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Methodological issues in studies of air pollution and reproductive health☆

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Abstract

In the past decade there have been an increasing number of scientific studies describing possible effects of air pollution on perinatal health. These papers have mostly focused on commonly monitored air pollutants, primarily ozone (O_3), particulate matter (PM), sulfur dioxide (SO_2), carbon monoxide (CO), and nitrogen dioxide (NO_2), and various indices of perinatal health, including fetal growth, pregnancy duration, and infant mortality. While most published studies

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have found some marker of air pollution related to some types of perinatal outcomes, variability exists in the nature of the pollutants and outcomes associated. Synthesis of the findings has been difficult for various reasons, including differences in study design and analysis. A workshop was held in September 2007 to discuss methodological differences in the published studies as a basis for understanding differences in study findings and to identify priorities for future research, including novel approaches for existing data. Four broad topic areas were considered: confounding and effect modification, spatial and temporal exposure variations, vulnerable windows of exposure, and multiple pollutants. Here we present a synopsis of the methodological issues and challenges in each area and make recommendations for future study. Two key recommendations include: (1) parallel analyses of existing data sets using a standardized methodological approach to disentangle true differences in associations from methodological differences among studies; and (2) identification of animal studies to inform important mechanistic research gaps. This work is of critical public health importance because of widespread exposure and because perinatal outcomes are important markers of future child and adult health.

Keywords

Air pollution; Perinatal outcomes; Low birthweight; Preterm delivery; Epidemiologic methods

1. Introduction

In the past decade, there has been a sharp increase in the number of research articles published describing possible effects of air pollution on perinatal health, including fetal growth and preterm delivery. These papers have examined various indicators of air pollution, mostly focused on commonly monitored air pollutants (ozone (O_3), particulate matter (PM), sulfur dioxide (SO_2), carbon monoxide (CO), and nitrogen dioxide (NO_2 or oxide (NO_x)) and various indices of perinatal health, including fetal growth, pregnancy duration, and infant mortality. This work is of critical public health importance because the exposure is widespread and perinatal outcomes are important markers of future child and adult health (e.g., Gillman, 2005). In 2004 and 2005, reviews of the preceding literature were published, generally concluding that the evidence was difficult to synthesize but was suggestive of small effects of air pollution on fetal and infant development (Lacasana et al., 2005; Glinianaia et al., 2004; Maisonet et al., 2004; Sram et al., 2005; Tong and Colditz, 2004). Many recent research articles have attempted to fill in the gaps mentioned in the reviews, but the results remain difficult to synthesize.

This relatively new combination of air pollution epidemiology with perinatal epidemiology faces the challenges of both disciplines. These challenges include air pollution exposure assessment, the identification of important exposure windows during pregnancy, adequate control for potential confounding factors, and identification of effect-measure modification. One important advantage to evaluating effects of air pollution exposure during pregnancy is that time spans of exposure are relatively short, up to 9 months (assuming pre-conceptional exposures have no effect), compared to time spans from studies of chronic exposure to air pollution in children and adults, which can be years. The shorter exposure windows in pregnancy studies (typically 9 months) can make it easier to better evaluate the exposures of interest compared to longer exposures in adult studies, as it can decrease the possibility of other risk factors, both environmental and other, influencing the outcomes.

Heterogeneity in the published findings may arise from differences in many aspects of the study designs and available data. For example, studies vary in the set of pollutants considered and the methods of assigning exposure. Most studies have examined particulate matter, although the measured component varies from total suspended particulates (TSP) in earlier studies (e.g., Wang et al., 1997) to particulate matter with an aerodynamic diameter smaller than 10μm (PM_{10}) (Hansen et al., 2008; Ritz et al., 2000; Sagiv et al., 2005) and finer particles, smaller than 2.5 μm ($PM_{2.5}$) in later studies (e.g., Slama et al., 2007; Huynh et al., 2006). Other pollutants examined in one or more studies include CO, O_3, SO_2, and NO_2 though not consistently from study to study. Further, some studies consider exposure to pollutants separately, while others consider the exposures simultaneously in an attempt to disentangle effects of specific pollutants. Multipollutant analyses have been hindered by strong between-pollutant correlations, air pollution data availability and heterogeneous degrees of spatial resolution for various pollutants. Regional and demographic differences in study populations also may contribute to the disparate findings; pollution components and mixtures can vary regionally and variation in underlying factors can contribute to population differences (such as access to care and susceptibility) and could contribute to the variations in study conclusions (Parker and Woodruff, 2008).

Another challenge toward synthesis is variability in the findings by exposure windows. Of the studies that examined trimester of exposure, some found stronger effects earlier in pregnancy, others identified later exposures as more harmful and still others did not single out a particular period of pregnancy for adverse outcomes. While the method for defining the exposure windows does not vary significantly, other contributing factors, even random variation, lead to variability in findings (Table 1).

The need to better understand the unique concerns of perinatal air pollution epidemiology, to assess how methodological differences could contribute to differences in findings, and to identify important areas for future research led to two workshops in 2007, held in Munich, Germany in May (Slama et al., 2008a) and in Mexico City in September. The report of the Munich workshop (Slama et al., 2008a) covers the effects of air pollution on a wider variety of reproductive outcomes, such as fecundity and sperm quality, discusses potential biological mechanisms, methods, and recommendations for future areas of research.

The findings presented in this paper are from the Mexico City workshop. The primary goal of the Mexico City workshop was to identify differences in methodologies used among the epidemiologic studies of air pollution and perinatal outcomes as a possible explanation for the array of findings in the literature. The discussion specifically focused on studies of fetal growth and preterm birth. This paper describes the four key methodological areas focused within the workshop. These four areas were selected by the Mexico City workshop planning committee because they were thought more likely to contribute to the variation in the findings in the epidemiologic literature. Specific recommendations from the workshop to improve future studies focused on the effects of air pollution on perinatal health are then provided.

2. Objectives

The overall objectives of the workshop were to: (1) review and discuss four methodological issues that may affect findings from perinatal air pollution studies; and (2) identify priorities for future research including practical suggestions for working with existing and future data. The four methodological issues discussed were: confounding and effect-measure modification; defining exposures: spatial and temporal exposure assessment; windows of vulnerability; and multiple pollutants.

An underlying theme throughout the discussion of the four methodological areas was how to best identify the outcomes of interest, and this is briefly reviewed (for further discussion see Slama et al. (2008a). The main findings from each of the four areas follow. We conclude this report by summarizing the key recommendations for future research to improve our understanding of the effects of air pollution on human pregnancy outcomes.

3. Identifying the outcome of interest

The majority of published air pollution and perinatal outcome studies have evaluated relationships between air pollution and different measures of fetal growth and preterm delivery (Glinianaia et al, 2004; Lacasana et al, 2005; Maisonet et al., 2004; Sram et al., 2005). There are some studies that have evaluated other adverse pregnancy outcomes, including birth defects, spontaneous abortions or stillbirths, and infant mortality. The Mexico City workshop discussion primarily focused on air pollution effects on fetal growth and preterm delivery, consistent with the majority of the scientific studies. Studies have evaluated a number of different metrics to describe potential effects on fetal growth, including reduction in birthweight (continuous variable), low birthweight (defined as <2500g), very low birthweight (<1500g), and intrauterine growth retardation (often measured as low birthweight in full-term infants or small for gestational age, which has been defined as birthweight below the 10th percentile of the birthweight distribution for a specific gestational age and sex based on national standards for livebirths) (Glinianaia et al., 2004). Most of the studies acknowledge the potentially different etiology of growth restriction (as compared to preterm birth) by assessing birthweight at term, and/or accounting for gestational age in the models. A number of studies have also evaluated preterm delivery, which is most often measured across the studies as birth at less than 37 completed weeks of gestation. Although the dating of gestational age can vary by study, many studies use the woman's recall of date of last menstrual period (LMP).

While participants noted difficulties in identifying appropriate pregnancy endpoints, these problems are not unique to studies of air pollution. Birthweight, for example, is a sensitive but not very specific endpoint for studies of exposure. Birthweight distributions for healthy infants can differ by subgroups characterized by a variety of factors (e.g., race or gender); and the consequences of low birthweight (and other fetal growth outcomes) can also differ among factors, including different exposures, hypothesized to be responsible for inadequate growth. Another problem common to perinatal epidemiology that affects studies of air pollution is distinguishing between reduced birthweight resulted from fetal growth restriction or from preterm delivery, or both. A recent study has used ultrasound images during mid-gestation to evaluate the relationship between fetal growth and air pollution (Hansen et al., 2008), which is one approach to distinguishing fetal growth effects from preterm delivery effects. Hansen et al. (2008) study accounted for gestational age in the model using a validated measure of last menstrual period which was not based on ultrasound data. Accounting for gestational age when using single ultrasound measurements in these types of studies is important because ultrasound is also used to establish gestational age, and smaller infants may be mistaken for younger gestational age, rather than as growth retarded (Slama et al., 2008b).

4. Confounding, effect-measure modification, and selection bias

The role of air pollution in perinatal outcomes and the potential for confounding can be considered by the following question: “Is the association of air pollution and birth outcome confounded by personal characteristics or is air pollution one explanation for the association of personal characteristics with birth outcome?” The intersection of air pollution epidemiology and perinatal epidemiology is not particularly straightforward. Air pollution epidemiology, on the one hand, has often relied on time-series analyses relating daily pollution levels to daily counts of health events, usually with a lag of a few days; in this setting there is concern for weather-related confounders such as temperature and less concern about confounding from personal characteristics constant over time which are controlled for by the study design. On the other hand, perinatal studies often use binomial regression models (e.g., logistic) to obtain risk ratios or odds ratios and often compare populations from different geographic areas. In this type of study, in addition to confounding due to seasonally varying factors, concerns arise about potential confounding by maternal characteristics such as age, race/ethnicity, body mass index, socioeconomic status, and behaviors, particularly smoking, which are usually not controlled by study design. The availability, quality, and impact of these potentially confounding factors can vary by study, though most published studies used covariate data collected from birth certificates.

Much of the research on air pollution and birth outcomes is based on data sets formed by combining individual information from birth records with measures of ambient air quality, typically from outdoor stationary monitors. While the birth records typically contain information related to birth outcomes, such as maternal age, educational attainment, and parity, there is concern that unmeasured individual-level characteristics, not available on the birth record, may confound observed relationships. Confounders were primarily considered as covariates that may distort the association between the pregnancy outcome and the air pollution exposure; more detailed definitions of confounding, excluding factors that are potential consequences of either exposure or outcome, can be found (e.g., Rothman et al., 2008; Jewell, 2004; Selvin, 1991). Social class indicators are thought to be important confounders, for example, because lower socioeconomic status women are at increased risk of poor birth outcomes and, at least in some countries, are more likely to live in polluted areas. Importantly, some covariates may have a different relationship in an analysis. If air pollution affects a birth outcome through its effect on one or more covariates, these covariates are not considered confounders. In studies of air pollution and perinatal outcomes, potential confounders which may be either poorly measured or absent in analyses include socioeconomic status indicators beyond those collected on the birth certificate, such as family income and behavioral variables, such as substance use. Confounding was discussed separately from effect-measure modification, which for specific statistical models could allow identification of subgroups more vulnerable to effects of air pollution. For example, there is speculation that associations may be stronger for male than female infants (Ghosh et al., 2007), and could be stronger for mothers in poorer neighborhoods compared to those in wealthier neighborhoods (Ponce et al., 2005), though another study suggests associations could be stronger for women in wealthier neighborhoods (Genereux et al., 2008). The same variables can be confounder or effect modifiers depending on the characteristics of the study population, or the underlying hypothesis. Associations between socioeconomic status and pollution exposure may vary geographically or according to the spatial resolution of the exposure model and could contribute to differing relationships with birth outcomes.

Recent results from a nested two-phase study provide insights into the potential influence of confounding (Ritz et al., 2007). Information from birth records was augmented with information from a detailed interview survey for a subset of the overall study population to examine whether factors not included on the birth certificate affected the air pollution - preterm delivery relationship. The authors reported that many initially hypothesized confounders, such as smoking or body mass index (BMI), did not have a large effect on the air pollution/preterm delivery relationship in their cohort and that existing variables on the birth certificate were apparently sufficient to control for potential confounding by these factors. However, they did note that other factors being more closely examined in future studies (time activity patterns) may have a larger impact on the effect estimates, either as confounders or as inputs into more precise exposure measures. A study from Germany reported that the covariates of maternal height, education, and gestational age had the largest effects on the estimated relationship between air pollution and birthweight based on comparison of adjusted and unadjusted models (Slama et al., 2007). A study of the potential confounding effects of smoking found that while maternal smoking was a risk factor for respiratory-related infant mortality, it did not confound the PM and infant mortality relationship (Darrow et al., 2006).

Confounding from unmeasured factors could depend upon the (spatial or temporal) resolution of the exposure model. For example, in a study in Connecticut/Massachusetts, air pollution was averaged at the county-level (Bell et al., 2007), corresponding to a comparison of different exposures within a county (e.g., different timeframes of births) as well as to a between-county comparison and thus estimated air pollution associations could be confounded by factors that also vary within the county (for example, certain personal characteristics). However, the relationship between PM and birthweight was similar to a study in Los Angeles using a smaller geographic area (zip code) (Wilhelm and Ritz, 2005). Effect-measure modification may be more difficult to identify over broad geographic areas which could also influence observed results (e.g., effect modification by race) though in some studies with relatively large spatial exposure scales still find effect modification by race (Bell et al., 2007). Some of these factors which differ among women, such as race and education, can be controlled for within an analysis, but other unconsidered factors, such as place-specific factors (e.g., neighborhood related) or individual factors (e.g., income), could still have an effect, either as confounders or effect modifiers.

An issue related to the scope of geographic coverage used in the studies is the potential for selection bias when mothers are excluded from the study because they are not living near monitoring locations. Studies vary in how exposure metrics are constructed from air monitoring data, with some using administrative units such as county or postal codes areas, and others constructing exposures directly for maternal residences. In either case, mothers living near monitors may differ from those living far from monitors (Basu et al., 2004; Slama et al., 2007; Parker and Woodruff, 2008). Agreement on whether geographic scope of constructed metrics of air pollution exposure contributed to selection bias was not reached; some workshop participants thought the inclusion of mothers living near monitors affected generalizability rather than bias.

It was also noted that it is important to consider the larger geopolitical context. The studies to date have primarily been done in industrialized countries, such as Australia, Canada, the US and Europe, where the sources and levels of pollutants are much different from non-industrialized countries. The impact of air pollution is likely to be much larger in non-industrialized countries, which have poorer air quality and more vulnerable populations. However, understanding the impacts of pollution on perinatal health in non-industrialized countries may be particularly complicated as confounding factors (diet, socioeconomic measures, co-morbidities, etc.) and contributions from other air pollutant sources, such as coal and indoor fuel use, probably have wider within-population variation than in the developed countries.

4.1. Next steps

One possible tool to clarify the role of intrinsic and extrinsic risk factors on the exposure-outcome relationship is to create a conceptual framework for distinguishing confounding variables from those on the causal path; for example, if air pollution is related to birthweight, in part, via a measured maternal outcome, such as pregnancy-induced hypertension, then controlling for hypertension (or excluding those records) in an analysis may lead to biased inferences. Essentially, there is difficulty in distinguishing between the possible direct effects of air pollution on fetal growth and the possible effects of air pollution on other pregnancy factors, which in turn can be independent risk factors of fetal growth restriction and/or make pregnancies more susceptible to air pollution. Pregnancies which are predisposed to poor pregnancy outcomes may form susceptible subgroups with increased vulnerability to air pollution or may have poor outcomes independently of air pollution. In other words, assessing air pollution effects among a potentially susceptible subgroup defined by a specific condition predisposed to adverse birth outcome requires care to disentangle any air pollution effects from effects of other factors related to the condition (e.g., severity of a condition, amount of exposure to other agents). To date, few studies have evaluated potential intermediate outcomes.

As in other epidemiological studies, even within a hypothesized conceptual framework it is difficult to assess the extent of residual confounding that may remain after control for available covariates, so the plausibility of the phenomenon being investigated is critical. Plausibility of residual confounding by poorly measured or unavailable covariates should also be considered by investigators in the context of each study location and design. Some assessment of plausibility must come through the investigator's experience and the weight of scientific evidence, although quantitative assessment of the underlying assumptions using sensitivity analyses is also critical. Clinical and/or animal studies would provide useful information on intrinsic and extrinsic risk factors that may influence air pollution and perinatal outcomes.

While the role of effect-measure modification in studies of air pollution and birth outcomes was not discussed thoroughly, it was mentioned that large data sets may be needed to sufficiently identify all subgroups of interest and assess effect-measure modification, though given a strong enough effect, smaller numbers could be used to identify differences. These data sets, if obtained from broad geographic areas, have an added advantage of wider exposure variation for analysis. However, large data sets tend to have fewer variables available for confounder control, and wider geographic coverage can increase the heterogeneity of the sample and thus increase the risk of residual confounding.

The following specific recommendations were suggested to further address potential issues of confounding:

- Consider time-series or temporal studies, as appropriate, which are less vulnerable to confounding by personal characteristics not varying in time.
- Compare characteristics and results for mothers residing at varying distances from air monitors to investigate the possible effects of choosing different study samples on results (e.g., Basu et al., 2004; Slama et al., 2007; Parker and Woodruff, 2008).
- Use a two-phase design and augment the large data sets with additional covariate information from a survey for a subset of the births. This detailed covariate data can be used to further assess potential confounding factors on the estimated relationships within the context of the larger data set.
- Identify natural experiments where locations experienced large changes in air pollution levels to assess changes in birth outcomes.
- Use matched birth records of siblings where underlying maternal characteristics may be similar but exposures may differ for subjects.
- Explore implications of less-commonly considered potential confounding factors such as house size, where a larger house is an indicator of wealth but could also affect air pollution exposure through various mechanisms, such as differing construction quality or air volume.
- Consider area-level indicators of potential confounders, such as area level median income or housing characteristics.

5. Defining exposures: spatial and temporal exposure assessment

Because pollution monitors are not sited everywhere people live and do not always provide continuously measured data (i.e., PM_2.5 in the US is often measured every 3–6 days, whereas other pollutants such as CO are measured hourly), there is a growing literature on the use of spatial and temporal models to predict air pollution exposure for places and times without monitoring data. Although the combination of both the spatial and temporal components of exposure variability has increased the statistical challenges for exposure estimation, for studies of air pollution and pregnancy outcome, spatial and temporal exposure models could improve exposure assignments. This could be accomplished by considering both the mother's residential locations and the timing of relevant periods of pregnancy in the predictions. Banerjee et al. (2003) and Diggle and Riberiro (2007) provide statistical overviews of these models; Slama et al. (2007) and Brauer et al. (2008) provide examples of land-use regression model-based exposure estimates in perinatal studies.

The Particulate Matter and Perinatal Events Research (PAMPER) study provides an example of how to consider spatial and temporal exposure surfaces for a health study (Fanshawe et al., 2008). The study was designed to examine associations between maternal exposure to black smoke and birth outcomes in Newcastle upon Tyne, England over a 32-year period starting in 1961. Since few monitoring data were available for black smoke, an important aspect of determining exposures was model black smoke predictions and their associated variances so that both could be used when assessing the strengths of the associations between black smoke and birth outcomes. In the case of the PAMPER study, temporal variation was more important than spatial variation for exposure predictions because of the long study period with a dramatic decline in black smoke levels. Strong seasonal patterns of the exposure over time also necessitated the development of flexible prediction models that allowed for locations and magnitudes of seasonal trends to vary annually. Additionally, "constructed covariates", surrogate measures of pollution sources that correlate well with exposure when there is insufficient exposure data, were found to be a practical way to reduce residual spatial-temporal correlations and allowed for less complicated model structures. As an example, chimney density was found to be a good predictor of black smoke in the PAMPER study. Surrogate measures may be appropriately used either to improve spatial-temporal models or as exposure indicators in epidemiological analyses. Using validated indicators on their own in an analysis is important, as air pollution data may not be available in all locations of interest. Other recently used exposure surrogates include traffic-use patterns, distance to roadways, and land-use patterns (Slama et al., 2007; Wilhelm and Ritz, 2005).

Another aspect to assessing exposures is the role of season in analytic models, especially if spatial/temporal prediction models are fitted seasonally. Season can represent many things, including variations in temperature and other weather patterns, allergy susceptibility, food availability, and environmental exposures (pesticides, water quality), any of which may contribute to observed geographic differences in associations between season and birth outcomes (e.g., Chodick et al., 2007; Matsuda et al., 1995; McGrath et al., 2005;]Rayco-Solon et al., 2005). Some seasonal factors that differ geographically - such as nutritional status - vary throughout the year in many locations but probably have greater impacts in non-industrialized than in industrialized countries. Other factors, such as temperature, can also differ geographically, but with different patterns (e.g., California versus Northern New England). In addition, just controlling for season may not fully account for the effects of some seasonally-varying factors. Temperature, for example, which varies with season, may need to be specifically accounted for in an analysis as variations in temperature within a season may be important, though temperature has not been thoroughly evaluated as a potential risk factor. Consequently, importance of season-related variables in air pollution studies likely differs by birth outcome and location under investigation.

5.1. Next steps

5.1.1. Spatial scale—The importance of temporal and geostatistical modeling for exposure assessment depends on the study's context, such as length of study period and the magnitude of the spatial and temporal variation of the pollutant being studied. In some cases, area-level average air pollution data may be sufficient enough to represent individual-level exposures, such as chronic exposure to pollutants that are evenly dispersed over relatively large geographic areas (e.g., coarse PM), for example, using average air pollution concentrations within a political unit, such as county. In other cases, modeling exposures at a finer scale will be more important. Different methods of exposure assignment capture different aspects of pollution. Some pollutants are spatially heterogeneous on a smaller scale and may be very sensitive to exposure definitions (e.g., CO, ultrafine particles), whereas others are more homogenous and can be represented by larger spatial averages (e.g., $PM_{2.5}$). Furthermore, some underlying pollution sources vary more locally, others more regionally (e.g., traffic as a contributor to area-level averages, wood smoke, industrial sources). It was hypothesized that smaller scale studies may be better for understanding biological mechanisms and contribute more information for local policies while larger scale studies may be better for looking at population-level factors and may be better for regional policy. However, the relative importance of small and/or large scale geographic areas in the study of air pollution and perinatal outcomes has not been systematically examined.

5.1.2. Surrogates—Surrogate measures of pollution may be important in the development of spatial and temporal prediction models, especially surrogates that incorporate seasonal trends and are relatively inexpensive to obtain. Monitoring network locations are sited for policy and regulatory purposes, not for health studies. Consequently, they are useful, but not ideal, for epidemiological investigations, and additional monitoring in targeted locations may not be possible for all studies. Several surrogates were mentioned or suggested, such as the chimneys in the PAMPER study, traffic patterns, and other characteristics used in land-use regression models. Satellite maps have potential for providing surrogate information for air pollution levels but can be limited due to various factors, such as weather (e.g., no measurements during cloudy days) and weekly reporting patterns. Surrogate measures of pollution obtained from non-conventional sources could also be used directly in epidemiological studies as alternatives to monitoring data or as inputs into prediction models; an initial list of proposed surrogate devices include contact lenses (which capture particle pollution), sleep apnea monitors (which have a filter that could be analyzed for air pollution), and house plants (which capture certain types of air pollution such as metals).

The potential influence of residual spatial and temporal correlation in analytic models was also considered. Workshop participants who had examined this issue did not report serious autocorrelation problems in their analyses; however, no comprehensive evaluations were mentioned and may be warranted. As mentioned above, the use of strong surrogates can reduce the need for more complicated models of spatial and temporal correlation.

5.1.3. Season—Further evaluation of the role of season and whether it is independently associated with birth outcomes, whether it is a surrogate for other factors that are associated with birth outcomes (e.g., temperature, food availability, etc.), whether it is a proxy for pollution exposure, or whether it may not be a confounder at all in certain locations was identified as an important area of further research.

The following specific recommendations were suggested to further address issues related to spatial and temporal exposures:

- Systematically assess the relative contributions of using small and large geographic scales to assess air pollutant exposures and any subsequent influence on effect estimates.
- Further evaluate and validate exposure surrogates or alternative exposure metrics.
- Evaluate the potential influence of spatial and temporal autocorrelation.
- Evaluate the most appropriate way to address season in different types of studies —this includes a better understanding of the implications of season as a variable in perinatal studies given the seasonal trends in births, air pollution exposures, and many other factors; both statistical approaches and seasonal indicators need to be explicitly examined.

6. Exposure windows

The third area of methodological challenge is identifying whether there are particular periods of susceptibility during pregnancy when air pollution exposure is particularly harmful to fetal health and development. Early pregnancy could be one time of enhanced susceptibility, as this is when placental attachment and development occurs, or susceptibility may increase toward the end of pregnancy when the fetal growth velocity is highest. Evaluating periods of susceptibility can provide insight into potential biological mechanisms and allow for defining more accurate measures of effect as the exposure estimate of interest can be more precisely defined. Most published studies have primarily focused on evaluating exposure by trimester, though a few have also assessed exposure by gestational month. The literature on air pollution and preterm delivery or growth restriction to date, has not identified a specific time window of susceptibility. In studies of fetal growth, some studies have reported effects due to first trimester exposures, while others report effects only for third trimester exposures (Table 1). Fewer studies report effects from second trimester exposure, and some report effects for more than one trimester of exposure. Findings are similar for preterm delivery. Some of the apparent differences by trimester may be due to the varied methods used to consider (or not consider) correlated exposures among trimesters or pollutants.

Identification of a particular window of susceptibility is difficult. If air pollution is associated with growth restriction or preterm delivery, yet there is no particular critical window, then the trimester (window) of exposure that will appear to be important is that which is most highly correlated with whole-pregnancy exposure. In addition, it is difficult to distinguish one trimester from other time periods as being important because exposures among the trimesters are correlated. In studies of preterm delivery, additional care is needed to define windows of exposure given the shorter length of pregnancy for the preterm compared to the term births (e.g., Huynh et al., 2006; O'Neill et al., 2003).

There are several new ideas that could provide insight into this issue. A recently applied method used by Bell et al. (2007) was highlighted as a potentially useful approach to simultaneously adjust for all trimester-specific exposure variables. In this study, exposure during each trimester was modeled as a function of exposure in the other trimesters, and the residuals from these trimester specific models were included in the subsequent trimester-specific regression models to control for other trimesters' exposure. The use of post-pregnancy exposure as a control category to examine the robustness of the whole or partial-pregnancy exposure has also been suggested (Slama et al., 2007); specifically, if whole-pregnancy exposure is an etiologically relevant window, then the pregnancy exposure variable should be more consistently associated with pregnancy outcome than the post-pregnancy exposure. A limitation to this approach is that observed associations between post-pregnancy exposure and pregnancy outcome may be due to a high correlation between post-pregnancy and within-pregnancy air pollution exposures.

6.1. Next steps

Trimesters have been used to define pregnancy periods for decades, but do not completely correspond to critical windows of fetal developmental. Periods of susceptibility depend on the outcome being evaluated; for example, potentially relevant exposure periods for congenital anomalies, in particular, differ from those for fetal growth or preterm delivery. Thus, using trimesters to define exposure windows could inaccurately define periods of susceptibility.

It was recommended that exposure windows shorter than trimesters (mostly gestational months) should be evaluated in epidemiological studies to try and capture more relevant fetal development periods. However, it was recognized that trimester-level results offer some comparability with existing studies, as this is the most common exposure window used, easing research synthesis. If shorter time exposure windows are used, it is important to consider that the accuracy of exposure metrics may differ by the size of the exposure windows. For example, shorter windows, such as a month, may entail larger exposure misclassification when frequent measurements are not available (i.e., in areas where PM is monitored every 6 days) compared to longer windows, such as the entire gestation. In addition, the question was posed whether it matters if the fetus is exposed early and late in pregnancy or just early or just late. The evaluation of different patterns of exposure throughout pregnancy was identified as important. Particularly in studies using short time frames, such as weeks, the non-linear pattern of fetal growth and development should be considered, although a particular method for accomplishing this was not defined. A large number of windows to be examined can lead to a multiple comparisons problem; to minimize the occurrence of random findings, one suggestion was to identify potential windows of importance *a priori* through animal experiments. Considering shorter and longer windows of exposure will inform considerations of the importance of acute and chronic exposures.

Defining more narrow windows of susceptibility requires some confidence in the gestational age, which is typically taken from the birth certificate, and in some locations, may be less precise than birthweight because it is based on recall of last menstrual period (e.g., many areas in the US). One possible approach to more precisely measure gestational age is to use data from fertility clinic-based studies, where exact dates of conception are known, and pre-conception exposures can be studied, including paternal exposures. However, it was noted that the high correspondence between paternal and maternal (non-occupational) exposures makes separating parental effects difficult when personal exposure estimates are not available. One drawback to fertility clinic records is that pregnancies resulting from assisted conception are at higher risk of adverse birth outcomes than naturally conceived pregnancies, which would reduce the generalizability of the results (Reddy et al., 2007). Nevertheless, while fertility clinic populations may be unique, their detailed data may offer important insights into gestational age issues related to windows of exposure.

Although human fetal development differs from other species, animal studies might be informative in understanding vulnerable windows; the current toxicological and biological knowledge for air pollution impacts on human health is limited and is particularly limited for reproductive outcomes. Animal studies may be particularly useful for studying effects of high exposures during specific pregnancy periods.

The following specific recommendations were suggested to evaluate potential periods of susceptibility:

- Exploring other potential periods of susceptibility besides trimesters, in particular shorter ones, such as gestational months (keeping in mind for pollutants not monitored daily, the fewer available monitored values). Further, examining exposure over time as a continuous rather than categorical metric, and considering peaks of exposure, may increase our understanding of windows of vulnerability.
- Applying comparative analyses across different study populations with efforts toward similar methods and definitions of both windows of exposure and outcomes represents a promising approach to resolve some of the inconsistencies observed in the literature.
- Identifying relevant gestational windows of susceptibility by outcome. This identification will likely be informed by general perinatal (e.g., risk factors other than environmental contaminants) and toxicological studies.

7. Multiple pollutants

A fourth issue in evaluating the existing air pollution and perinatal outcomes literature is the variability in the types of air pollutants evaluated and which individual pollutants or combination of pollutants are identified as the pollutant(s) associated with the perinatal outcome. Existing studies in the US primarily assessed exposures to “criteria” air pollutants (particulate matter, ozone, carbon monoxide, sulfur dioxide, nitrogen dioxide), with most studies evaluating exposure to particulate matter (both $PM_2.5$ and PMi_0), ozone, carbon monoxide, nitrogen dioxide, and to a lesser extent sulfur dioxide (Table 1). Assessing which pollutants, if any, are risk factors for poor birth outcomes is complicated by using ambient air monitors for exposure assessment. Ambient air monitoring introduces measurement error into the exposure estimates. In addition, the monitoring schedule for the pollutants varies, as some pollutants such as ozone are reported every hour, and others, such as PM, maybe reported once every six days, which can affect how well the monitoring data represent exposures over shorter periods of times (e.g., weeks).

The workshop focused on two fundamental issues in exposure assessment of multiple pollutants, measurement error and surrogate exposures using four scenarios as examples (Table 2). In general, model results may be very sensitive to measurement error (the difference between measured ambient levels and personal exposure to ambient pollution) and correlations between the pollutants. However, because pollutants are often from common sources it is difficult to separate the etiological agents, the surrogates, and confounders (Tolbert et al., 2007; Sarnat et al., 2001; Kim et al., 2007). Using *a priori* knowledge about the measurement error of the pollutants and their interrelations can help guide interpretation of models for multi-pollutant exposures. Identifying the sources of the pollution and assessing pollution mixtures offer complementary strategies to the more common approach of evaluating specific pollutants individually and may be particularly important if source or the mixture is the important risk factor.

7.1. Next steps

There has been variability in which pollutants have been considered in perinatal studies and how they are considered (individually or simultaneously). An effort to systematically evaluate the contribution of different pollutants across multiple studies using the same methods for specifying exposure metrics could be helpful in evaluating the robustness of findings across different studies.

It was noted that focusing on individual pollutants as the single risk factor is likely not to reflect the effect of combined exposure to multiple air pollutants, and it could be the mixture represents a higher risk than the individual components, similar to tobacco smoke. The primary source of many pollutants is combustion, and one potentially fruitful area of inquiry is to consider the source of the pollutants as the metric for exposure, rather than the individual constituents. The case of tobacco smoke, which is similar to traffic-related air pollution in that it is a mixture of constituents from a combustion source, provides an example of evaluating exposure on a source basis. An additional advantage of a source-based approach is that it is not necessary to identify the individual etiologic components for public health interventions. In the case of combustion, it is a little more nuanced, as there are multiple environmental combustion sources of pollution (e.g., motor vehicle versus wood burning), and knowing the specific components of exhaust responsible for health effects could help regulation and technologies for harm reduction.

To consider combustion sources, a next step is to identify measures of combustion and describe how they differ by source. It was suggested that CO might be a good surrogate for motor vehicle exhaust. The similarity of associations in perinatal studies in Los Angeles over a fairly long time span when CO levels were dropping suggests that some other agent in motor vehicle exhaust that is correlated with CO may be the etiological agent (Ritz and Yu, 1999; Wilhelm and Ritz, 2005; Ritz and Wilhelm, 2008). However, CO is a spatially heterogeneous pollutant, and measured levels at monitoring stations may only reflect concentrations within a small distance of the monitor. Future efforts to identify which pollutants are good surrogates of exposure and using a source-based approach are important areas for future research.

It was noted that there could be a synergistic response from exposure to multiple pollutants. Understanding this effect would require different study designs or analytical strategies than those that have been used to date. It was suggested that creating informal graphical models of different multiple pollutant scenarios, including supplemental information on the specific pollutants, would help direct future studies (Woodruff et al., 2003). These models would be more consistent with an interval estimation framework (e.g., credible intervals in a Bayesian context as discussed in Dunson, 2001; Gelman and Hill, 2007) than significance testing or p-values. Small validation studies of pregnant women (e.g., assessing personal-ambient exposure correlations) would help researchers disentangle the influences of multiple pollutants and identify which pollutants act as etiologic agents, confounders, and/or surrogates.

As noted above, there is a tendency for multiple pollutant studies to focus on regulated, and routinely monitored, common air pollutants, even though these pollutants may not be the only pollutants of etiologic interest. In the United States, measurements of PM, O_3, NO_2, SO_2 and CO are readily available for many urban areas, although every pollutant is not monitored in all locations. Other air pollutants, such as those listed as hazardous air pollutants under the Clean Air Act, should also be examined. For these pollutants, there is less wide-spread monitoring data readily available. The increasing use of modeled exposure data may promote studies of other air pollution indices, and these data are available for several years for the hazardous air pollutants in the United States (information available at http://www.epa.gov/ttn/atw/natal999/).

Workshop participants further recommended:

- Incorporate indicators of exposure precision into statistical models explicitly rather than speculating on effects of measurement error; this is important for both model-based estimates and also for the exposure estimates based on temporal and spatial averaging of ambient air monitoring data (Van Roosbroeck et al., 2008).
- Evaluate the effect of residential and occupational mobility during pregnancy, which can affect exposure estimates based on maternal address at birth.

8. Summary and conclusion

The research of air pollution and perinatal outcomes is a rich and growing field. The evidence to date suggests that air pollution may play some role in adverse pregnancy outcomes, and the importance of pregnancy outcomes in future health of the child make air pollution an important area of further inquiry and intervention. Perinatal outcomes have only been recently considered in policy and regulatory activities related to air pollution, and their contribution as a source of preventable disease could be substantial internationally. In this paper, we explored four areas of methodological interest that the workshop planning committee identified as varying among the published studies to date and/or were thought more likely to contribute to the variation in the findings in the epidemiologic literature. We provided recommendations specific to these areas to move this field forward and extend the discussions and recommendations from a previous workshop on the broader topic of air pollution and reproductive outcomes (Slama et al., 2008a).

To leverage the existing literature to date, participants noted the importance of collaboration among researchers in different countries worldwide who have been investigating this phenomenon. In addition to the topic-specific suggestions above, participants made several general recommendations for future research priorities to better elucidate the role of air pollution and perinatal outcomes.

- A key next step would be to develop an international collaborative among researchers in the field to apply the same or similar methods to analyzing the existing data sets. Some of the methodological differences identified at the workshop included gestational exposure windows, the set of adjustment variables (including co-pollutants), use of seasonal variation, and spatial resolution. Applying a consistent analytic strategy across many data sets may help to reconcile some of the apparent inconsistencies in effect estimates observed across studies. Furthermore, this type of research synthesis would help in guiding policy.
- Participants noted that it is critical to identify animal and cell studies to inform each of the areas discussed above. In particular, animal studies can be used to inform gestational windows of susceptibility to air pollution, reproductive endpoints that are difficult to ascertain with available epidemiological data (e.g., miscarriage, placental development), and specific pollutants or pollutant mixtures of etiologic interest. These studies can also be used to evaluate more precise measures of exposure in a homogenous population. Collaborating more closely with toxicologists to develop a priority list of experiments was noted as an important next step.
- Expanding the types of outcomes considered in studies, including fetal loss (both as a pregnancy outcome and as a potential bias in studies of live births) and pregnancy related hypertension or preeclampsia, may provide insights into both mechanisms and other susceptible outcomes.

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The findings and conclusions in this paper are those of the authors and do not necessarily represent the views of the US Centers for Disease Control and Prevention or the US Environmental Protection Agency. To focus the report, an effort was made to represent the conversation during the workshop. However, particular points raised and noted here may not be universally agreed upon by all participants; time constraints did not allow for all counter points to be made during the workshop.

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Table 1

Twelve studies[a] examining fetal growth and air pollution: number of studies examining a particular pollutant and, of these, the number of studies reporting associations between fetal growth and trimester-specific exposure, 2004–2007.

Pollutant	Number of studies	Trimester-exposure reported as significantly associated with fetal growth		
		First	Second	Third
PM_{10}	9	1	2	2
$PM_{2.5}$	5	3	2	3
CO	9	5	2	4
O_3	8	0	1	1
NO_2	9	3	3	3
SO_2	6	2	0	1

[a]Bell et al., 2007, US; Dugandzic et al., 2006, Canada; Gouveia et al., 2004, Brazil; Hansen et al., 2007, Australia; Lin et al., 2004, Taiwan; Liu et al., 2007, Canada; Mannes et al., 2005, Australia; Medeiros and Gouveia, 2005, Brazil; Parker et al., 2005, US; Salam et al., 2005, US; Slama et al., 2007, Germany; Wilhelm and Ritz, 2005, US. (Bell et al., 2007; Dugandzic et al., 2006; Gouveia et al., 2004; Hansen et al., 2008; Lin et al., 2004; Liu et al., 2007; Mannes et al., 2005; Medeiros and Gouveia, 2005; Parker et al., 2005; Salam et al., 2005; Slama et al., 2007; Wilhelm and Ritz, 2005).

Table 2

Different interpretations of the same multi-pollutant regression model under four different scenarios of two correlated pollutants, pollutant1(P1) and pollutant(P2).

Scenario	Specifications	Pollutant 1	Pollutant 2	Interpretation
1	Well measured? Effect on outcome?	Well measured Etiologic agent	Well measured Not etiologic agent	Results from a multi-pollutant model are more valid than those from single-pollutant models because the apparent effect of P2 is confounded by P1
2	Well measured? Effect on outcome?	Well measured Etiologic agent	Well measured Etiologic agent	Estimated effects for each pollutant may be confounded by the other, multi-pollutant models may provide better estimates of effect size
3	Well measured? Effect on outcome?	Poorly measured Etiologic agent	Well measured Not etiologic agent	Becauseofthemeasurementerror[a] in thisscenario, thesurrogate (P2) mayappearmorepredictivethantheagent(P1)andwould lead ustothewrongconclusions
4	Well measured? Effect on outcome?	Poorly or well measured Not etiologic agent Correlated with unmeasured etiologic agent	Poorly or well measured Not etiologic agent Correlated with unmeasured etiologic agent	Multi-pollutant models may identify the better surrogate, but can be misleading if the goal is to identify the etiologic agent

[a]The difference between measured ambient levels and true personal exposure to ambient pollution.