV1 (defined as <80% of the predicted value) at 15 years of age declined significantly, from 7.9% to 6.3% to 3.6% across the three periods, as the air quality improved (P = 0.001). CONCLUSIONS—We found that long-term improvements in air quality were associated with statistically and clinically significant

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Islam, T., Gauderman, W.J., Berhane, K., McConnell, R., Avol, E., Peters, J.M., Gilliland, F.D.	Relationship between air pollution, lung function and asthma in adolescents	2007	Thorax	O3, NO2, PM10, PM2.5, acid vapour and elemental carbon	Air pollution as an effect modifier of the relationship between lung function (as measured by FEV1, FVC and FEF25-75) and asthma diagnosis	Southern California	Adolescents who participated in the Children's Health Study (CHS) who did not have asthma at entry into the cohort in 1993 (n=2057)	Study hypothesis is that higher lung function is associated with reduced risk for childhood asthma, but that ambient air pollution attenuates this effect.	Yes (The modifying effect of PM2.5, PM10 and organic carbon was statistically significant (p(0.05) and that of NO2, elemental carbon and acid vapour was marginally significant (p(0.08). Of all the pollutants, PM2.5 appeared to have the strongest modifying effect on the association between lung function with asthma as it had the highest R2 value (0.42).	The authors fitted Cox proportional hazards models with sex- and age specific (age defined as integer age at study entry) baseline hazards to investigate the association between new onset asthma and lung function at study entry. The authors report results using lung function as a continuous term. The hazard ratio (HR) can be interpreted as the change in risk of new onset asthma as the lung function increases over the 10th–90th percentile range of the corresponding lung function. They also fitted proportional hazard models treating annual lung function as 1- or 2-year lagged time-dependent covariates. To assess the effect of ambient air pollution on the relationship between lung function and new onset asthma, authors estimated the heterogeneity of association using community levels of air pollutants measured at one monitor in each community. To address this issue they fitted hierarchical two stage models to these time-dependent data (for details see Methods section in online supplement available at http://thorax.bmj.com/supplemental).	All models adjusted for community and race/ethnicity. Additional covariates (birth weight, premature birth, maternal smoking, maternal allergies, family history of asthma, BMI,parental education, health insurance and personal characteristics and househo ld and indoor exposures such as pets or second hand smoke exposure or humidifier use), were considered for inclusion in the model based on whether their inclusion changed the lung function effect estimate by more than 10%.	Yes	Discusses sensitivity analyses, alternative hypotheses and study limitations	Background: The interrelationships between air pollution, lung function and the incidence of childhood asthma have yet to be established. A study was undertaken to determine whether lung function is associated with new onset asthma and whether this relationship varies by exposure to ambient air pollutants. Methods: A cohort of children aged 9–10 years without asthma or wheeze at study entry were identified from the Children's Health Study and followed for 8 years. The participants resided in 12 communities with a wide range of ambient air pollutants that were measured continuously. Spirometric testing was performed and a medical diagnosis of asthma was ascertained annually. Proportional hazard regression models were fitted to investigate the relationship between lung function at study entry and the subsequent development of asthma and to determine whether air pollutants modify these associations. Results: The level of airway flow was associated with new onset asthma. Over the 10th–90th percentile range of forced expiratory flow over the mid-range of expiration (FEF25–75, 57.1%), the hazard ratio (HR) of new onset asthma was 0.50 (95% CI 0.35 to 0.71). This protective effect of better lung function was reduced in children exposed to higher levels of particulate matter with an aerodynamic diameter ,2.5 mm (PM2.5). Over the 10th–90th percentile range of FEF25–75, the HR of new onset asthma was 0.34 (95% CI 0.21 to 0.56) in communities with low PM2.5 (,13.7 mg/m3) and 0.76 (95% CI 0.45 to 1.26) in communities with high PM2.5 (>13.7 mg/m3). A similar pattern was observed for forced expiratory volume in 1 s. Little variation in HR was
Jerrett, M., Burnett, R.T., Pope, C.A., Ito, K., Thurston, G., Krewski, D. Shi, Y., Calle, E., Thun, M.	Long-Term Ozone Exposure and Mortality	2009	New England Journal of Medicine	O3, PM2.5	Mortality from Cardiopulmonary causes, cardiovascular cases, ischemic heart disease, respiratory causes	48 contiguous states of District of Columbia	American Cancer Society Can	Examines the potential contribution of exposure to ozone to the risk of death from cardiopulmonary causes and, specifically, to death from respiratory causes	Estimated standard and multilevel random-effects Cox proportional hazard models to assess the risk of death in relation to exposure to pollution. Matched subjects according to age (in years), sex, and race. Estimated models both for just PM2.5 and just O3 and then with both pollutants. Then modified basic Cox models to include an adjustment for community-level random effects, which allowed them to take into account residual variation in mortality among communities.	Included 20 control variables, including individual-level controls and ecological covariates for census tracts, including median household income, proportion of people living in households of a certain income, education proportions, proportion homes with air conditioning, etc. Looked for threshold for association between exposure to ozone and risk. Acknowledge potential exposure misclassification because of people moving.	Calculated average exposures for April-June and July-September, and then calculated average of those two for each year	Yes	No	Background: Although many studies have linked elevations in tropospheric ozone to adverse health outcomes, the effect of long-term exposure to ozone on air pollution–related mortality remains uncertain. We examined the potential contribution of exposure to ozone to the risk of death from cardiopulmonary causes and specifically to death from respiratory causes. Methods: Data from the study cohort of the American Cancer Society Cancer Prevention Study II were correlated with air-pollution data from 96 metropolitan statistical areas in the United States. Data were analyzed from 448,850 subjects, with 118,777 deaths in an 18-year follow-up period. Data on daily maximum ozone concentrations were obtained from April 1 to September 30 for the years 1977 through 2000. Data on concentrations of fine particulate matter (particles that are 2.5 µm in aerodynamic diameter [PM2.5]) were obtained for the years 1999 and 2000. Associations between ozone concentrations and the risk of death were evaluated with the use of standard and multilevel Cox regression models. Results: In single-pollutant models, increased concentrations of either PM2.5 or ozone were significantly associated with an increased risk of death from cardiopulmonary causes. In two-pollutant models, PM2.5 was associated with the risk of death from cardiovascular causes, whereas ozone was associated with the risk of death from respiratory causes. The estimated relative risk of death from respiratory causes that was associated with an increment in ozone concentration of 10 ppb was 1.040 (95% confidence interval, 1.010 to 1.067). The association of ozone with the risk of death from respiratory causes was insensitive to adjustment for confounders and to the type of statistical model used. Conclusions: In this large study, we were not able to detect an effect of ozone on the risk of death from cardiovascular causes when the concentration of PM2.5 was taken into account. We did, however, demonstrate a significant increase in the risk of death from respiratory causes in association with an increase in ozone concentration.
Karr, C., Lumley, T., Schreuder, A., Davis, R., Larson, T., Ritz, B., Kaufman, J.	Effects of Subchronic and Chronic Exposure to Ambient Air Pollutants on Infant Broncholitis	2007	American Journal of Epidemiology	O3	Acute bronchiolitis (ICD-9: 466.1)	South Coast Air Basin	Infants born 1995-2000	Studies the effect of longer-term exposures to O3 on infant bronchiolitis		Matched 10 controls to each case, matched on date of birth and gestational age. Used conditional logistic regression, stratified analysis of infants of differing gestational ages and ages at diagnosis.	Consider effect modification by gestationl maturity and age. Also consider risk modification by underlying cardiopulmonary disease conditions. Control for confounders like gender, parity, chronic lung disease, cardiac or pulmonary anomalies, socioeconomic status, and age, gestational age, and season of birth are controlled for by matching. Also control for residual SES confounding using zip-code-level information on median family income.			Ambient air pollutant exposure has been linked to childhood respiratory disease, but infants have received little study. The authors tested the hypotheses that subchronic and chronic exposure to fine particulate matter (particulate matter 2.5 lm in aerodynamic diameter (PM2.5)), nitrogen dioxide, carbon monoxide, and ozone increases risk of severe infant bronchiolitis requiring hospitalization. Study subjects were derived from linked birth–hospitaldischarge records of infants born in 1995–2000 in the South Coast Air Basin of California. Cases with a hospital discharge for bronchiolitis in infancy were matched to 10 age- and gestational-age-matched controls. Exposures in the month prior to hospitalization (subchronic) and mean lifetime exposure (chronic) referenced to the case diagnosis date were assessed on the basis of data derived from the California Air Resources Board. In conditional logistic regression, only subchronic and chronic PM2.5 exposures were associated with increased risk of bronchiolitis hospitalization after adjustment for confounders (per 10-lg/m3 increase, adjusted odds ratio ¼ 1.09 (95% confidence interval: 1.04, 1.14) for both). Ozone was associated with reduced risk in the single-pollutant model, but this relation did not persist in multipollutant models including PM2.5. These unique US data suggest that infant bronchiolitis may be added to the list of adverse effects of PM2.5 exposure.

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Klea Katsouyanni, Jonathan M. Samet, H. Ross Anderson, Richard Atkinson, Alain Le Tertre, Sylvia Medina, Evangelia Samoli, and Giota Touloumi, Richard T. Burnett, Daniel Krewski, Timothy Ramsay, Francesca Dominici, Roger D. Peng, Joel Schwartz, and Antonella Zanobetti	Air Pollution and Health: A European and North American Approach (APHENA)	2009	Health Effects Institute	PM10, O3, SO2, NO2, CO	Mortality (all-cause, respiratory, cardiovascular): morbidity (respiratory, cardiovascular hospital admissions)	90 U.S. cities, 32 European cities, and 12 Canadian cities	Ages 65-99	The study evaluated the effects of air pollutant exposures on morbidity and mortality in the U.S., Canada, and Europe.	Yes	Time series analysis	Yes	Lags of 0 and 1 day	Yes	This report provides the methodology and findings from the project: Air Pollution and Health: a European and North American Approach (APHENA*). The principal purpose of the project was to provide an understanding of the degree of consistency among findings of multicity time-series studies on the effects of air pollution on mortality and hospitalization in several North American and European cities. The project included parallel and combined analyses of existing data. The investigators sought to understand how methodological differences might contribute to variation in effect estimates from different studies, to characterize the extent of heterogeneity in effect estimates, and to evaluate determinants of heterogeneity. The APHENA project was based on data collected by three groups of investigators for three earlier studies: (1) Air Pollution and Health: A European Approach (APHEA), which comprised two multicity projects in Europe. (Phase 1 [APHEA1] involving 15 cities, and Phase 2 [APHEA2] involving 32 cities); (2) the National Morbidity, Mortality, and Air Pollution Study (NMMAPS), conducted in the 90 largest U.S. cities; and (3) multicity research on the health effects of air pollution in 12 Canadian cities.
Li, T., Lin, G.	Examining the Role of Location-Specific Associations Between Ambient Air Pollutants and Adult Asthma in the United States	2013	Health and Place	PM2.5, O3	Asthma	United States	>=18 with known asthma sta	Assesses the association between asthma risk and ozone and PM2.5 exposure in both metropolitan and non-metropolitan areas		Used multilevel logistic regression models to account for individual-level risk factors nested within county-level risk factors. Ran both a co-pollutant model and single-pollutant model. Assessed place-specific effects by interacting different metropolitan and non-metropolitan settings with pollutant concentrations in single-pollutant models. Provides results specified for "West North Central" and "West South Central"	Ran both co-pollutant model to account for confounding and single-pollutant models. Included county-level controls for race/ethnicity, education, poverty. Included individual-level characteristics like gender, age, race/ethnicity, marital status, education, general health status, obesity status, smoking status, insurance and access to care.	Average PM2.5 exposure 2006-2009, and 2006-2009 average of annual fourth-highest daily max ozone concentration	Yes	This study examined the association between ozone and fine particulate (PM2.5) exposure and asthma risk by place of residence. We linked 412,832 adult respondents from the 2009 U.S. Behavioral Risk Factor Surveillance System to their residence counties. Observed and interpolated ozone and PM2.5 concentration data from 2006 to 2009 were used as exposures. We linked self-reported current asthma status and other individual risk factors to county-level risk factors in multilevel logistic regressions. Results indicated spatially varied asthma risks and spatially varied associations between ambient air pollution and asthma risk. Residents in counties not located within a metropolitan statistical area (MSA) and in inner ring suburbs had a relatively higher asthma risk. Positive ozone-asthma associations were detected across all spatial settings, while positive PM2.5-asthma associations were detected only in central cities of an MSA and in outer ring suburbs, indicating that residence location modified the relationship between ambient air pollution and asthma risk.
Mar, T.F., Koenig, J.Q.	Relationship Between Visits to Emergency Departments for Asthma and Ozone Exposure in Greater Seattle, Washington	2009	Annals of Allergy, Asthma, and Immunology	O3, PM2.5	ER visits for asthma (ICD-9: 493-493.9)	Seattle, WA	Hospital cases 1998-2002	Determines whether ozone exposure in Seattle is associated with increased use of hospital emergency departments		Used Poisson regression models to assess the association, using maximum daily 1- and 8-hour average ozone concentrations and daily PM2.5 concentrations				
McConnell, R., Islam, T., Shankardass, K., Jerrett, M., Lurmann, F., Gilliland, F., Gauderman, J., Avol, E., Kunzli, N., Yao, L., Peters, J., Berhane, K.	Childhood Incident Asthma and Traffic-Related Air Pollution at Home and School	2010	EHP	NOX, O3	New-onset asthma resulting from traffic-related pollution near homes and schools	Southern California	2,497 children who were pariticipants of the Southern California Childrens Health Study	Study evaluated the relationship of new-onset asthma with traffic-related pollution near homes and schools.	Yes	Authors fitted a multilevel Cox proportional hazards model that allows for assessment of residual variation in time to asthma onset and also for clustering of children around schools and communities (Ma et al. 2003). The model allowed for joint evaluation of the effects of exposure to traffic-related pollutants at homes and at schools and to ambient pollutants measured at community central sites, with effects scaled to the interquartile range (IQR) for each metric of residential exposure (e.g., for TRP from the line source dispersion model) and to the total range across the 13 communities, respectively. Traffic exposure at homes and school were correlated. Therefore, in models including both exposures, home traffic estimates were deviated from the corresponding school metric to minimize the chance of collinearity and allow for valid independent effect estimates. The authors assessed heterogeneity of traffic pollution effects by level of community central site regional pollutant measurements by comparing nested models using a partial likelihood ratio test with and without interaction terms. They examined any potential nonlinearity in the exposure–response relationship using cubic spline terms, piecewise polynomials joined smoothly at a number of break points (Hastie and Tibshirani 1990), for the exposure terms and comparing the nested models using a partial likelihood ratio test.	All models included race/ethnicity. Other individual covariates included secondhand smoke exposure, pets in the home, and other possible confounders.	Yes	Discusses sensitivity analyses and study limitations	Background: Traffic-related air pollution has been associated with adverse cardiorespiratory effects, including increased asthma prevalence. However, there has been little study of effects of traffic exposure at school on new-onset asthma. Objectives: We evaluated the relationship of new-onset asthma with traffic-related pollution near homes and schools. Methods: Parent-reported physician diagnosis of new-onset asthma (n = 120) was identified during 3 years of follow-up of a cohort of 2,497 kindergarten and first-grade children who were asthma- and wheezing-free at study entry into the Southern California Children's Health Study. We assessed traffic-related pollution exposure based on a line source dispersion model of traffic volume, distance from home and school, and local meteorology. Regional ambient ozone, nitrogen dioxide (NO2), and particulate matter were measured continuously at one central site monitor in each of 13 study communities. Hazard ratios (HRs) for new-onset asthma were scaled to the range of ambient central site pollutants and to the residential interquartile range for each traffic exposure metric. Results: Asthma risk increased with modeled traffic-related pollution exposure from roadways near homes [HR 1.51; 95% confidence interval (CI), 1.25–1.82] and near schools (HR 1.45; 95% CI, 1.06–1.98). Ambient NO2 measured at a central site in each community was also associated with increased risk (HR 2.18; 95% CI, 1.18–4.01). In models with both NO2 and modeled traffic exposures, there were independent associations of asthma with traffic-related pollution at school and home, whereas the estimate for NO2 was attenuated (HR 1.37; 95% CI, 0.69–2.71). Conclusions: Traffic-related pollution exposure at school and homes may both contribute to the development of asthma.

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Meng, Y.Y, Wilhelm, M., Rull, R.P., English, P., Ritz, B.	Traffic and outdoor air pollution levels near residences and poorly controlled asthma in adults	2007	AnnAllergy Asthma Immunol.	O3, NO2, PM2.5, PM10, CO	Prevalence of poorly controlled asthma in adults as indicated by daily or weekly asthma symptoms or at least one ED vistit or hospitalization due to asthma in the previous 12 months.	Los Angeles and San Diego counties	1,609 adults (age 18 and older) with asthma in Los Angeles and San Diego counties using 2001 California Health Intrview Survey (CHIS) Data	Study investigated association between traffic density (TD) and outdoor air pollution levels near residences and poorly controlled asthma (defined poorly controlled asthma during the preceding 12 months as having (1) daily or weekly asthma symptoms or (2) at least 1 ED visit or hospitalization because of asthma) among adults previously diagnosed with asthma by a physician.	Yes	We used logistic regression to evaluate associations between TD and annual average air pollution concentrations and poorly controlled asthma. The analyses incorporated sampling weights that adjusted for unequal probabilities of selection into the CHIS sample. Measured air pollutants were evaluated as continuous measures, as well as categorical measures, by comparing respondents with annual average concentrations in the 90th percentile or higher to those with concentrations in the less than 90th percentile based on the distribution in the study population. Age, sex, race/ethnicity, and poverty level are included in our final models. In stratified analyses, we examined whether pollutant association measures were modified by age and sex. We also performed analyses that included multiple pollutants in the same model.	Age, sex, socioeconomic status, access to care, health behaviors, overall health status, race/ethnicity, poverty level, insurance status, smoking behavior, employment, asthma medication use, and county (covriates included in the analysis were from CHIS).			Background: Air pollution may exacerbate asthma. Objective: To investigate associations between traffic and outdoor air pollution levels near residences and poorly controlled asthma among adults diagnosed as having asthma in Los Angeles and San Diego counties, California. Methods: We estimated traffic density within 500 ft of 2001 California Health Interview Survey respondents' reported residential cross-street intersections. Additionally, we assigned annual average concentrations of ozone, nitrogen dioxide, particulate matter 2.5 and 10 micrometers or less in diameter, and carbon monoxide measured at government monitoring stations within a 5-mile radius of the reported residential cross-street intersections. Results: We observed a 2-fold increase in poorly controlled asthma (odds ratio [OR], 2.11; 95% confidence interval [CI], 1.38 –3.23) among asthmatic adults in the highest quintile of traffic density after adjusting for age, sex, race, and poverty. Similar increases were seen for nonelderly adults, men, and women, although associations seemed strongest in elderly adults (OR, 3.00; 95% CI, 1.13–7.91). Ozone exposures were associated with poorly controlled asthma among elderly adults (OR, 1.70; 95% CI, 0.91–3.18 per 1 pphm) and men (OR, 1.76; 95% CI, 1.05–2.94 per 1 pphm), whereas particulate matter 10 micrometers or less seemed to affect primarily women (OR, 2.06; 95% CI, 1.17–3.61), even at levels below the national air quality standard. Conclusions: Heavy traffic and high air pollution levels near residences are associated with poorly controlled asthma.
Meng, Y.Y., Rull, R.P., Wilhelm, M., Lombardi, C., Balmes, J., Ritz, B.	Outdoor Air Pollution and Uncontrolled Asthma in the San Joaquin Valley, California	2010	Journal of Epidemiology and Community Health	O3, PM10, PM2.5	Uncontrolled asthma: (1) daily or weekly asthma symptoms or (2) asthma-related ED visits or hospitalization	San Joaquin Valley, CA	Residents of San Joaquin Valley	Examines associations between air pollution and asthma morbidity in the San Joaquin Valley		Employed logistic regression to evaluate associations between air pollution metrics and asthma morbidity. Regression incorporated sampling weights to account for unequal probability of selection into the sample. Looked at pollutants as continuous measures and then at quartiles of their distribution in the study population. Used exposure at levels below 25th percentil as referent category for each pollutant. Looked at pollutant associations in single- and multi-pollutant crude and adjusted models.	Looked at multipollutant models to assess confounding by other pollutants. Also looked for effect modification by race/ethnicity, poverty level, gender, insurance status, delays in care for asthma, cigarette smoking, and employment. Controled for SES using poverty level and for access to care using insurance status.			Background: The San Joaquin Valley (SJV) in California ranks among the worst in the United States in terms of air quality, and its residents report some of the highest rates of asthma symptoms and asthma-related emergency department (ED) visits or hospitalizations in California. Using California Health Interview Survey (CHIS) data, we examined associations between asthma morbidity and air pollution in this region. Methods: Eligible subjects were SJV residents (CHIS 2001) who reported physician-diagnosed asthma (n=1,502, 14.6%). We considered two outcomes indicative of uncontrolled asthma: (1) daily or weekly asthma symptoms, and (2) asthma-related ED visits or hospitalization in the past year. Based on residential zip code, subjects were assigned annual average concentrations of ozone, PM10 and PM2.5 for the one-year period prior to the interview date from their closest government air monitoring station within a 5-mile radius. Results: Adjusting for age, gender, race/ethnicity, poverty level, and insurance status, we observed increased odds of experiencing daily or weekly asthma symptoms for ozone, PM10 and PM2.5 (ORozone: 1.23, 95% CI: 0.94, 1.60 per 10 ppb; ORPM10: 1.29, 95% CI: 1.05, 1.57 per 10 ?g/m3; and ORPM2.5: 1.82; 95% CI: 1.11, 2.98 per 10 ?g/m3) We also observed a 49% increase in asthma-related ED visits or hospitalizations for ozone (OR: 1.49, 95% CI: 1.05, 2.11 per 10 ppb) and a 29% increase in odds for PM10 (OR: 1.29, 95% CI: 0.99, 1.69 per 10 ?g/m3). Conclusions: Overall, these findings suggest that asthmatic individuals living in areas of the SJV with high ozone and particulate pollution levels are more likely to have frequent asthma symptoms and asthma-related ED visits and hospitalizations.

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Moore, K., Neugebauer, R., Lurmann, F., Hall, J., Brajer, V., Alcorn, S., Tager, I.	Ambient Ozone Concentrations Cause Increased Hospitalizations for Asthma in Children: An 18-Year Study in Southern California	2008	Environmental Health Perspectives	NO2, CO, PM10, PM2.5, O3	Hospital discharges for asthma (ICD-9: 493, ICD-10: J45, J46)	South Coast Air Basin	Children and adolescents from birth-19, 1980, 1990, 2000	Investigates time trends in associations between declining warm-season O3 concentrations and hospitalizations for asthma in children		They estimate the effect of O3 on the proportion of asthma-related hospital discharges using traditional method of regression and a method based on history-restricted marginal structural models. For both, use semiparametric linear models. Confined analyses to April-June and July-September.	Controls for potential confounders, including socioeconomic and demographic variables, co-pollutants, and meteorologic variables.			BACKGROUND: Asthma is the most important chronic disease of childhood. The U.S. Environmental Protection Agency has concluded that children with asthma continue to be susceptible to ozone-associated adverse effects on their disease. OBJECTIVES: This study was designed to evaluate time trends in associations between declining warm-season O(3) concentrations and hospitalization for asthma in children. METHODS: We undertook an ecologic study of hospital discharges for asthma during the high O(3) seasons in California's South Coast Air Basin (SoCAB) in children who ranged in age from birth to 19 years from 1983 to 2000. We used standard association and causal statistical analysis methods. Hospital discharge data were obtained from the State of California; air pollution data were obtained from the California Air Resources Board, and demographic data from the 1980, 1990, and 2000 U.S. Census. SoCAB was divided into 195 spatial grids, and quarterly average O(3), sulfurdioxide, particulate matter with aerodynamic diameter < or = 10 microm, nitrogen dioxide, and carbon monoxide were assigned to each unit for 3-month periods along with demographic variables. RESULTS: O(3) was the only pollutant associated with increased hospital admissions over the study period. Inclusion of a variety of demographic and weather variables accounted for all of the non-O(3) temporal changes in hospitalizations. We found a time-independent, constant effect of ambient levels of O(3) and quarterly hospital discharge rates for asthma. We estimate that the average effect of a 10-ppb mean increase in any given mean quarterly 1-hr maximum O(3) over the 18-year median of 87.7 ppb was a 4.6% increase in the same quarterly outcome. CONCLUSIONS: Our data indicate that at current levels of O(3) experienced in Southern California, O(3) contributes to an increased risk of hospitalization for children with asthma.
Moore, K., Neugebauer, R., Lurmann, F., Hall, J., Brajer, V., Alcorn, S., Tager, I.	Ambient Ozone Concentrations Cause Increased Hospitalizations for Asthma in Children: An 18-Year Study in Southern California	2008	EHP	O3	Asthma hospitalizations (discharges with first diagnosis of asthma - ICD-9 code 493, ICD-10 code J45/46- or second diagnosis of asthma (with first diagnosis of acute sinusitis or pneumonia) among children with asthma.	California	Children ranging from newborn to 19 mospitalized in California for asthma between 1983 ad 2000	Study was designed to evaluate time trends in associations between O3 concentrations and hospitalization for asthma in children.	Yes	We estimated this effect of O3 on the proportion of asthma-related hospital discharges with two approaches: the traditional method of regression of the proportion of asthma-related hospital discharges on O3 and confounder; and a method based on history-restricted marginal structural models (HRMSMs) (Neugebauer et al. 2007). In contrast to the usual MSM approach, HRMSMs allow the investigator to specify the time interval over which the history of exposure is to be considered—a critical issue for this analysis. For both approaches, working models considered were semiparametric linear models. The deletion/substitution/addition (DSA) algorithm was used for all model selections required for the traditional approach and the nuisance parameters in the HRMSM approach (Sinisi and van der Laan 2004). This is a dataadaptive model selection procedure based on cross-validation that relies on deletion, substitution, and addition moves to search through a large space of possible polynomial models. The criterion for model selection is based not on p-values but on a loss function (empirical and cross-validated residual sum of squares).	Using the U.S. Census Bureau's decadal surveys (1980, 1990, 2000) the authors reviewed all income, demographic, and residential data and selected covariates that were considered likely to affect asthma morbidity and were likely to show spatial clustering and temporo-spatial trends (graphs available on request from authors). They selected 57 sociodemographic variables to be included in modeling efforts.	Yes (through study design)	No but may be discussed in supplemental materials where model selection is discussed in more detail (http://www.ehponline.org/members/2008/10497/suppl.pdf)	BACKGROUND: Asthma is the most important chronic disease of childhood. The U.S. Environmental Protection Agency has concluded that children with asthma continue to be susceptible to ozone-associated adverse effects on their disease. OBJECTIVES: This study was designed to evaluate time trends in associations between declining warm-season O3 concentrations and hospitalization for asthma in children. METHODS: We undertook an ecologic study of hospital discharges for asthma during the high O3 seasons in California's South Coast Air Basin (SoCAB) in children who ranged in age from birth to 19 years from 1983 to 2000. We used standard association and causal statistical analysis methods. Hospital discharge data were obtained from the State of California; air pollution data were obtained from the California Air Resources Board, and demographic data from the 1980, 1990, and 2000 U.S. Census. SoCAB was divided into 195 spatial grids, and quarterly average O3, sulfur dioxide, particulate matter with aerodynamic diameter ≤ 10 µm, nitrogen dioxide, and carbon monoxide were assigned to each unit for 3-month periods along with demographic variables. RESULTS: O3 was the only pollutant associated with increased hospital admissions over the study period. Inclusion of a variety of demographic and weather variables accounted for all of the non-O3 temporal changes in hospitalizations. We found a time-independent, constant effect of ambient

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Mortimer,K.M ., L.M. Neas, D.W. Dockery, S. Redlinez, I.B. Tager	The effect of air pollution on inner-city children with asthma	2002	Eur Respir J	O3, SO2, NO2, PM10	Peak expiratory flow rate (PEFR) and asthma symptoms (cough, chest tightness, wheeze).	Participants are from one of the following 8 urban areas: Bronx and East Harlem, NY; Baltimore, MD; Washington, DC; Detroit, MI; Cleveland, OH; Chicago, IL; and St. Louis, MO.	Children aged 4-9 yrs old with asthma from the National Cooperative Inner-City Asthma Study (NCICAS).	Study evaluated air pollution-related health effects in a large cohort of inner-city children with asthma.	Yes	The per cent change in PEFR was analysed using linear mixed effect models (SAS Proc Mixed), while the incidence of symptoms and incidence of a 10% decline in median PEFR were modelled with generalized estimating equations, using a logistic link. Change-in-estimate criteria and likelihood ratio tests were used to determine the choice of covariates, with an alpha level of 0.05. AIC was used to evaluate the best correlation structure and to determine if a covariate should be entered as a fixed or random effect. Models with the AIC closest to zero were considered to best fit the data. Standard errors were insensitive to the use of several covariance structures, therefore results from models assuming the most simple structure (independence) were reported. Lagged air pollution effects were evaluated using moving averages, unrestricted distributed lags, and polynomial distributed lags. Within-model lag-specific estimates were combined to create a cumulative effect over a specified interval and estimates were then compared across models.	Yes	Yes	Yes	ABSTRACT: The effect of daily ambient air pollution was examined within a cohort of 846 asthmatic children residing in eight urban areas of the USA, using data from the National Cooperative Inner-City Asthma Study. Daily air pollution concentrations were extracted from the Aerometric Information Retrieval System database from the Environment Protection Agency in the USA. Mixed linear models and generalized estimating equation models were used to evaluate the effects of several air pollutants (ozone, sulphur dioxide (SO2), nitrogen dioxide (NO2) and particles with a 50% cut-off aerodynamic diameter of 10 mm (PM10) on peak expiratory flow rate (PEFR) and symptoms in 846 children with a history of asthma (ages 4–9 yrs). None of the pollutants were associated with evening PEFR or symptom reports. Only ozone was associated with declines in morning % PEFR (0.59% decline (95% confidence interval (CI) 0.13–1.05%) per interquartile range (IQR) increase in 5-day average ozone). In single pollutant models, each pollutant was associated with an increased incidence of morning symptoms: (odds ratio (OR)=1.16 (95% CI 1.02–1.30) per IQR increase in 4-day average ozone, OR=1.32 (95% CI 1.03–1.70) per IQR increase in 2-day average SO2, OR=1.48 (95% CI 1.02–2.16) per IQR increase in 6-day average NO2 and OR=1.26 (95% CI 1.0–1.59) per IQR increase in 2-day average PM10. This longitudinal analysis supports previous time-series findings that at levels below current USA air-quality standards, summer-air pollution is significantly related to symptoms and decreased pulmonary function among children with asthma.
Nishimura, K.K., Joshua M. Galanter, Lindsey A. Roth, Sam S. Oh, Neeta Thakur, Elizabeth A. Nguyen, Shannon Thyne, Harold J. Farber, Denise Serebrisky, Rajesh Kumar, Emerita Brigino-Buenaventura , Adam Davis, Michael A. LeNoir, Kelley Meade, William Rodriguez-Cintron, Pedro C. Avila, Luisa N. Borrell, Kirsten Bibbins-Domingo, Jose R. Rodriguez	Early-Life Air Pollution and Asthma Risk in Minority Children: The GALA II and SAGE II Studies	2013	Am J Respir Crit Care Med	O3, NO2, SO2, PM10, PM2.5	Physician-diagnosed asthma plus two or more symptoms of coughing, wheezing, or shortness of breath	Participants from Chicago, IL; Bronx, NY; Houston, TX; San Francisco Bay Area, CA) and Puerto Rico	Latino (n = 3,343) and African American (n = 977) children (ages 8-21 years old) with and without asthma from five urban regions in the mainland United States and Puerto Rico who are participants in the Genes–environments and Admixture in Latino Americans (GALA II) and the Study of African Americans, Asthma, Genes and Environments (SAGE II) studies.	Study seeks to assess the relationship between traffic-related air pollution and childhood asthma, in high-risk racial/ethnic minorities (African Americans and Puerto Ricans)	Yes	To account for regional characteristics, the authors used a two-stage analysis, allowing us to measure the between-region heterogeneity and to obtain a representative estimate across all regions. In the first stage, associations for each pollutant were determined separately for each study and region. Unadjusted logistic regression models and models adjusted for age, sex, ethnicity, and composite socioeconomic status (SES) were used to calculate the association between pollutant exposures during the first 3 years of life and subsequent asthma diagnosis as a dichotomous outcome. We also performed a sensitivity analysis examining additional potential covariates for maternal in utero smoking, environmental tobacco smoke in the household between 0 and 2 years old, and maternal language of preference (as an indicator of acculturation). These variables were included in the final site-specific adjusted models if the sample size was large enough and their inclusion improved the fit of the model as indicated by the Akaike Information Criterion (AIC). In the second stage, the regression coefficients for each region were combined, using a random-effects meta-analysis with a restricted maximum-likelihood estimator to generate a summary OR for each pollutant. The authors performed three stratified analyses: with or without family history of asthma, male or female sex, and high or low total IgE (above/ below 200 IU/ml, the approximate median among case subjects).	Yes: age, sex, ethnicity, and composite SES (calculated for each participant by assigning a low, medium, or high score for income, level of education, and insurance type, and then by taking the sum of these three values). The investigators also performed a sensitivity analysis examining additional potential covariates for maternal in utero smoking, environmental tobacco smoke in the household between 0 and 2 years old, and maternal language of preference (as an indicator of acculturation).	Yes (through study design)	Yes (reports confidence intervals around Ors and discusses study limitations)	Rationale: Air pollution is a known asthma trigger and has been associated with short-term asthma symptoms, airway inflammation, decreased lung function, and reduced response to asthma rescuemedications. Objectives: To assess a causal relationship between air pollution and childhood asthma using data that address temporality by estimating air pollution exposures before the development of asthma and to establish the generalizability of the association by studying diverse racial/ethnic populations in different geographic regions. Methods: This study included Latino (n = 3,343) and African American (n = 977) participants with and without asthma from five urban regions in the mainland United States and Puerto Rico. Residential history and data from local ambient airmonitoring stationswere used to estimate average annual exposure to five air pollutants: ozone, nitrogen dioxide (NO2), sulfur dioxide, particulatematter not greater than 10 mm in diameter, and particulatematter not greater than 2.5 mmindiameter. Within each region, we performed logistic regression to determine the relationship between early-life exposure to air pollutants and subsequent asthma diagnosis. A random-effects model was used to combine the region specific effects and generate summary odds ratios for each pollutant. Measurements and Main Results: After adjustment for confounders, a 5-ppb increase in average NO2 during the first year of life was associated with an odds ratio of 1.17 for physician-diagnosed asthma (95% confidence interval, 1.04–1.31). Conclusions: Early-life NO2 exposure is associated with childhood asthma in Latinos and African Americans. These results add to a growing body of evidence that traffic-related pollutants may be causally related to childhood asthma.

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George T. O'Connor; Lucas Neas; Benjamin Vaughn; Meyer Kattan; Herman Mitchell; Ellen F. Crain; Richard Evans, III; Rebecca Gruchalla; Wayne Morgan; James Stout; G. Kenneth Adams; and Morton Lippmann	Acute respiratory health effects of air pollution on children with asthma in US inner cities	2008	U.S. Environmental Protection Agency Papers	PM2.5, NO2, SO2, CO, and O3	Acute respiratory morbidity	Low-income Census tracts in Boston, the Bronx, Chicago, Dallas, New York, Seattle, and Tucson	Low-income children	The association between changes in ambient air pollutants and asthma morbidity in inner city children.	Yes	Mixed-effects models; both single and three pollutant models	No	Yes; 1-, 3-, and 5-day lags	Yes	Background: Children with asthma in inner-city communities may be particularly vulnerable to adverse effects of air pollution because of their airways disease and exposure to relatively high levels of motor vehicle emissions. Objective: To investigate the association between fluctuations in outdoor air pollution and asthma morbidity among inner-city children with asthma. Methods: We analyzed data from 861 children with persistent asthma in 7 US urban communities who performed 2-week periods of twice-daily pulmonary function testing every 6 months for 2 years. Asthma symptom data were collected every 2 months. Daily pollution measurements were obtained from the Aerometric Information Retrieval System. The relationship of lung function and symptoms to fluctuations in pollutant concentrations was examined by using mixed models. Results: Almost all pollutant concentrations measured were below the National Ambient Air Quality Standards. In singlepollutant models, higher 5-day average concentrations of NO2, sulfur dioxide, and particles smaller than 2.5 mm were associated with significantly lower pulmonary function. Higher pollutant levels were independently associated with reduced lung function in a 3-pollutant model. Higher concentrations of NO2 and particles smaller than 2.5 mm were associated with asthma-related missed school days, and higher NO2 concentrations were associated with asthma symptoms. Conclusion: Among inner-city children with asthma, short-term increases in air pollutant concentrations below the National Ambient Air Quality Standards were associated with adverse respiratory health effects. The associations with NO2 suggest that motor vehicle emissions may be causing excess morbidity in this population.
Rodopoulou, S., Chalbot, M.C., Samoli, E., Dubois, D.w., San Filippo, B.D., Kavouras, I.G.	Air Pollution and Hospital Emergency Room and Admissions for Cardiovascular and Respiratory Diseases in Dona Ana County, New Mexico	2014	Environmental Research	PM10, PM2.5, O3	Respiratory (ICD-9: 493, 466, 490, 491, 492, 496, 480-486, 460-465) and cardiovascular (ICD-9: 410-414, 426-427, 402, 428, 390-459)	Dona Ana County, New Mexico	Residents of Dona Ana count	Evaluates the association between short-term exposure to ambient PM10, PM2.5, and O3 and respiratory and cardiovascular emergency room visits and hospitalizations		Used Poisson regression models allowing for overdispersion, allowed nonlinearity by using natural splines. Remove dlong-term trends and seasonal patterns with a natural cubic regression spline for each season and year. Estimate effects separately for all ages and 65+	Controlled for long-term time trends and seasonal patterns, as well as temperature, daily humidity. Evaluated effect modification by season and tried removing days with outlier pollution. Also tried doing two day average lag.	Uses same day and day before pollution, and then two-day moving average	Yes	**Introduction:** Doña Ana County in New Mexico regularly experiences severe air pollution episodes associated with windblown dust and fires. Residents of Hispanic/Latino origin constitute the largest population group in the region. We investigated the associations of ambient particulate matter and ozone with hospital emergency room and admissions for respiratory and cardiovascular visits in adults. **Methods:** We used trajectories regression analysis to determine the local and regional components of particle mass and ozone. We applied Poisson generalized models to analyze hospital emergency room visits and admissions adjusted for pollutant levels, humidity, temperature and temporal and seasonal effects. **Results:** We found that the sources within 500km of the study area accounted for most of particle mass and ozone concentrations. Sources in Southeast Texas, Baja California and Southwest US were the most important regional contributors. Increases of cardiovascular emergency room visits were estimated for PM10 (3.1% (95% CI: -0.5 to 6.8)) and PM10-2.5 (2.8% (95% CI: -0.2 to 5.9)) for all adults during the warm period (April-September). When high PM10 (>150μg/m(3)) mass concentrations were excluded, strong effects for respiratory emergency room visits for both PM10 (3.2% (95% CI: 0.5-6.0)) and PM2.5 (5.2% (95% CI: -0.5 to 11.3)) were computed. **Conclusions:** Our analysis indicated effects of PM10, PM2.5 and O3 on emergency room visits during the April-September period in a region impacted by windblown dust and wildfires.
Wendt, J.K., Symanski, E., Stock, T.H., Chan, W., Du., X.L.	Association of Short-Term Increases in Ambient Air Pollution and Timing of Initial Asthma Diagnosis Among Medicaid-Enrolled Children in a Metropolitan Area	2014	Environmental Research	O3, NO2, PM2.5	Diagnosis of new-onset asthma	Harris County, Texas	Incident asthma cases among	Investigates whether short-term increases in O3, NO2, and PM2.5 levels were related to timing of initial diagnosis in children with asthma		Used a time-stratified, case-crossover design. Specified forty 28-day strata, matching each asthma case-day with the three referent dates in the pre-defined strata that were the same weekday. Ran conditional logistic regression to estimate Ors for each exposure metric and pollutant. Ran various lags and average cumulative exposures, and tested for non-linearity of effect using restricted cubic splines.	Case-crossover design allowed them to control for person-level factors and design also controlled for time-dependent exposures. Adjusted for temperature, mean relative humidity, and all aeroallergen variables. Also ran both single and co-pollutant models. Stratified analysis by age group, gender, race, and season.	Considered various lags and average cumulative exposures, with single-day values lagged 1 through 5 days, cumulative values averaged over 2 day through 6 days	Yes	**Objective:** We investigated associations of short-term changes in ambient ozone (O3), fine particulate matter (PM2.5) and nitrogen dioxide (NO2) concentrations and the timing of new-onset asthma, using a large, high-risk population in an area with historically high ozone levels. **Methods:** The study population included 18,289 incident asthma cases identified among Medicaid-enrolled children in Harris County Texas between 2005-2007, using Medicaid Analytic Extract enrollment and claims files. We used a time-stratified case-crossover design and conditional logistic regression to assess the effect of increased short-term pollutant concentrations on the timing of asthma onset. **Results:** Each 10 ppb increase in ozone was significantly associated with new-onset asthma during the warm season (May-October), with the strongest association seen when a 6-day cumulative average period was used as the exposure metric (odds ratio [OR]=1.05, 95% confidence interval [CI], 1.02-1.08). Similar results were seen for NO2 and PM2.5 (OR=1.07, 95% CI, 1.03-1.11 and OR=1.12, 95% CI, 1.03-1.22, respectively), and PM2.5 also had significant effects in the cold season (November-April), 5-day cumulative lag (OR=1.11. 95% CI, 1.00-1.22). Significantly increased ORs for O3 and NO2 during the warm season persisted in co-pollutant models including PM2.5. Race and age at diagnosis modified associations between ozone and onset of asthma. **Conclusion:** Our results indicate that among children in this low-income urban population who developed asthma, their initial date of diagnosis was more likely to occur following periods of higher short-term ambient pollutant levels.

Table 3. O_x Other Morbidity

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Becerra, T.A., Wilhelm, M., Olsen, J., Cockburn, M., Ritz, B.	Ambient Air Pollution and Autism in Los Angeles County, California	2013	Environmental Health Perspectives	CO, NO2, O3, PM10, PM2.5	Autism Disorder	Los Angeles County, CA	Children born 1995-2006 to mothers living in LA County at time of giving birth	Examines associations between measured and modeled exposures to prenatal air pollution and autism in children		First calculated Pearson's correlation coefficients to examine relations between various pollutant measures. Then looked at associations between air pollution exposure and odds of AD diagnosis using one- and two-pollutant models.	Adjusted for maternal age, maternal place of birth, race/ethnicity, and education, type of birth, parity, insurance type, gestational age at birth. Also excluded control for gestational age, since that might be a step on the causal pathway. Looks at potential confounding by co-pollutant exposure.	Estimated pollutant exposure for full pregnancy and for each trimester	Yes	Background: The prevalence of autistic disorder (AD), a serious developmental condition, has risen dramatically over the past two decades, but high-quality population-based research addressing etiology is limited. Objectives: We studied the influence of exposures to traffic-related air pollution during pregnancy on the development of autism using data from air monitoring stations and a land use regression (LUR) model to estimate exposures. Methods: Children of mothers who gave birth in Los Angeles, California, who were diagnosed with a primary AD diagnosis at 3–5 years of age during 1998–2009 were identified through the California Department of Developmental Services and linked to 1995–2006 California birth certificates. For 7,603 children with autism and 10 controls per case matched by sex, birth year, and minimum gestational age, birth addresses were mapped and linked to the nearest air monitoring station and a LUR model. We used conditional logistic regression, adjusting for maternal and perinatal characteristics including indicators of SES. Results: Per interquartile range (IQR) increase, we estimated a 12–15% relative increase in odds of autism for ozone [odds ratio (OR) = 1.12, 95% CI: 1.06, 1.19; per 11.54-ppb increase] and particulate matter ≤ 2.5 μm (OR = 1.15; 95% CI: 1.06, 1.24; per 4.68-μg/m3 increase) when mutually adjusting for both pollutants. Furthermore, we estimated 3–9% relative increases in odds per IQR increase for LUR-based nitric oxide and nitrogen dioxide exposure estimates. LUR-based associations were strongest for children of mothers with less than a high school education. Conclusion: Measured and estimated exposures from ambient pollutant monitors and LUR model suggest associations between autism and prenatal air pollution exposure, mostly related to traffic sources.
Ensor, K.B., Raun, L.H., Persse, D.	A Case-Crossover Analysis of Out-of-Hospital Cardiac Arrest and Air Pollution	2013	Circulation	PM2.5, O3, NO2, SO2, CO	Out of hospital cardiac arrest (ER visits)	Houston, TX	All non-dead-on-arrival adults	Studies the association between air pollution and risk of out-of-hospital cardiac arrest.	Yes	Used a time-stratified case-crossover design coupled with conditional logistic regression. Uses ambient air pollution concentrations at times when the study individual is not experiencing the OHCA health event as reference for each case. Use conditional logistic regression to estimate the association of pollution and increased relative risk of health event. Did sensitivity analysis with single lag models to look at hour and day time scales. Implemented constrained distributed lag models to estimate the cumulative effect over 2-hour average or 2-day average increments.	Case-crossover design should control for individual-level confounders. When there was a significant association between individual pollutants and OHCA, looked at potential confounding between pollutants by estimating correlations and including pollutants as covariates in the model. Looked at effect modification by age, sex, race, and season. Acknowledge the possibility of exposure time misclassification and selection bias from not including individuals dead on arrival.	Assessed lags on hourly and daily time scale, for 1-8 lag hours and 1-5 day lags	Yes	**Background:** Evidence of an association between the exposure to air pollution and overall cardiovascular morbidity and mortality is increasingly found in the literature. However, results from studies of the association between acute air pollution exposure and risk of out-of-hospital cardiac arrest (OHCA) are inconsistent for fine particulate matter, and, although pathophysiological evidence indicates a plausible link between OHCA and ozone, none has been reported. Approximately 300 000 persons in the United States experience an OHCA each year, of which >90% die. Understanding the association provides important information to protect public health. **Methods and Results:** The association between OHCA and air pollution concentrations hours and days before onset was assessed by using a time-stratified case-crossover design using 11 677 emergency medical service–logged OHCA events between 2004 and 2011 in Houston, Texas. Air pollution concentrations were obtained from an extensive area monitor network. An average increase of 6 μg/m3 in fine particulate matter 2 days before onset was associated with an increased risk of OHCA (1.046; 95% confidence interval, 1.012–1.082). A 20-ppb ozone increase for the 8-hour average daily maximum was associated with an increased risk of OHCA on the day of the event (1.039; 95% confidence interval, 1.005–1.073). Each 20-ppb increase in ozone in the previous 1 to 3 hours was associated with an increased risk of OHCA (1.044; 95% confidence interval, 1.004–1.085). Relative risk estimates were higher for men, blacks, or those aged >65 years. **Conclusions:** The findings confirm the link between OHCA and fine particulate matter and introduce evidence of a similar link with ozone.

Table 3. O_3 Other Morbidity

Authors	Title	Year Published	Journal Published	Pollutant(s) Studied	Causes of Mortality or Morbidity Considered	Geographic scope	Population studied	Study question	Statistically significant relationships?	Analysis method	Controls for factors that could obscure relationship?	Assesses potential lag between exposure and outcome?	Reports uncertainty?	Abstract
Eze, I.C., Hemkens, L.G., Bucher, H.C., Hoffmann, B., Schindler, C., Kunzli, N., Schikowski, T., Probst-Hensch, N.M.	Association Between Ambient Air Pollution and Diabetes Mellitus in Europe and North America: Systematic Review and Meta-Analysis	2015	Environmental Health Perspectives	PM2.5, Nox	Type 2 diabetes mellitus	Europe and North American	Electronic literature databases	Reviewed epidemiological evidence on the association between air pollution and diabetes, and synthesized results of studies on type 2 diabetes mellitus (T2DM)	Yes	Evaluated risk of bias and role of potential confounders in all studies. Synthesized reported associations with T2DM in meta-analyses using random-effects models and conducted various sensitivity analyses.	Controlled for air pollution, sex, BMI, age, type of study	Different lag times across different studies	Yes	**Background**: Air pollution is hypothesized to be a risk factor for diabetes. Epidemiological evidence is inconsistent and has not been systematically evaluated. **Objectives:** We systematically reviewed epidemiological evidence on the association between air pollution and diabetes, and synthesized results of studies on type 2 diabetes mellitus (T2DM). **Methods:** We systematically searched electronic literature databases (last search, 29 April 2014) for studies reporting the association between air pollution (particle concentration or traffic exposure) and diabetes (type 1, type 2, or gestational). We systematically evaluated risk of bias and role of potnetial confounders in all studies. We synthesized reported associations with T2DM in meta-analyses using random-effects models and conducted various sensistivity analyses. **Results:** We included 13 studies (8 on T2DM, 2 on type 1, 3 on gestational diabetes), all conducted in Europe or North America. Five studies were longitudinal, 5 cross-sectional, 2 case-control, and 1 ecologic. Risk of bias, air pollution assessment, and confounder control varied across studies. Dose-response effects were not reported. Meta-analyses of 3 studies on PM2.5 and 4 studies on NO2 showed increase risk of T2DM by 8-10% per 10 ug/m3 increase in exposure [PM2.5:1.10 (95% CI: 1.02, 1.18); NO2: 1.08 (95% CI: 1.00, 1.170]. Associations were stronger in females. Sensitivity analyses showed similar results. **Conclusion:** Existing evidence indicates a positive association of air pollution and T2DM risk, albeit there is high risk of bias. High-quality studies assessing dose-response effects are needed. Research should be expanded to developing countries where outdoor and indoor air pollution are high.
Laurent, O., Hu, J., Li, L., Cockburn, M., Escobedo, L., Kleeman, M.J., Wu, J.	Sources and Contents of Air Pollution Affecting Term Low Birth Weight in Los Angeles County, California, 2001-2008	2014	Environmental Research	PM2.5, NO2, O3	Low Birth Weight	Los Angeles County, CA	Singleton livebirths with plaus	Studies the relationships between LBW in term born infants and exposures to particles by size fraction, source, and chemical composition, and complementary components of air pollution	Yes (with significant effect modification by socioeconomic status, chronic hypertension, diabetes, BMI)	Estimated generalized additive models, using a logistic link function with a quasi-binomial distribution. Did sensitivity analysis looking at the effect of adjustent for population density, diabetes, chronic hypertension, and preeclampsia.	Adjusted for maternal race/ethnicity, education level, parity, trimester of pregnancy during which primary care began and infant's gender. Also adjusted for maternal age, length of gestation and median household income by census block group. Tried controlling for both seasonal and long-term temporal trends using a smoothed function of the day of conception. Looks at adjustment for maternal height, BMI, and weight gain during pregnancy. Looked at effect modification by maternal race/ethnicity, education, median block group income, hypertension, diabetes, and preeclampsia. Evaluated correlation between pollutants, but seems to use single pollutant models--unsure	Looked at average pollutant concentration for entire pregnancy and for each trimester	Yes	Background: Low birth weight (LBW, <2500 g) has been associated with exposure to air pollution, but it is still unclear which sources or components of air pollution might be in play. The association between ultrafine particles and LBW has never been studied. Objectives: To study the relationships between LBW in term born infants and exposure to particles by size fraction, source and chemical composition, and complementary components of air pollution in Los Angeles County (California, USA) over the period 2001–2008. Methods: Birth certificates (n=960,945) were geocoded to maternal residence. Primary particulate matter (PM) concentrations by source and composition were modeled. Measured fine PM, nitrogen dioxide and ozone concentrations were interpolated using empirical Bayesian kriging. Traffic indices were estimated. Associations between LBW and air pollution metrics were examined using generalized additive models, adjusting for maternal age, parity, race/ethnicity, education, neighborhood income, gestational age and infant sex. Results: Increased LBW risks were associated with the mass of primary fine and ultrafine PM, with several major sources (especially gasoline, wood burning and commercial meat cooking) of primary PM, and chemical species in primary PM (elemental and organic carbon, potassium, iron, chromium, nickel, and titanium but not lead or arsenic). Increased LBW risks were also associated with total fine PM mass, nitrogen dioxide and local traffic indices (especially within 50 m from home), but not with ozone. Stronger associations were observed in infants born to women with low socioeconomic status, chronic hypertension, diabetes and a high body mass index. Conclusions: This study supports previously reported associations between traffic-related pollutants and LBW and suggests other pollution sources and components, including ultrafine particles, as possible risk factors.

Table 3. O_x Other Morbidity

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Lisabeth, L.D., Escobar, J.D., Dvonch, J.T., Sanchez, B.N., Majersik, J.J., Brown, D.L., Smith, M.A., Morgenstern, L.B.	Ambient Air Pollution and Risk for Ischemic Stroke and Transient Ischemic Attack	2008	Annals of Neurology	PM2.5, O3	Ischemic strokes and transient ischemic attacks	Nueces County, TX	All strokes, from surveillance t	Investigates the assoication between short-term exposure to ambient PM2.5 and risk of ischemic cerebrovascular events		Used Poisson regression models to examine the association between PM2.5 and stroke/TIA risk. Fit a semiparametric model with daily stroke/TIA counts as the dependent variable. Assessed relationships between PM2.5 and O3 and outcomes independently and then in a co-pollutant model.	Estimated a co-pollutant model with both O3 and PM2.5 to eliminate confounding. Controlled for seasonal trends, same day average peak hourly temperature. Considered possible effect modification between season and PM2.5 using an interaction term. Also adjusted for day of the week.			Data on the association between air pollution and cerebrovascular disease in the United States are limited. The objective of this study was to investigate the association between short-term exposure to ambient air pollution and risk for ischemic cerebrovascular events in a US community. METHODS: Daily counts of ischemic strokes/transient ischemic attacks (TIAs) (2001-2005) were obtained from the population-based Brain Attack Surveillance in Corpus Christi (BASIC) Project. Daily particulate matter less than 2.5microm in diameter (PM(2.5)), ozone (O(3)), and meteorological data were obtained from Texas Commission on Environmental Quality. To examine the association between PM(2.5) and stroke/TIA risk, we used Poisson regression. Separate models included same-day PM(2.5), PM(2.5) lagged 1 to 5 days, and an averaged lag effect. All models were adjusted for temperature, day of week, and temporal trends in stroke/TIA. The effects of O(3) were also investigated. RESULTS: Median PM(2.5) was 7.0microg/m(3) (interquartile range, 4.8-10.0microg/m(3)). There were borderline significant associations between same-day (relative risk [RR], 1.03; 95% confidence interval [CI], 0.99-1.07 for an interquartile range increase in PM(2.5)) and previous-day (RR, 1.03; 95% CI, 1.00-1.07) PM(2.5) and stroke/TIA risk. These associations were independent of O(3), which demonstrated similar associations with stroke/TIA risk (same-day RR, 1.02; 95% CI, 0.97-1.08; previous-day RR, 1.04; 95% CI, 0.99-1.09). INTERPRETATION: We observed associations between recent PM(2.5) and O(3) exposure and ischemic stroke/TIA risk even in this community with relatively low pollutant levels. This study provides data on environmental exposures and stroke risk in the United States, and suggests future research on ambient air pollution and stroke is warranted.
Miller, K.A., Siscovick, D.S., Sheppard, L., Shepherd, K., Sullivan, J.H., Anderson, G.L., Kaufman, J.D.	Long-Term Exposure to Air Pollution and Incidence of Cardiovascular Events in Women	2007	The New England Journal of Medicine	PM10, SO2, NO2, CO, O3	Cardiovascular events, myocardial infarction, coronary revascularization, stroke, and death from either coronary heart disease or cerebrovascular disease	United States	Participants in the Women's H	Looks at the effect of long-term exposure to air pollution on the incidence of cardiovascular disease among women		Used Cox proportional hazards regressions to estimate hazard ratios for the time to the first cardiovascular event. Stratified with use of separate baseline hazards according to current treatment for diabetes, age, and BMI. Created exposure variables to estimate between-city and within-city effects. Averaged exposures for all women in a metropolitan area into a weighted citywide exposure. Then, to look at within-city effects, fit indicator variables for each metropolitan area or subtracted the weighted citywide mean exposure.	In all models, controlled for age, BMI, smoking status, the number of cigarettes smoked per day, the number of years of smoking, systolic blood pressure, education level, household income, race or ethnic group, and presence or absence of diabetes, hypertension, hypercholestrolemia. Also evaluated possible confounding by presence or absense of environmental tobacco smoke, occupation, physical activity, diet, alcohol consumption, waist circumference, medical history etc. Looked at effect modification by many of these controls. Considered multipollutant models to assess confounding.	Used long-term average PM2.5 concentration, measured in 2000	Yes	Background: Fine particulate air pollution has been linked to cardiovascular disease, but previous studies have assessed only mortality and differences in exposure between cities. We examined the association of long-term exposure to particulate matter of less than 2.5 μm in aerodynamic diameter (PM2.5) with cardiovascular events. Methods: We studied 65,893 postmenopausal women without previous cardiovascular disease in 36 U.S. metropolitan areas from 1994 to 1998, with a median follow-up of 6 years. We assessed the women's exposure to air pollutants using the monitor located nearest to each woman's residence. Hazard ratios were estimated for the first cardiovascular event, adjusting for age, race or ethnic group, smoking status, educational level, household income, body-mass index, and presence or absence of diabetes, hypertension, or hypercholesterolemia. Results: A total of 1816 women had one or more fatal or nonfatal cardiovascular events, as confirmed by a review of medical records, including death from coronary heart disease or cerebrovascular disease, coronary revascularization, myocardial infarction, and stroke. In 2000, levels of PM2.5 exposure varied from 3.4 to 28.3 μg per cubic meter (mean, 13.5). Each increase of 10 μg per cubic meter was associated with a 24% increase in the risk of a cardiovascular event (hazard ratio, 1.24; 95% confidence interval [CI], 1.09 to 1.41) and a 76% increase in the risk of death from cardiovascular disease (hazard ratio, 1.76; 95% CI, 1.25 to 2.47). For cardiovascular events, the between-city effect appeared to be smaller than the within-city effect. The risk of cerebrovascular events was also associated with increased levels of PM2.5 (hazard ratio, 1.35; 95% CI, 1.08 to 1.68). Conclusions: Long-term exposure to fine particulate air pollution is associated with the incidence of cardiovascular disease and death among postmenopausal women. Exposure differences within cities are associated with the risk of cardiovascular disease.

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Mobasher, Z., Salam, M.T., Goodwin, T.M., Lurmann, F., Ingles, S.A., Wilson, M.L.	Associations Between Ambient Air Pollution and Hypertensive Disorders of Pregnancy	2013	Environmental Research	CO, NO2, O3, PM10, PM2.5	Hypertensive Disorders of Pregnancy	Southern California	Women giving birth in Los Angeles 1999-2008 at Los Angeles County+USC Women's and Children's Hospital, predominately Hispanic	Investigates the role of trimester-specific ambient air pollution on risk for hypertensive disorder of pregnancy	Yes (with 1st trimester exposure, modified by BMI)	Retrospective case-control study. Performed correlation analysis to determine Pearson's correlation coefficients for all air pollutants. Then used unconditional logistic regression to examine the association between ambient air pollution and odds of hypertensive disorder of pregnancy	Adjusted analysis for maternal age, parity, maternal smoking status, exposure to secondhand smoke during pregnancy, indicator of calendar year of pregnancy, BMI. Acknowledge the possibility of exposure misclassification, response rate may introduce bias.	Uses average pollution in each trimester	Yes	**Background:** Exposure to ambient air pollution is linked to adverse pregnancy outcomes. Previous reports examining the relationship between ambient air pollution and Hypertensive Disorders of Pregnancy have been inconsistent. **Objectives:** We evaluated the effects of ambient air pollution on the odds of Hypertensive Disorder of Pregnancy and whether these associations varied by body mass index (BMI). **Methods:** We conducted a retrospective, case-control study among 298 predominantly Hispanic women (136 clinically confirmed cases) who attended the Los Angeles County+University of Southern California Women's and Children's Hospital during 1996–2008. Trimester-specific carbon monoxide (CO), nitrogen dioxide (NO2), ozone (O3), and particulate matter with aerodynamic diameter <10 μm and <2.5 μm (PM10, PM2.5) exposure were estimated based on 24-hour exposure level at residential address. Logistic regression models were fitted to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for two standard deviation increase in exposure levels. **Results:** Exposures to CO and PM2.5 in the 1st trimester were significantly associated with Hypertensive Disorders of Pregnancy, and these associations were modified by BMI. In non-obese women (BMI <30), 1st trimester exposures to PM2.5 and CO were significantly associated with increased odds of Hypertensive Disorder of Pregnancy (ORs per 2-standard deviation increase in PM2.5 (7 μg/m3) and CO (1 ppm) exposures were 9.10 [95% CI: 3.33–24.6] and 4.96 [95% CI: 1.85–13.31], respectively). Additionally, there was a significantly positive association between exposure to O3 in the 2nd trimester and Hypertensive Disorder of Pregnancy (OR per 15 ppb=2.05; 95% CI: 1.22–3.46). **Conclusion:** Among non-obese women, 1st trimester exposure to PM2.5 and carbon monoxide are associated with increased odds of Hypertensive Disorder of Pregnancy.
Morello-Frosch, R., Jesdale, B.M., Sadd, J.L., Pastor, M.	Ambient Air Pollution Exposure and Full-term Birth Weight in California	2010	Environmental Health	PM2.5, PM10, CO, NO2, SO2, O3	Average birth weight and low birth weight	California	Singleton live births with gestational age between 37-44, from California residents, 1996-2006	Analyzes the effect of air pollution on average birth weight and risk of low birth weight in California		Used linear multivariable models to estimate the impact of air pollutants on birth weight as a continuous measure, and logistic regression models to estimate air pollution effects on birth weight as dichotomous outcome. Examined trimester-specific models as well as full-pregnancy models.	Controlled for maternal age, educational attainment, maternal race/ethnicity, maternal birthplace, calendar year, season of delivery, marital status, partiy, Kotelchuk index of prenatal care, and presence of other pregnancy risk factors, like anemia, diabetes, chronic or pregnancy-associated hypertension, and/or herpes. Also included neighborhood socio-economic status variables. Also stratified by maternal race/ethnicity and neighborhood-level poverty rate to look at effect modification. Also ran copollutant models to assess potential confounding effects.			Background:Studies have identified relationships between air pollution and birth weight, but have been inconsistent in identifying individual pollutants inversely associated with birth weight or elucidating susceptibility of the fetus by trimester of exposure. We examined effects of prenatal ambient pollution exposure on average birth weight and risk of low birth weight in full-term births. Methods: We estimated average ambient air pollutant concentrations throughout pregnancy in the neighborhoods of women who delivered term singleton live births between 1996 and 2006 in California. We adjusted effect estimates of air pollutants on birth weight for infant characteristics, maternal characteristics, neighborhood socioeconomic factors, and year and season of birth. Results: 3,545,177 singleton births had monitoring for at least one air pollutant within a 10 km radius of the tract or ZIP Code of the mother's residence. In multivariate models, pollutants were associated with decreased birth weight; -5.4 grams (95% confidence interval -6.8 g, -4.1 g) per ppm carbon monoxide, -9.0 g (-9.6 g, -8.4 g) per pphm nitrogen dioxide, -5.7 g (-6.6 g, -4.9 g) per pphm ozone, -7.7 g (-7.9 g, -6.6 g) per 10 μg/m3 particulate matter under 10 μm, -12.8 g (-14.3 g, -11.3 g) per 10 μg/m3 particulate matter under 2.5 μm, and -9.3 g (-10.7 g, -7.9 g) per 10 μg/m3 of coarse particulate matter. With the exception of carbon monoxide, estimates were largely unchanged after controlling for co-pollutants. Effect estimates for the third trimester largely reflect the results seen from full pregnancy exposure estimates; greater variation in results is seen in effect estimates specific to the first and second trimesters. Conclusions: This study indicates that maternal exposure to ambient air pollution results in modestly lower infant birth weight. A small decline in birth weight is unlikely to have clinical relevance for individual infants, and there is debate about whether a small shift in the population distribution of birth weight has broader health implications. However, the ubiquity of air pollution exposures, the responsiveness of pollutant levels to regulation, and the fact that the highest pollution levels in California

Table 3. O_x Other Morbidity

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Padula, A.M., Tager, I.B., Carmichael, S.L., Hammond, S.K., Yang, W., Lurmann, F., Shaw, G.M.	Ambient Air Pollution and Traffic Exposures and Congenital Heart Defects in the San Joaquin Valley of California	2014	Paediatric and Perinatal Epidemiology	CO, NO2, PM10, PM2.5, O3	Congenital heart defects--heterotaxia, d-Transposition of the great arteries, tetralogy of fallot, double outlet right ventricle (TGA and other)	San Joaquin Valley, CA	All births in San Joaquin valley	Investigates the association between ambient air pollution and congenital heart defects	Yes (with transposition of great arteries and inversely associated with perimembranous ventricular septal defects)	Cases included live births, stillbirths, and pregnancy terminations with congenital heart defects, and controls were non-malformed live-born infants randomly selected from birth hospitals to represent the population. First analyzed the association between pollutants and traffic metrics. Then did multivariate logistic regression analyses to estimate adjusted odds ratios.	In analysis adjusted for maternal race/ethnicity, education, and early prenatal vitamin use. Considered other controls, like maternal age, parity, infant sex, year of birth etc., but did not include them. Investigated effect modification by cigarette smoking. Acknowledge that they may have misclassified exposure, particularly if vulnerable windows for certain heart defects are narrower than they expected. Also potential bias from early fetal loss, possible other confounders	Used average air pollution measurements from the first and second month of pregnancy	Yes	**Background:** Congenital anomalies are a leading cause of infant morbidity and mortality. Studies suggest associations between environmental contaminants and some anomalies, although evidence is limited. **Methods:** We used data from the California Center of the National Birth Defects Prevention Study and the Children's Health and Air Pollution Study to estimate the odds of 27 congenital heart defects with respect to quartiles of seven ambient air pollutant and traffic exposures in California during the first 2 months of pregnancy, 1997-2006 (n = 822 cases and n = 849 controls). **Results:** Particulate matter < 10 microns (PM10) was associated with pulmonary valve stenosis [adjusted odds ratio (aOR)Fourth Quartile = 2.6] [95% confidence intervals (CI) 1.2, 5.7] and perimembranous ventricular septal defects (aORThird Quartile = 2.1) [95% CI 1.1, 3.9] after adjusting for maternal race/ethnicity, education and multivitamin use. PM2.5 was associated with transposition of the great arteries (aORThird Quartile = 2.6) [95% CI 1.1, 6.5] and inversely associated with perimembranous ventricular septal defects (aORFourth Quartile = 0.5) [95% CI 0.2, 0.9]. Secundum atrial septal defects were inversely associated with carbon monoxide (aORFourth Quartile = 0.4) [95% CI 0.2, 0.8] and PM2.5 (aORFourth Quartile = 0.5) [95% CI 0.3, 0.8]. Traffic density was associated with muscular ventricular septal defects (aORFourth Quartile = 3.0) [95% CI 1.2, 7.8] and perimembranous ventricular septal defects (aORThird Quartile = 2.4) [95% CI 1.3, 4.6], and inversely associated with transposition of the great arteries (aORFourth Quartile = 0.3) [95% CI 0.1, 0.8]. **Conclusions:** PM10 and traffic density may contribute to the occurrence of pulmonary valve stenosis and ventricular septal defects, respectively. The results were mixed for other pollutants and had little consistency with previous studies.
Ritz, B., Wilhelm, M., Hoggatt, K.J., Ghosh, J.K.	Ambient Air Pollution and Preterm Birth in the Environment and Pregnancy Outcomes Study at the University of California, Los Angeles	2007	American Journal of Epidemiology	CO, NO2, O3, PM2.5	Preterm birth (<37 completed weeks of gestation)	Los Angeles County, CA	Singleton livebirths 2003 with no recorded defects, extreme gestional ages or birth weights	Assesses the extent to which residual confounding and exposure misclassification impact air pollution effect estimates.		Seleted all cases of low birth weight or preterm birth and an equal number of randomly sampled controls, matched on ZIP code and birth month. Estimated effects of air pollution exposure on odds of preterm birth within birth cohort and nested case-control sample using single- and multiple-variable logistic regression models. Treated pollutants as both continuous and categorical variables.	Adjusted final models for maternal age, race/ethnicity, partiy, education, and season of birth, maternal smoking, alcohol consumption, living with a smoker, and marital status during pregnancy. Try to address selection bias by using known sampling fractions.			The authors conducted a case-control survey nested within a birth cohort and collected detailed risk factor information to assess the extent to which residual confounding and exposure misclassification may impact air pollution effect estimates. Using a survey of 2,543 of 6,374 women sampled from a cohort of 58,316 eligible births in 2003 in Los Angeles County, California, the authors estimated with logistic regression and two-phase models the effects of pregnancy period-specific air pollution exposure on the odds of preterm birth. For the first trimester, the odds of preterm birth consistently increased with increasing carbon monoxide exposures and also at high levels of exposure to particulate matter less than or equal to 2.5 µm in diameter (>21.4 µg/m3), regardless of type of data (cohort/sample) or covariate adjustment (carbon monoxide exposures of >1.25 ppm increased the odds by 21-25%). Women exposed to carbon monoxide above 0.91 ppm during the last 6 weeks of pregnancy experienced increased odds of preterm birth. Crude and birth certificate covariate-adjusted results for carbon monoxide differed from each other. However, further adjustment for risk factors assessed in the survey did not change effect estimates for short-term pollutant averages appreciably, except for time-activity patterns, which strengthened the observed associations. These results confirm the importance of reducing exposure misclassification when evaluating the effect of traffic-related pollutants that vary spatially.
Robledo, C.A., Mendola, P., Yeung, E., Mannisto, T., Sundaram, R., Liu, D., Ying, Q., Sherman, S., Grantz, K.L.	Preconception and Early Pregnancy Air Pollution Exposures and Risk of Gestational Diabetes Mellitus	2015	Environmental Research	PM2.5, PM10, NOx, CO, SO2, O3	Gestational diabetes mellitus (ICD-9: 648.8)	United States	Singleton births without prege	Investigates the association between critera air pollutants regulated by the US EPA and the risk of gestational diabetes mellitus	No	First calcualted Spearman rank correlations between each pollutants. Then fitted binary regression models with the log link function to estimate relative risks for IQR increase for each pollutant. Used a first order autoregressive covariance structure to account for within-cluster correlation for women with more than one singleton pregnancy during study period. Made separate models for air pollutants during each exposure window.	Assessed potential confounding by maternal characteristics, including parity, marital status, insurance status, hospital type, prenatal history of smoking and alcohol, study sites. Looked at effect modification by maternal BMI. Also looked at multi-pollutant models to look at confounding by other pollutants.	Included pre-conception exposure (91 days before last menstrual period), average exposure during 1st trimester, weekly averages for gestational weeks 1 through 24	Yes	Background: Air pollution has been linked to gestational diabetes mellitus (GDM) but no studies have evaluated impact of preconception and early pregnancy air pollution exposures on GDM risk. Methods: Electronic medical records provided data on 219,952 singleton deliveries to mothers with (n=11,334) and without GDM (n=208,618). Average maternal exposures to particulate matter (PM) ≤ 2.5µm (PM2.5) and PM2.5 constituents, PM ≤ 10µm (PM10), nitrogen oxides (NOx), carbon monoxide, sulfur dioxide (SO2) and ozone (O3) were estimated for the 3-month preconception window, first trimester, and gestational weeks 1-24 based on modified Community Multiscale Air Quality models for delivery hospital referral regions. Binary regression models with robust standard errors estimated relative risks (RR) for GDM per interquartile range (IQR) increase in pollutant concentrations adjusted for study site, maternal age and race/ethnicity. Results: Preconception maternal exposure to NOX (RR=1.09, 95% CI: 1.04, 1.13) and SO2 (RR=1.05, 1.01, 1.09) were associated with increased risk of subsequent GDM and risk estimates remained elevated for first trimester exposure. Preconception O3 was associated with lower risk of subsequent GDM (RR=0.93, 0.90, 0.96) but risks increased later in pregnancy. Conclusion: Maternal exposures to NOx and SO2 preconception and during the first few weeks of pregnancy were associated with increased GDM risk. O3 appeared to increase GDM risk in association with mid-pregnancy exposure but not in earlier time windows. These common exposures merit further investigation.

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Rodopoulou, S., Chalbot, M.C., Samoli, E., Dubois, D.w., San Filippo, B.D., Kavouras, I.G.	Air Pollution and Hospital Emergency Room and Admissions for Cardiovascular and Respiratory Diseases in Dona Ana County, New Mexico	2014	Environmental Research	PM10, PM2.5, O3	Respiratory (ICD-9: 493, 466, 490, 491, 492, 496, 480-486, 460-465) and cardiovascular (ICD-9: 410-414, 426-427, 402, 428, 390-459)	Dona Ana County, New Mexico	Residents of Dona Ana county	Evaluates the association between short-term exposure to ambient PM10, PM2.5, and O3 and respiratory and cardiovascular emergency room visits and hospitalizations		Used Poisson regression models allowing for overdispersion, allowed nonlinearity by using natural splines. Remove dlong-term trends and seasonal patterns with a natural cubic regression spline for each season and year. Estimate effects separately for all ages and 65+	Controlled for long-term time trends and seasonal patterns, as well as temperature, daily humidity. Evaluated effect modification by season and tried removing days with outlier pollution. Also tried doing two day average lag.	Uses same day and day before pollution, and then two-day moving average	Yes	**Introduction:** Doña Ana County in New Mexico regularly experiences severe air pollution episodes associated with windblown dust and fires. Residents of Hispanic/Latino origin constitute the largest population group in the region. We investigated the associations of ambient particulate matter and ozone with hospital emergency room and admissions for respiratory and cardiovascular visits in adults. **Methods:** We used trajectories regression analysis to determine the local and regional components of particle mass and ozone. We applied Poisson generalized models to analyze hospital emergency room visits and admissions adjusted for pollutant levels, humidity, temperature and temporal and seasonal effects. **Results:** We found that the sources within 500km of the study area accounted for most of particle mass and ozone concentrations. Sources in Southeast Texas, Baja California and Southwest US were the most important regional contributors. Increases of cardiovascular emergency room visits were estimated for PM10 (3.1% (95% CI: -0.5 to 6.8)) and PM10-2.5 (2.8% (95% CI: -0.2 to 5.9)) for all adults during the warm period (April-September). When high PM10 (>150µg/m(3)) mass concentrations were excluded, strong effects for respiratory emergency room visits for both PM10 (3.2% (95% CI: 0.5-6.0)) and PM2.5 (5.2% (95% CI: -0.5 to 11.3)) were computed. **Conclusions:** Our analysis indicated effects of PM10, PM2.5 and O3 on emergency room visits during the April-September period in a region impacted by windblown dust and wildfires.
Stingone, J.A., Luben, T.J., Daniels, J.L, Fuentes, M., Richardson, D.B., Aylsworth, A.S,. Herring, A.H., Anderka, M., Botto, L., Correa, A., Gilboa, S.M., Langlois, P.H., Mosley, B., Shaw, G.M>, Siffel, C., Olshan, A.F.	Maternal Exposure to Criteria Air Pollutants and Congenital Heart Defects in Offspring: Results from the National Birth Defects Prevention Study	2014	Environmental Health Perspectives	CO, NO2, O3, PM10, PM2.5, SO2	Simple, isolated congenital heart defects with no extra-cardiac birth defects present		Participants in National Birth D	Investigates the association between maternal exposure to air pollutants during weeks 2-8 of pregnancy and their associations with congenital heart defects	Yes (with hypoplastic left heart syndrome, inversely associated with atrial septal defects, some attenuation of results by multipollutant models)	Construfted two-stage hierarchical regression models to account for correlation between estimates and partially address multiple inference. In first stage, ran uconditional, polytomous logistic regression model of individual CHDs on exposure defined as either all 1-week average exposure or single 7-week average. Looked at sensitivity to changes in the model specification.	Controled for maternal age, race/ethnicity, educational attainment, household income, tobacco smoking in the first month of pregnancy, alcohol consumption during the first trimester, maternal nativity. Also controlled for distance to closest major road, prepregnancy BMI, maternal occupational status. Looked at multipollutant models using a principal component analysis.	Calculated average pollutant concentration for weeks 2-8 of pregnancy and 1-week averages for each week	Yes	Background: Epidemiologic literature suggests that exposure to air pollutants is associated with fetal development. Objectives: We investigated maternal exposures to air pollutants during weeks 2-8 of pregnancy and their associations with congenital heart defects. Methods: Mothers from the National Birth Defects Prevention Study, a nine-state case-control study, were assigned 1-week and 7-week averages of daily maximum concentrations of carbon monoxide, nitrogen dioxide, ozone, and sulfur dioxide and 24-hr measurements of fine and coarse particulate matter using the closest air monitor within 50 km to their residence during early pregnancy. Depending on the pollutant, a maximum of 4,632 live-birth controls and 3,328 live-birth, fetal-death, or electively terminated cases had exposure data. Hierarchical regression models, adjusted for maternal demographics and tobacco and alcohol use, were constructed. Principal component analysis was used to assess these relationships in a multipollutant context. Results: Positive associations were observed between exposure to nitrogen dioxide and coarctation of the aorta and pulmonary valve stenosis. Exposure to fine particulate matter was positively associated with hypoplastic left heart syndrome but inversely associated with atrial septal defects. Examining individual exposure-weeks suggested associations between pollutants and defects that were not observed using the 7-week average. Associations between left ventricular outflow tract obstructions and nitrogen dioxide and between hypoplastic left heart syndrome and particulate matter were supported by findings from the multipollutant analyses, although estimates were attenuated at the highest exposure levels. Conclusions: Using daily maximum pollutant levels and exploring individual exposure-weeks revealed some positive associations between certain pollutants and defects and suggested potential windows of susceptibility during pregnancy.
Symanski, E., McHugh, M.K., Zhang, X., Craft, E.S., Lai, D.	Evaluating Narrow Windows of Maternal Exposure to Ozone and Preterm Birth in a Large Urban Area in Southeast Texas	2015	Journal of Exposure Science and Environmental Epidemiology	O3	Preterm birth	Harris County, Texas	Singleton livebirths, 2005-200	Evaluates the relationship between exposure to ozone and preterm birth.		Calculated two sets of exposure metrics during every 4 weeks of pregnancy, accounting for temporal variability and then for temporal and spatial sources of variability in ambient O3 levels. Assessed associations using multiple logistic regressions.	Looked for fixed cohort bias. Looked for effect modification by women's occupation.			

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Vinikoor-Imler, L.C., Stewart, T.G., Luben, T.J., Davis, J.A., Langlois, P.H.	An Exploratory Analysis of the Relationship Between Ambient Ozone and Particulate Matter Concentrations During Early Pregnancy and Selected Birth Defects in Texas	2015	Environmental Pollution	PM2.5, O3	Birth defects: anencephaly, spinal bifida, hydrocephalus, anotia or microtia, conotruncal heart defects, septal heart defects, atrioventricular septal defects, obstructive heart defects, anomalous pulmonary venous return, oral clefts, esophageal atresia, intestinal atresia, biliary atresia, hypospadias, longitudinal limb deficiency defects, transverse limb deficiency defects, craniosynostosis, diaphragmatic hernia, omphalocele, gastroschisis	Texas	All singleton live births 2002-2	Examines associations between O3 and PM2.5 concentrations	No	Calculated exposure using heirarchical Bayesian model combining data from air monitors with estimates from EPA's CMZQ model. Calculated associations using logistic regression in single-pollutant models and co-pollutant models.	Covariates included prenatal care in first trimester, number of previous live births, maternal age, maternal education, maternal race/ethnicity, urbanicity. Performed co-pollutant and single-pollutant models to evaluate confounding.	Average concentrations during the first trimester	Yes	We performed an exploratory analysis of ozone (O3) and fine particulate matter (PM2.5) concentrations during early pregnancy and multiple types of birth defects. Data on births were obtained from the Texas Birth Defects Registry (TBDR) and the National Birth Defects Prevention Study (NBDPS) in Texas. Air pollution concentrations were previously determined by combining modeled air pollution concentrations with air monitoring data. The analysis generated hypotheses for future, confirmatory studies; although many of the observed associations were null. The hypotheses are provided by an observed association between O3 and craniosynostosis and inverse associations between PM2.5 and septal and obstructive heart defects in the TBDR. Associations with PM2.5 for septal heart defects and ventricular outflow tract obstructions were null using the NBDPS. Both the TBDR and the NBPDS had inverse associations between O3 and septal heart defects. Further research to confirm the observed associations is warranted.
Zhu, Y., Zhang, C., Liu, D., Grantz, K.L., Wallace, M., Mendola, P.	Maternal Ambient Air Pollution Exposure Preconception and During Early Gestation and Offspring Congenital Orofacial Defects	2015	Environmental Research	CO, NOx, O3, PM2.5, PM10, SO2	Orofacial defects (isolated/multiple cleft palate and cleft lip with or without cleft palate)	United States	Consortium on Safe Labor	Investigates the association between maternal exposure to various air pollutants with risks of orofacial defects		Performed separate analysis for each outcome and exposure window of interest combination. Estimate generalized estimating equations to calculate robust standard errors accounting for clustering due to multiple pregnancies of the same woman. Performed sensitivity analysis excluding multiple gestation pregnancies and infants born to women with preexisting or gestational diabetes.	Controlled for site/region, maternal age, race/ethnicity, marital status, insurance, prepregnancy body mass index, nulliparity, season of conception, smoking and/or alcohol consumption during pregnancy, multiple birth, preexisting or gestational diabetes mellitus. Performed simulation extrapolation procedures to correct for potential exposure misclassification. I believe they did not do co-pollutant models.	Three months preconception and early gestation (both an average over weeks 3-8 and weekly averages from weeks 1 through 10)	Yes	**Background:** Maternal air pollution exposure has been related to orofacial clefts but the literature is equivocal. Potential chronic preconception effects have not been studied. **Objectives:** Criteria air pollutant exposure during three months preconception and gestational weeks 3-8 was studied in relation to orofacial defects. **Methods:** Among 188,102 live births and fetal deaths from the Consortium on Safe Labor (2002-2008), 63 had isolated cleft palate (CP) and 159 had isolated cleft lip with or without cleft palate (CL ±CP). Exposures were estimated using a modified Community Multiscale Air Quality model. Logistic regression with generalized estimating equations adjusted for site/region and maternal demographic, lifestyle and clinical factors calculated the odds ratio (OR) and 95% CI per interquartile increase in each pollutant. **Results**: Preconception, carbon monoxide (CO; OR=2.24; CI: 1.21, 4.16) and particulate matter (PM) ≤10μm (OR=1.72; CI: 1.12, 2.66) were significantly associated with CP, while sulfur dioxide (SO2) was associated with CL ±CP (OR=1.93; CI: 1.16, 3.21). During gestational weeks 3-8, CO remained a significant risk for CP (OR=2.74; CI: 1.62, 4.62) and nitrogen oxides (NOx; OR=3.64; CI: 1.73, 7.66) and PM ≤2.5μm (PM2.5; OR=1.74; CI: 1.15, 2.64) were also related to the risk. Analyses by individual week revealed that positive associations of NOx and PM2.5 with CP were most prominent from weeks 3-6 and 3-5, respectively. **Conclusions:** Exposure to several criteria air pollutants preconception and during early gestation was associated with elevated odds for CP, while CL ±CP was only associated with preconception SO2 exposure.