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Surveys

Residential exposure to traffic emissions and adverse pregnancy outcomes

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Abstract

Motor vehicle traffic emissions are the single largest contributor to ambient air pollution in many developed countries and it has been suggested that these emissions can affect outcomes of pregnancy. An individual's exposure experience is greatly influenced by where they live as emission concentrations are much higher closer to roads.

A systematic review was conducted using the MOOSE guidelines in order to synthesise studies published 1989-2009 which investigated pregnancy outcomes in relation to residential exposure to traffic emissions. Twelve studies met the inclusion criteria and were consequently reviewed. We identified exposure assessment methods and the scope of health endpoints that have been investigated.

Gestational duration, intrauterine growth, mortality and pregnancy complications have been studied using simple distance, distance-weighted traffic density, annually averaged daily traffic counts, dispersion models and land-use regression models. Few studies investigated mortality and pregnancy complications and no study investigated the risk of congenital anomalies. The evidence to date suggests an adverse effect was consistently reported for gestational duration and less consistently reported yet plausible for intrauterine growth. However, the small number of studies, the possibility of publication bias and the limited research conducted on biological mechanisms precluded more formal statements on the existence of an effect.

The ubiquity of motor vehicle traffic emissions, the biological vulnerability of the fetus, and the adverse associations detected among many of the twelve reviewed studies motivates a multi-disciplinary collaborative effort toward further research on the topic.

Keywords: Motor vehicle, traffic, emissions, birth, pregnancy, environmental epidemiology.

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1. PREFACE

Motor vehicle traffic emissions are the single largest contributor to ambient air pollution in many developed countries. The adoption of cleaner fuels and the installation of catalytic converters in motor vehicles have initiated a secular improvement in air quality according to statutory monitoring, introduced to keep track of background levels and industrial pollutants. However, human exposure to the toxicants present in motor vehicle emissions is inadequately characterised by such monitoring. Intuitively, emission concentrations are much higher closer to roads than further away from roads. Therefore, an individual's exposure experience is greatly influenced by where they live, and the air pollution standards adopted by governments for wide areas can not be applied at this local level.

The ubiquity of traffic in an urban environment leads to unavoidable long-term exposure resulting in the accumulation of toxicants in the body. The potential of these toxicants to cause an adverse health outcome is greatest during vulnerable periods such as pregnancy, infancy, very late adulthood or when the immune system has been suppressed by pathogens. From a medical perspective, a particularly vulnerable period in life is the time spent in utero, when organ systems develop and the immune system is not fully functional. From an epidemiological standpoint, a comprehensive study of the effects of traffic emissions during pregnancy is uniquely positioned as most countries either have access to comprehensive clinical records for births or have access to administrative by-product data such as birth certificate records. Such studies may be backed by toxicological evidence, particularly when overlaps exist with tobacco research. For instance, carbon monoxide is a toxicant common to both cigarette smoking and inhaling vehicle emissions. Environmentally, the atmospheric chemistry and dispersion of traffic emissions from roads is well understood. Additionally, technological developments in the field of Geographic Information Systems (GIS) have led to greater accessibility and a concomitant push for health data that is accurate to residential addresses, rather than aggregate areas. The socioeconomic determinants of adverse birth or pregnancy outcomes and activity patterns during pregnancy must also be determined. Such broad scope warrants an interdisciplinary approach.

The overarching objective of this analysis was to motivate further research on the topic of adverse pregnancy outcomes in relation to residential exposure to motor vehicle traffic, preferably through interdisciplinary collaboration.

2. BACKGROUND

In many developed nations, motor vehicle use is increasing and emissions from motor vehicles have been identified as the largest single contributor to urban air pollution (Jensen 1998). There is increasing evidence to support the hypothesis that exposure to traffic-related ambient air pollution defined at the wide-area level is associated with adverse health outcomes at birth (Sram, Binkova *et al.* 2005; Hansen, Neller *et al.* 2006; Ritz, Wilhelm *et al.* 2007; Ritz and Wilhelm 2008). Although there is some evidence that links air pollution to preterm delivery (PTD) and intrauterine growth restriction (IUGR), past systematic reviews have concluded that the level of evidence is insufficient at present (Glinianaia, Rankin *et al.* 2004; Maisonet, Correa *et al.* 2004; Sram, Binkova *et al.* 2005). Even so, the existence of positive findings highlights the potential vulnerability of the fetus to traffic-related environmental pollutants; partly as a result of an immature immune system that is less capable of removing such toxicants (Perera, Jedrychowski *et al.* 1999).

The term 'vehicle emissions' can be defined as the set of all traffic-related pollutants emitted directly by motor vehicles. Theoretically, this definition may encapsulate all related emissions: fuel vapours, tyre and road particulate matter (PM), as well as excessive noise and light. More commonly, vehicle emissions are characterized by exhaust emissions. These emissions are the outcome of combustion processes and include metals and polycyclic aromatic hydrocarbons (PAH) each of which may be adsorbed to ultra-fine particulates (UFP, defined as PM with aerodynamic diameter less than 0.1μm), and certain criteria pollutants such as carbon monoxide (CO), nitric oxide (NO), nitrogen dioxide (NO_2) and larger particulate matter. In practice, the specificity of criteria air pollutants as an indication of exposure to vehicle exhaust is reduced by the existence of other non-traffic sources of these pollutants such as natural, industrial, indoor, occupational and other anthropogenic sources. Seasonal fluctuations and photochemical reactions also influence the levels of these pollutants in the atmosphere. For example, although some NO_2 is present in exhaust gases, the greatest proportion of the nitrogen oxides (NO_x) in vehicle exhaust exists as NO which quickly reacts to produce NO_2. Conversely tropospheric ozone (O_3) is a criteria air pollutant that is not present in exhaust gases but is formed from the combination of NO_x and volatile organic compounds (VOC), both of which are constituents of vehicle exhaust. Therefore, a wide-area study that relies on measurements of criteria pollutants obtained from background monitoring stations may only adequately represent

exposure to *traffic-related* ambient air pollution rather than exposure to the primary emissions. That is, the background levels measured by environmental air monitoring stations may adequately represent the variation in secondary pollutants, such as tropospheric O_3 and secondary particulates. However, it is important to consider localised spatial variability for other pollutants, particularly the constituents of primary emissions.

Historically, studies have tended to use wide-area estimates of individual pollutants based on data obtained from environmental air monitoring stations (Wilhelm and Ritz 2005; Rankin, Chadwick *et al.* 2009). However, the spatial variability of certain traffic-related air pollutants is paramount (Slama, Darrow *et al.* 2008; Woodruff, Parker *et al.* 2009). Several studies have shown significant spatial contrasts in concentrations of air pollutants near major roads. It has been demonstrated that concentrations of NO_2 decrease as distance from the highway increases, and that the major decrease occurred within 200m of the highway (Gilbert, Woodhouse *et al.* 2003). Furthermore, it has been shown that both PM with an aerodynamic diameter of less than 2.5 microns ($PM_{2.5}$) and soot concentrations were 20% and 50% higher at 50m than 400m from the motorway, respectively (Janssen, van Vliet *et al.* 2001), and that the concentration of UFP can drop to approximately half between 90m and 150m from a freeway, compared with those at origin (Zhu, hinds *et al.* 2002). Perhaps as a result of such spatial contrast, studies that have relied on wide-area measurements of air pollutants/toxicants such as PM, NO_x and VOC have yielded mixed results (Glinianaia, Rankin *et al.* 2004; Maisonet, Correa *et al.* 2004; Sram, Binkova *et al.* 2005; Hansen, Neller *et al.* 2006; Hansen, Barnett *et al.* 2008), prompting the use of measures that adequately capture the localised variation in exposure.

The localised variation in exposure may be more adequately captured by the measurement or modelling of primary traffic emissions at finer spatial scales. Candidate indicators of primary traffic emissions include lead (Pb), CO, NO_x, UFP and PAH. Vehicles can be responsible for almost all of the Pb and CO pollution and around half of the hydrocarbons and oxides of nitrogen (Department of Environmental Protection 2000). There is also evidence that motor vehicle traffic is the main contributor to both fine and ultra-fine particles (Zhu, hinds *et al.* 2002). Vehicle exhaust is the largest contributor to PAH emissions in highly urbanised areas, with benzo*[ghi]*perylene a possible marker PAH for petrol (gasoline) vehicles (Bostrom, Gerde *et al.* 2002; Hyunok, Rauh *et al.* 2008). In order to capture the local variation in exposure, these primary traffic emissions need to be measured or modelled on a fine spatial scale. In terms of accuracy in the context of other typical exposure assessment methods, spatially defined exposures lie below those based on personal monitoring and biomarkers, but above those based on wide-area estimates. However, they may be more desirable in terms of specificity as a marker for traffic exposure.

The increasing use of GIS in environmental epidemiology has enabled recent research to shift from using exposures defined using wide-area metrics to those that capture localised spatial variability, usually defined in relation to residential location. Typically, GIS can be used to model primary traffic emissions at fine spatial scales or be used to calculate proxies for exposure. Restriction to a review of studies that explicitly assessed residential exposure to traffic emissions necessitates the inclusion of those that applied *traffic-proximity* proxies for exposure; distance to a road being the simplest form. Computationally intensive traffic-proximity measures of exposure usually necessitate the use of GIS. *Distance-weighted traffic density (DWTD)* is calculated by obtaining traffic counts from road segments about a residential address and then aggregating these counts after weighting by distance. DWTD is a distance-weighted traffic volume, rather than a density of traffic over an area. As the distance between the residence and a road increases the weight smoothly approaches zero using a function which assumes that 96% of the traffic exhaust emissions disperse at 152.4m (500ft) from the road according to a Gaussian distribution equation (Pearson, Wachtel *et al.* 2000). Traffic-proximity measures of exposure inherently represent exhaust emissions, fuel vapours (PAH, NO and ammonia), tyre and road PM (such as latex and zinc), as well as excessive noise and light that may be associated with closer proximity to roads frequented by traffic. In some locations, traffic-proximity is also a marker for spatial gradients in socioeconomic status (Lipfert, Wyzga *et al.* 2006).

More sophisticated methods of characterising the localised variability of traffic emissions have also been developed. *Dispersion models* characterise the path and concentration of motor vehicle pollutants as they are emitted from the roadway. These deterministic models require a considerable amount of information: emission factors, road attributes, meteorological information, atmospheric mixing heights and spatio-temporal traffic distributions. More recently, a stochastic method commonly known as *land-use regression (LUR)* has emerged. This method employs multiple linear regression to develop a predictive model for a specific air pollutant based on characteristics of the area surrounding the residential address. These characteristics are used as explanatory variables and typically include traffic counts, population density and land-use information (Briggs, de Hoogh *et al.* 2000). The predictive model is developed using measured pollutant concentrations at a number of fixed sites, used as the response variable. The model is then applied to the addresses of the subjects of the study in order to calculate the expected concentration at that location. Often used in LUR models are NO, NO_2 and $PM_{2.5}$, as they are amongst the most widely available and appropriate indicators of traffic emissions at the localised (street or block) level (Brauer, Hoek *et al.* 2003; Cyrys, Hochadel *et al.* 2005; Morgenstern, Zutavern *et al.* 2007). Less common has been the application of LUR to PM_{10}, elemental carbon, and the benzene, toluene, ethylbenzene and xylene (BTEX) group of VOC (Hoek, Beelen *et al.* 2008).

It is advantageous to explore different exposure assessment methodologies in relation to their ability to detect such associations. A thorough comparison of exposure methods ideally requires a suitable number of qualitatively homogeneous studies applied to the same study population. This is often not the case as environmental

epidemiological studies generally apply different designs, applied to different populations, and control for different factors. Studies may also apply different indicators for the same general health outcome. Studies may also apply different techniques for the estimation of residential traffic exposure. Such heterogeneity impedes a formal meta-analysis. However, for a research topic in its infancy, this diversity may be considered advantageous as it can be used to steer the direction of future research.

Under the assumption that a biological effect does indeed exist, some information may be gleaned by identifying those methods that have been applied in a past study and have successfully detected an association, particularly when the same study incorporates multiple methods to characterise exposure. Categorising the health outcomes into broad classes may either enable the identification of the *type* of health outcome which is influenced by residential exposure to motor vehicle traffic emissions, or may enable the identification of outcomes that have not been studied at all.

3. SYSTEMATIC REVIEW

3.1 OBJECTIVE

The objectives of this review were:

- to identify all pregnancy outcomes that have been assessed in relation to residential exposure to motor vehicle traffic emissions;
- to identify the methods used to assess residential exposure to motor vehicle traffic emissions;
- to synthesise these studies in order to determine whether an adverse association exists between birth or pregnancy outcomes and exposure to motor vehicle traffic emissions; and
- to identify opportunities for further research

3.2 METHODS

In order to identify relevant published papers, the search strategy included all English language articles and published abstracts of studies on human subjects available through Medline, Embase, and the Web of Science (Science Citation Index). To maintain relevance, the search was restricted to papers that were published 1989-2009 to take into account earlier changes in fuel composition and combustion engines. The terms "vehicle emissions" and "traffic" were mapped to subject headings in Medline and Embase respectively. Note that these keywords both map to the same subject headings in the respective databases and are therefore interchangeable. Articles in the Web of Science were searched for "traffic" or "vehicle" in the title fields. The matches were then refined to those which also included "pregnancy outcome" in the subject heading in Medline and Embase, and "pregnan*" in the topic in the Web of Science. Titles and abstracts were then reviewed and selected if they assessed any adverse birth or pregnancy outcome and if they incorporated a residential measure of exposure to traffic emissions. Reference lists of identified papers were also searched for additional publications. All criteria were defined a priori.

Residential exposure was defined in this search strategy as an exposure which is either an indication for traffic volume (e.g. vehicle kilometres travelled), an indication of proximity (e.g. distance to major road), or a traffic toxicant measured at (or modelled to) the maternal residential address. Studies that have used personal monitoring or biomarkers to assess traffic exposure were excluded from the review. To ensure that the exposure estimate is specific to traffic emissions at the residential address, personal monitors would have to be worn or positioned only at the subject's home. Personal monitoring may result in traffic-emission exposure misclassification due to the contribution of indoor air pollution. The use of biomarkers for traffic emissions is more specific to motor vehicle traffic emissions. However, it may be difficult to identify a biomarker that represents a meaningful period of exposure. It is also difficult to ascertain whether exposure defined using biomarkers can be attributed to traffic at the residential address, rather than elsewhere. Therefore, personal monitoring and biomarker studies were excluded from review.

Due to heterogeneity of studies, this review is not presented as a formal meta-analysis. Instead, the methods and findings were synthesised and summarised and key elements of studies presented. The MOOSE guidelines for reporting meta-analyses and systematic reviews of observational studies were adopted (Stroup 2000).

3.3 RESULTS

3.3.1 PREGNANCY OUTCOMES

The literature search resulted in the identification of twelve studies, summarised in Table 1. The pregnancy outcomes that were studied in relation to residential traffic exposure can be classified into four broad topic groups: gestational duration, intrauterine growth, mortality and complications. We found no studies that assessed congenital anomalies. Seven studies each investigated gestational duration and intrauterine growth outcomes but only two studies investigated mortality outcomes or complications of pregnancy.

Preterm delivery was defined as birth prior to 37 completed weeks of gestation counted from the first day of the mother's last menstrual period by all studies that investigated this outcome. Also studied were Moderate PTD (birth before 35 completed weeks of gestation) and Very PTD (birth before 30 completed weeks of gestation) which are indicators of more severe restriction of gestational length (Wu, Ren *et al.* 2009).

Intrauterine growth restriction is broadly defined as an event indicated by a birth weight lower than that expected for a particular gestational duration (Maisonet, Correa *et al.* 2004). The identified studies assessed a range of outcomes that related to intrauterine

growth; including term LBW, term BW and small for gestational age (SGA). The LBW outcome was classified as a birth weight of less than 2500g. Term LBW identified LBW infants that sustained at least 37 weeks of gestation. Birth weight was also investigated as a continuous variable. There were various methods used to identify SGA births. In the Vancouver study, SGA births were defined as lowest decile of birth weights of the cohort, stratified by sex, for each week of gestation (Brauer, Lencar *et al.* 2008). The Montreal study defined SGA births as those less than the 10th percentile based on updated Canadian birth weight for gestational age and sex reference values (Kramer, Platt *et al.* 2001; Généreux, Auger *et al.* 2008). The Rotterdam study defined an infant with SGA at birth as having a z-score for birth weight below -2 (van den Hooven, Jaddoe *et al.* 2009). The study conducted in Eastern Massachusetts defined SGA as the lowest decile of the distribution of birth weights by gestational week, maternal race, and infant gender among all term births (Zeka, Melly *et al.* 2008).

Mortality was assessed in the fetal period as well as the early neonatal period (0-28 days of life). Spontaneous abortion, defined as mortality within the first 20 weeks of pregnancy, was also investigated. Only two studies investigated mortality outcomes (de Medeiros, Gouveia *et al.* 2008; Green, Malig *et al.* 2009).

Pregnancy complications were investigated by two studies (van den Hooven, Jaddoe *et al.* 2009; Wu, Ren *et al.* 2009). Pre-eclampsia was defined by Wu *et al* as the occurrence of three conditions: mild pre-eclampsia, severe pre-eclampsia and hemolysis elevated liver enzymes and low platelets (HELLP) syndrome. Mild pre-eclampsia was defined by blood pressure over 140/90 mm Hg and proteinuria. Severe pre-eclampsia was defined by blood pressure over 160/110 mm Hg with or without signs of end-organ involvement, including oliguria, liver function abnormalities, thrombocytopenia and headache. Van den Hooven *et al* used a similar definition but included eclampsia, which are seizures (convulsions) in pregnant women that are not related to brain conditions, often preceded by pre-eclampsia. Pregnancy-induced hypertension was defined as the development of systolic blood pressure above 140/90 mm Hg without proteinuria after 20 weeks of gestation in a previously normotensive woman. Gestational diabetes was also investigated and defined as the occurrence of a random glucose level above 11 mmol/L, a fasting glucose level above 7 mmol/L or fasting glucose between 6.1 and 6.9 mmol/L with a subsequent abnormal glucose tolerance test, among women without pre-existing diabetes.

3.3.2 STUDY POPULATIONS

Two of the twelve studies were conducted on the same population, which corresponded to births between 1994 and 1996 to women living in Los Angeles County, California (Wilhelm and Ritz 2003; Ponce, Hoggatt *et al.* 2005). Due to the overlap in study populations, the results from these studies can not be interpreted as independent. The other studies spanned independent populations in the Americas, Asia and Europe. No studies were conducted in the other regions of the world, such as Oceania.

3.3.3 STUDY DESIGN

The most common study design was a retrospective cohort design, most likely due to the relatively recent ease of accessibility of large health databases. The number of cases differed considerably among studies, being highly dependent on the study location, design, method of exposure assessment and health outcome. In general, studies that used simple distance (SD) indicators of traffic exposure were able to study larger populations, with the exception being the study conducted in Kaohsiung (Yang, Chang *et al.* 2003). All of the prospective studies were also the most recently published, indicating a possible movement towards this design.

3.3.4 EXPOSURE ASSESSMENT

As residential addresses were not available, the study conducted in Montreal, which assessed exposure using a SD metric, used the postcode as the location of maternal residence, which resulted in spatial exposure misclassification albeit most likely non-differential (Généreux, Auger *et al.* 2008).

Various terms were used to define *major* roads by the reviewed studies. The studies conducted in California investigated proximity to freeways, state highways, primary arterials, secondary arterials and collectors (Wilhelm and Ritz 2003; Green, Malig *et al.* 2009). The study conducted in Rotterdam defined a major road as having at least 10,000 vehicles per day (van den Hooven, Jaddoe *et al.* 2009). The study conducted in Vancouver defined a highway as having 114,000 vehicles per day and a major road as having 21,000 vehicles per day (Brauer, Lencar *et al.* 2008). The study conducted in Kaohsiung investigated proximity to the Zhong-Shan freeway, which was traversed by 93,000 vehicles per day (Yang, Chang *et al.* 2003). In the Montreal study, highways were defined as roads having a maximum speed limit of at least 70 km/h and excluded roads with intersections controlled by stop signs or traffic lights and those designed for low speed operation of motor vehicles (Généreux, Auger *et al.* 2008). The Eastern Massachusetts study defined major highways as roadways with limited access, multiple lanes and no direct intersection with other roads (Zeka, Melly *et al.* 2008).

The DWTD method was applied to population groups in Sao Paulo, Los Angeles and Rotterdam (Wilhelm and Ritz 2003; Ponce, Hoggatt *et al.* 2005; de Medeiros, Gouveia *et al.* 2008; van den Hooven, Jaddoe *et al.* 2009). The DWTD method weights annual average daily traffic (AADT) counts by a Gaussian function that depreciates with distance (Pearson, Wachtel *et al.* 2000). All studies that adopted this method used a function in which traffic counts were allocated a weight close to zero beyond a distance of approximately 150m, resulting in an effective *buffer* radius (Pearson, Wachtel *et al.* 2000). It should be noted that all effect estimates observed by studies using DWTD were reported relative to increments of vehicles per day, using this function, and are therefore derived counts rather than actual counts. The study conducted in Rotterdam also incorporated the length of road

segments into the product with AADT (van den Hooven, Jaddoe *et al*. 2009). This study used variable length road segments rather than partitioning them into sub-segments of equal length, which has been applied in asthma research (Pereira, De Vos *et al*. 2009).

Two other studies characterised exposure using AADT values (Zeka, Melly *et al*. 2008; Green, Malig *et al*. 2009). The study conducted in California investigated maximum AADT values within buffer radii to a maximum distance of 150m, and also investigated the maximum AADT weighted by distance using the same weighting function as that applied by other studies in the calculation of DWTD. The study conducted in Eastern Massachusetts calculated cumulative AADT using a radius of 100m on a grid of locations 200m apart. Bi-linear interpolation was then applied to the cumulative AADT values corresponding to the four grid locations around the residential location. This method is not amenable to a simple interpretation of a convex buffer distance for exposure. However, for a home located at the centroid of a grid square, traffic no further than approximately 241m from the home would be incorporated into the exposure estimate.

Despite being a highly specific marker for motor vehicle traffic emissions, a dispersion model was only applied in the most recent study conducted in Los Angeles (Wu, Ren *et al*. 2009). These models characterise pollutant dispersion from the source locations (roadways) to the receptor locations (maternal residence).

The LUR method was applied to BTEX, $PM_{2.5}$, $PM_{2.5}$ absorbance, NO and NO_2 (Slama, Morgenstern *et al*. 2007; Brauer, Lencar *et al*. 2008; Aguilera, Guxens *et al*. 2009). Number concentration for UFP was not used as a measure of exposure by any study, although it has been modelled using LUR recently in Amsterdam (Hoek, Kos *et al*. 2009). The LUR model yields annual average concentrations. The studies conducted in Barcelona and Munich estimated trimester-specific exposure by temporally adjusting these annual average concentrations using statutory monitoring station data. The study conducted in Munich achieved this by using data from a statutory monitoring station distant from traffic, while the Barcelona study used data from a station located on a traffic island in the middle of a main road. No study reported on the validity of temporal adjustment using statutory monitoring station data or on the sensitivity to the choice of the type of monitoring station (background versus traffic). The sampling campaigns differed slightly across the studies. For instance, the Vancouver study deployed NO_2 samplers twice for 2-week periods, the Barcelona study deployed their samplers four times for 1-week periods, and the Munich study deployed their samplers four times for 2-week periods.

3.3.5 ADJUSTMENT

Most studies controlled for maternal, child and pregnancy characteristics in their analyses (Table 2). However, not all studies controlled for maternal exposure to tobacco smoke. Moreover, not all studies controlled for complications of labour or pregnancy, although such health outcomes may be considered on the causal pathway between traffic exposures and adverse birth or pregnancy outcomes. All studies controlled for variables relating to socio-economic position, three employing a stratified approach (Ponce, Hoggatt *et al*. 2005; Généreux, Auger *et al*. 2008; Green, Malig *et al*. 2009).

3.3.6 TRAFFIC AND PRETERM BIRTH

Seven studies investigated the relationship between traffic-proximity and preterm birth (Table 3). A range of exposure assessment methods were applied, excluding LUR. The studies employed SD measures of exposure along with DWTD and dispersion models for $PM_{2.5}$ and NO_x. The variety of methods and categorised exposure contrasts did not enable a composite risk estimate to be defined. The Los Angeles study that applied a dispersion model indicated that NO_x was more strongly associated with all PTD outcomes than $PM_{2.5}$ (Wu, Ren *et al*. 2009). Slightly higher relative risks were observed for the VPTD outcome. An interquartile increase in NO_x over the whole pregnancy was associated with a relative risk of 1.25 (1.17, 1.33). Relative to the lowest quartile of exposure, the relative risk of VPTD among women exposed to highest quartile of exposure was 2.28 (2.15, 2.42). The Los Angeles studies that applied DWTD (both to the same population) also observed elevated risks which increased from 8% (1%, 15%) to 15% (5%, 26%) after restriction to women whose 3rd trimester fell in winter months, which then increased to 30% (7%, 58%) after further restriction to women from a low socio-economic area, comparing the highest to lowest categories of DWTD (Wilhelm and Ritz 2003; Ponce, Hoggatt *et al*. 2005). However, there was considerable overlap in these confidence intervals which impeded a firmer formal interpretation. The studies conducted in Montreal and Kaohsiung also observed adverse effects using SD contrasts by comparing subjects that lived within 200m and 500m of a freeway to those that resided further away (Yang, Chang *et al*. 2003; Généreux, Auger *et al*. 2008). No effect was observed when other SD exposure metrics or AADT were applied (Wilhelm and Ritz 2003; Zeka, Melly *et al*. 2008; van den Hooven, Jaddoe *et al*. 2009). Trimester specific results did not provide any evidence of a period of particular vulnerability as there was considerable overlap among most of the confidence intervals and a dearth of studies that compared effects across the different trimesters of exposure (Wilhelm and Ritz 2003; Ponce, Hoggatt *et al*. 2005; Wu, Ren *et al*. 2009). Six of the seven studies observed an association between PTD and residential exposure to traffic, and the vast majority of comparisons presented in Table 3 yielded an adverse direction of effect although not always statistically significant. Taken as a whole, these findings suggest that an adverse effect has been consistently reported for PTD.

3.3.7 TRAFFIC AND INTRAUTERINE GROWTH RESTRICTION

All types of exposure (LUR, DWTD, AADT and SD) except for dispersion were examined in relation to IUGR (Table 4). The seven studies were conducted in different locations and outcome measures were inconsistent between these studies. Intrauterine

growth was assessed using binary definitions of IUGR (SGA, Term LBW, LBW, Term BW 2.5-3kg) but was also analysed on a continuum (BW).

Four studies investigated SGA. The Vancouver study observed that living within 50m of a highway (defined in this context as an expressway carrying approximately 114,000 vehicles per day or a principal highway carrying approximately 21,000 vehicles per day) was associated with a 26% (7%, 49%) increased risk of SGA. (Brauer, Lencar *et al.* 2008) This association was not observed at greater distances or for less trafficked roads although the associations were marginal for proximities to a major road. The same study employed LUR models to approximate exposure to NO, NO_2 and $PM_{2.5}$ absorbance as a marker for diesel emissions, and observed that the levels of elevated risk were 2% (0%, 4%) per 10μgm^{-3} of NO. The study conducted in Eastern Massachusetts also observed an adverse effect with AADT and the distance to the nearest major highway (Zeka, Melly *et al.* 2008). Risk of SGA increased by 2% (0% 3%) per 1veh.km/day and by 1% (0%, 3%) with each 1m of proximity to a major highway. No adverse association between local traffic exposure and SGA was observed among the Montreal and Rotterdam study populations, which used SD or DWTD methods for exposure assessment (Généreux, Auger *et al.* 2008; van den Hooven, Jaddoe *et al.* 2009). Specific exposure periods during pregnancy were not assessed by any study.

Three studies investigated the influence of localised variations in traffic emissions on BW (Zeka, Melly *et al.* 2008; Aguilera, Guxens *et al.* 2009; van den Hooven, Jaddoe *et al.* 2009). The study conducted in Barcelona applied LUR and detected an effect for BTEX exposure among women who spent less than 2 hours a day outdoors in non-residential environments (Aguilera, Guxens *et al.* 2009). This study observed a decrease in birth weight of 76.6g (7.0g, 146.3g) per interquartile increase in BTEX over the whole pregnancy and a 101.9g (27.6g, 176.2g) decrease in birth weight per interquartile increase in BTEX over the second trimester of pregnancy. No association was observed for BTEX in the third trimester although trimester exposures were highly correlated. No association was observed for NO_2 or when the analysis was restricted to women who spent at least 15 hours per day at home. Birth weight decreased by 3.8g (1.9g, 5.7g) for per metre of distance approaching the nearest major highway in Eastern Massachusetts, but no association was observed for AADT (Zeka, Melly *et al.* 2008). The Rotterdam study reported a 41g (12g, 69g) reduction in birth weight for those living 100-150m from a major road compared to those living further than 200m, but did not observe an association at closer distances despite comparable sample sizes between the exposure group categories (van den Hooven, Jaddoe *et al.* 2009).

Term LBW was assessed in both the Vancouver study and the Los Angeles study (Wilhelm and Ritz 2003; Brauer, Lencar *et al.* 2008). The Vancouver study used LUR (NO, NO_2, $PM_{2.5}$ absorbance) and SD metrics for exposure assessment but none of these exposures were associated with an increase in risk. Indicators for the presence of a freeway within a 152.4m radius, as well as all other SD metrics relating to residential proximity to highways and major roads, were also not associated with term LBW. In the Los Angeles (2003) study the upper three DWTD quintiles exhibited an elevated risk of 17% (4%, 32%), 16% (2%, 31%) and 14% (0%, 29%) respectively, relative to the lowest DWTD quintile exposure group. When the analysis was restricted to women whose third trimester fell in winter months, these effect estimates approximately doubled, with a possible dose-response relationship. The Montreal study reported a 17% (4%, 33%) increase in risk of LBW among women within 200m of a freeway compared to those living beyond this distance (Généreux, Auger *et al.* 2008). This study did not restrict the sample for the LBW analysis to term births and therefore the results may also reflect the association which was also observed for PTD.

Term BW between 2500g and 3000g was assessed as an outcome in relation to LUR-modelled $PM_{2.5}$ absorbance and NO_2 in the study conducted in Munich (Slama, Morgenstern *et al.* 2007). The highest quartile of whole pregnancy $PM_{2.5}$ absorbance was associated with a 78% (10%, 270%) increase in risk relative to the lowest quartile, and a unit (0.5x10-5m-1) increase in $PM_{2.5}$ absorbance corresponded to a 45% (6%, 87%) increased risk of Term BW between 2500g and 3000g. These risk estimates were based on prevalence ratios. Trimester-specific associations were not found in the first trimester and only marginal significant effects were shown in the third trimester. Second trimester exposures exhibited between 76% (7%, 291%) and 83% (11%, 281%) increased risk for the quartile metrics and a 27% (4%, 54%) increase in risk per unit increase in $PM_{2.5}$ absorbance concentration. However, second trimester concentrations were highly correlated with the whole pregnancy average concentrations (Pearson correlation 0.84).

Preterm birth and LBW was combined into a single outcome in the study conducted in Los Angeles (2003) (Wilhelm and Ritz 2003). When analysis was limited to women whose third trimester fell within the winter months, those residing within the highest DWTD category exhibited a 24% (3%, 48%) increased risk of PTD and LBW, compared to an elevated risk of 15% (5%, 26%) for PTD alone.

Taken as a whole the findings of the seven studies indicate a somewhat consistently reported association between traffic exposure and IUGR as each study reported at least one adverse effect. However, the broad range of fetal growth outcomes that were investigated diluted the number of studies available on any single outcome, which prevented a more formal conclusion.

3.3.8 TRAFFIC AND MORTALITY

Two studies investigated mortality outcomes (Table 5) (de Medeiros, Gouveia *et al.* 2008; Green, Malig *et al.* 2009). No association was observed for fetal mortality in Sao Paulo using DWTD as the exposure measure. DWTD was associated with more than a two-fold (RR 2.82 (1.32, 6.03)) increase in risk of early neonatal mortality comparing the third quartile of

exposure to the lowest quartile, although a statistically significant association was not observed for the fourth (highest) quartile of exposure. Spontaneous abortion was investigated by restricting analyses to subpopulations in California using maximum AADT. An association was detected among African Americans and non-smokers but not among the non-Hispanic white or smoker groups.

3.3.9 TRAFFIC AND COMPLICATIONS

Two studies investigated complications of pregnancy (Table 6) (van den Hooven, Jaddoe *et al.* 2009; Wu, Ren *et al.* 2009). The study conducted in Los Angeles observed an association between dispersion modelled traffic-related air pollutants and pre-eclampsia. Effect sizes were similar across trimester exposures and were also similar for both pollutants, although exposures were very highly correlated. Whole pregnancy exposure to NO_x was associated with an 11% (6%, 16%) increase in risk while $PM_{2.5}$ was also associated with an 11% (6%, 15%) increase in risk. The study conducted in Rotterdam did not observe an effect for any of the complications investigated, which included pre-eclampsia/eclampsia/HELLP, hypertension and gestational diabetes. This study applied DWTD and SD metrics.

4 DISCUSSION

Our review synthesised studies that investigated pregnancy outcomes in relation to residential exposure to traffic emissions, and examined the consistency of results among studies in relation to the existence of an association. In doing so, we also identified the scope of pregnancy outcomes that have been investigated and the breadth of methods used to assess exposure.

4.1 EXISTENCE OF AN ASSOCIATION

Only twelve studies have directly assessed the relationship between traffic-proximity and preterm birth, measures of intrauterine growth, mortality or pregnancy complications. As a consequence, there were insufficient studies on any outcome to form conclusions on the strength of the relationship or to formally conclude the existence of an effect.

Some studies lacking statistically significant findings might not have been published, possibly decreasing the number of candidate studies for review. It is also not known whether all associations, regardless of statistical significance, were reported by the reviewed studies. Moreover, as we were not able to conduct a formal meta-analysis we were unable to account for multiple comparisons. Despite these considerations, this review highlighted an elevated risk of PTD associated with increased residential traffic exposure. Although the evidence was less strong for intrauterine growth restriction, the reviewed studies indicated a potential adverse effect. As only two studies investigated mortality outcomes and pregnancy complications further research is required, particularly to corroborate the adverse direction of effect observed for pre-eclampsia.

4.2 PREGNANCY OUTCOMES

There are a number of pregnancy outcomes that have potential to be included in future studies. Congenital anomalies has been investigated in relation to wide-area traffic-related air pollution but has not been assessed by capturing the more localised spatial variation in traffic emissions (Ritz, Yu *et al.* 2002; Hansen, Barnett *et al.* 2009; Rankin, Chadwick *et al.* 2009). Preterm pre-labour rupture of membranes is an event in which the amniotic sac ruptures more than an hour before the onset of labour and before 37 weeks of gestation. It is inherently associated with PTD, yet has not been studied in relation to residential traffic exposure. Although a biologic mechanism may not have been established for other health outcomes, epidemiological studies may prompt further toxicological studies. Therefore, there is scope for a wide variety of other health outcomes to be incorporated into an exploratory study. These health outcomes may include: threatened abortions, threatened PTD, antepartum haemorrhage, fetal distress and emergency caesarean procedures. In some countries, particularly those with established linked health databases, information on these outcomes may be obtained from clinical records or midwife notifications. However, this data is typically not easily accessible by researchers in many locations and it is unlikely that such detail is provided on administrative records such as birth certificates.

Intrauterine growth was defined using measures such as SGA and term LBW. Hypothetically, a perfectly healthy singleton infant population would still contain a proportion of SGA infants, which are constitutionally small, as the SGA definition uses a cut-off (usually the 10^{th} percentile) based on the distribution of birth weights. Moreover, this birth weight distribution varies by parental size, ethnicity and parity. Therefore the 2500g cut-off applied under term LBW is inherently inappropriate. Although this issue may be partially addressed by adjustment (adopted by all of the reviewed studies), the study then becomes more vulnerable to multi-colinearity. Further research is required to develop or apply more appropriate measures of intrauterine growth to this topic. A previous methodological review made the comment that birth weight is a sensitive but non-specific endpoint, and provided an example of an alternative approach is the use of anthropometric measurements from fetal ultrasounds at different stages of pregnancy (Hansen, Barnett *et al.* 2008; Woodruff, Parker *et al.* 2009).

4.3 LOCALISED SPATIAL VARIABILITY IN TRAFFIC EMISSIONS

This review assessed studies that attempted to capture local spatial variation in traffic emissions. The studies adopted a range of methods for residential exposure assessment: SD, AADT DWTD, dispersion models and LUR. However, *local* was defined differently among the reviewed studies. Most of the studies that applied SD metrics defined a subject as exposed if the residential address was within a threshold distance to a highly trafficked road. This threshold distance varied from 50m to 500m. Bi-linear interpolation was applied in order to calculate Cumulative AADT which effectively

excluded traffic beyond a distance of 241m. Maximum AADT was investigated using threshold distances that ranged up to 150m from the residential address. The studies that applied DWTD also used an effective buffer radius of approximately 150m based on a Gaussian dispersion model of air pollutant dispersion profiles (Pearson, Wachtel *et al.* 2000) but captured variable exposure within this buffer as well. Dispersion models accurately capture the local spatial variation in emissions as they directly model concentrations from the location of emission (source location) to the residential address (receptor location) using traffic, meteorological and topographic conditions. Inclusion of non-traffic related variables and *large* radii also diluted the effectiveness of LUR-modelled concentration as a measure of traffic exposure at the residential address, despite being adequate as a measure of locally generated air pollution. For example, the Vancouver study reported that the NO, NO_2 and $PM_{2.5}$ absorbance LUR models explained 62%, 56% and 56% of the total variation respectively, and were heavily based on traffic proxies, but included large areas of up to 2.5km radii (Brauer, Lencar *et al.* 2008). Certainly, the characterisation of locally generated emissions is blurred by the contribution of wide-area (traffic and non-traffic) emissions to local levels. Despite this challenge, in order to appropriately characterise the localised variability in traffic emissions there is a need to restrict the LUR-predictor variables to measures of local traffic exposure rather than area sources, reduce the buffer radii, and report the associated proportion of variation explained by such a model. Further progress would also result from the development of LUR models that use pollutants which are more specific markers of traffic exhaust than NO, NO_2, NO_x and $PM_{2.5}$.

4.4 TEMPORAL VARIABILITY IN RELATION TO EXPOSURE AND WINDOWS OF SUSCEPTIBILITY

In urban locations within western countries, motor vehicle traffic typically exhibits greatest variation within a 24-hour period, although different levels may be observed on weekends, during school holidays and on public holidays. While seasonal variation in motor vehicle traffic is minimal, seasonal changes in meteorological conditions have potential to significantly influence exposure. Seasonal variations in sunlight and temperature influence atmospheric photochemical reactions, while seasonal changes in mixing depth and wind speed affect the dilution of air toxicants. Wind direction in relation to road and house location is also an important consideration. Dispersion models directly account for many of these temporally relevant factors, while LUR can be adapted to account for temporal variability (Hoek, Beelen *et al.* 2008). Diurnal variation is not usually relevant to many pregnancy outcomes as the vehicle emission levels are generally too low to be considered as acute exposures. Cumulative exposure over longer periods is of most significance. Although the development of the fetus is continuous, substantial changes are observed over gestational weeks, months and particularly trimesters. For example, intrauterine growth rapidly increases approaching birth in the 3rd trimester, making the fetus susceptible to traffic emissions such as carbon monoxide during this period. Carbon monoxide binds to haemoglobin (carboxyhaemoglobin) and, at worst, remains in the system until the haemoglobin is replaced after approximately 127 days (Shemin and Rittenberg 1946). This 127-day period coincides reasonably well with the duration of a season, and a trimester. Therefore, an LUR model that captures seasonal variation and used to assess trimester specific exposure may be just as well suited to such a problem as a hypothetical LUR model that captures daily variation. The temporal resolution of the exposure model may be offset against the period of biological relevance.

While SD metrics provide purely spatial contrasts, the temporal variation in exposure can be captured by other exposure models. Temporal variation is an inherent component of dispersion models, which can model pollutant concentrations using traffic counts and meteorological information on an hourly scale. As AADT is an annual measure of daily traffic it also inherently incorporates a temporal component but will not vary within the averaging period of a year. This averaging period is wider than the exposure period used to investigate pregnancy outcomes, which tend to range from months and trimesters of (pre-)pregnancy to whole of pregnancy exposure. Measurements of NO_2, a marker for traffic exposure, were obtained from statutory monitoring stations and used as to incorporate temporal variation into the AADT counts in the Californian study that investigated spontaneous abortion (Green, Malig *et al.* 2009). This required the assumption that the actual temporal variability in local traffic pollutant concentrations is well represented by the temporal variability in NO_2 measurements taken from monitoring stations. The studies conducted in Barcelona and Munich temporally adjusted their LUR measurements using measurements obtained from monitoring stations under a similar assumption (Slama, Morgenstern *et al.* 2007; Aguilera, Guxens *et al.* 2009). Moreover, the Munich study used measurements from a monitoring station distant from an important source of traffic while the Barcelona study used measurements from a monitoring station in the middle of a main road. Therefore, there is a need to validate this assumption, particularly in relation to the *type* of monitoring station that is used to incorporate such temporal adjustment.

4.5 BACKGROUND AIR POLLUTION AND METEOROLOGY

The contribution of background air pollution to the elevated risk of adverse pregnancy outcomes may be taken into account in order to separate the effect of local traffic exposure from that of wider area level exposure. However, there is a somewhat blurred distinction between the two sources due to traffic emission contribution to wider area air pollution, photochemical reactions and interactions with meteorological conditions. Accordingly, some of the reviewed studies adjusted for background levels of pollution. Consideration of climatic differences is also important as it is debatable whether it is the pollutant or the co-linear meteorological condition that is a greater contributor to the likelihood of the adverse health outcome. Some reports suggest that much of the seasonal variation in mortality and morbidity thought due to particulate matter might be explained by

meteorological and climatic information (Cox 2000). Both PTD and IUGR may be associated with meteorological factors (Noller, Resseguie *et al*. 1996; Lajinian, Hudson *et al*. 1997; Murray, O'Reilly *et al*. 2000; Yackerson, Piura *et al*. 2008). As some of the reviewed studies that reported an association detected this association in winter months, it is important to note the possibility of climatic influence or effect measure modification.

Timing of exposure in relation to the susceptible windows of fetal development in conjunction with timing of elevated doses (e.g. seasonal variation) is an important consideration in pregnancy outcome studies (Ritz and Wilhelm 2008). This is particularly important for studies that focus on intrauterine growth as growth rapidly increases approaching birth, notably during the 3rd trimester. This period may also overlap with a season in which background levels are higher. For example, in temperate climates, winter months often bring cooler conditions associated with inversion layers and less vertical mixing of air pollutants, trapping vehicle emissions. In such climates, winters are often accompanied by higher levels of particulate matter (Flachsbart 1995; Wilhelm and Ritz 2003).

4.6 EXPOSURE DATA REQUIREMENTS

The LUR method requires sampling the traffic-related air pollutants of interest. A recent review recommended using at least two and preferably four sampling campaigns to capture seasonal variation (Hoek, Beelen *et al*. 2008). The number of sampling sites required is generally dependent upon the size of the study area. However, it is intuitive that the distribution of road types and other point and area sources of pollution within the study area will also influence the density of sampling sites required.

The DWTD, LUR and dispersion methods of calculating exposure all require traffic count data. Such data may not be routinely collected by governments. The temporal resolution of the exposure model is typically a function of the level of traffic data available – rarely are hourly or daily counts available for a large number of sites over a particular period of interest. The reviewed studies that applied LUR circumvented this issue by incorporating annually averaged daily counts into the exposure model rather than traffic counts observed for the specific 1-2 week air sampling period. Government road or planning authorities obtain traffic counts for many more roads over a period of a year, than over the 1-2 week period required for passive air pollution sampling. Although more costly, obtaining traffic counts over the particular sampling period may improve model performance or validate the use of annually averaged counts.

Dispersion models necessitate hourly counts, which require information on a 24-hour traffic distribution. The data requirements for dispersion models are more demanding than for the other exposure models applied by the reviewed studies as mixing depths and hourly meteorological data are also required. Conversely, SD metrics require only the residential location, electronic maps and a GIS.

4.7 MODEL COMPARABILITY

The LUR method models pollutant concentrations highly correlated with the traffic emission constituents hypothesized to influence the risk of the adverse birth or pregnancy outcome. The plausibility of effects from co-pollutant mixtures usually prohibits stronger statements as to the adverse relationship between the pollutant and the health outcome. The LUR method typically includes predictors such as traffic density, population density and land-use area (e.g. residential, industrial) and is therefore less specific to traffic-sourced concentrations as it includes other variables potentially related to area sources. Dispersion models are more specific to traffic-sourced concentrations as they directly incorporate traffic emission factors. These models are derived deterministically, and calibrated and validated through air sampling. Conversely, LUR models are derived stochastically through air sampling. In terms of the proportion of variation explained by the exposure model (R^2), it may appear that LUR performs better than dispersion models (Briggs, de Hoogh *et al*. 2000; Hoek, Beelen *et al*. 2008). However, in terms of modelling traffic emissions, this is an unbalanced comparison as LUR includes non-traffic predictors that may be indicative of area sources. The performance in terms of their validity as models for residential exposure to traffic emissions would require the development of an LUR that only includes traffic predictors, excluding other variables and subsequent comparison with a traffic emission dispersion model. This is a potential avenue for future research, particularly among health geographers and environmental scientists.

If a true association exists between the birth or pregnancy outcome and toxicants not captured by statutory monitoring (e.g. PAH) then surrogates which apply a generic form for pollutant concentration decay from the roadway, such as DWTD, may be more appropriate to use than LUR or dispersion models in terms of minimising exposure misclassification. Simpler measures, such as DWTD, may better represent the mixtures of toxicants, which together produce a compounded adverse effect on health. However, these methods are less specific to the vehicle emission toxicants, and are more likely to have been influenced by variables that are also closely related to distances to heavily trafficked roads, such as socioeconomic status, resulting in the detection of spurious associations.

4.8 CONFOUNDING

The influence of factors that contribute to socioeconomic position is important to take into account due to potential environmental inequality in relation to residential proximity to traffic, which have been demonstrated in other studies (Finkelstein, Jerrett *et al*. 2005). Confounding of risk estimates due to maternal smoking is also plausible, perhaps through its association with socioeconomic status. It is plausible that smoking status and residential proximity to traffic are positively associated, and that exposure to tobacco smoke is the underlying reason for any positive associations between traffic proximity and elevated risk of adverse birth or pregnancy outcomes. Not all of the reviewed studies directly

included maternal smoking or environmental tobacco smoke (ETS) in their analyses, most likely because such information is rarely available from large population data sources. In relation to PTD, the sole study that stratified analyses by socioeconomic status reported a 30% increased risk among women living in the low socioeconomic area, comparing the highest to lowest DWTD quintiles (Ponce, Hoggatt *et al.* 2005). This result alone is insufficient to imply that socioeconomic-related variables modified the effect of traffic emissions because all of the confidence intervals significantly overlapped (Kaufman 2009). Rather, the power to detect an effect may have been enhanced by such stratification. Interestingly, the only study that stratified analysis by smoking status observed a 47% increased risk of spontaneous abortion among the non-smoker group and a reduced risk of 64% (i.e. a protective effect) among the smoker group not explained by the authors (Green, Malig *et al.* 2009). This study assessed exposure as the maximum AADT within 50m of the residence.

The influence of spatial gradients in socioeconomic status on the effect estimate differs with the choice of exposure model, which dictates the extent to which the exposure contrasts are driven by spatial versus temporal variability. For example, such gradients are more likely to have a greater correlation with distance from a major roadway than with a LUR-derived concentration that uses area-based predictors such as population density and type of land-use. However, spatial variability in socioeconomic status may also be correlated with population density or proximity to certain types of land-use, such as industrial areas. Moreover, this correlation may operate in either direction. For example, inner-city gentrification may lead to greater population density with the development of newer higher-density housing, while in outer suburbs population density may reflect the financial inaccessibility of larger homes. Socioeconomic position may also be associated with population density through differential family sizes within households. Therefore, the relationship between these LUR predictor variables and socioeconomic position is likely to be study-area specific, both within and between cities.

Stratification of analyses into homogeneous socioeconomic strata may be accompanied by the use of a population of *healthy* births or pregnancies, defined as a population for which there are no known pathologic determinants of the birth or pregnancy outcome of interest. Although infants whose parents are of a low socioeconomic background may be more susceptible to environmental insults such as motor vehicle traffic emissions, other pathological (e.g. intrauterine infection), nutritional (e.g. lack of folate in the diet), and toxicological (e.g. maternal smoking during pregnancy) factors are perhaps more influential determinants of the adverse birth or pregnancy outcome. An unfortunate consequence of such an approach is the exclusion of competing risks. For example, traffic emissions may increase susceptibility to intrauterine infection through suppression of the immune system, which may in turn result in an adverse pregnancy outcome. Restriction to a healthy population also enables the calculation of independent risk estimates, and may be considered in future studies.

4.9 RESIDENTIAL EXPOSURE AND TIME-ACTIVITY INFORMATION

A further methodological factor for consideration in studies of traffic-proximity on pregnancy outcomes is the introduction of time-activity information. One study weighted exposure by time spent at each residential address (Brauer, Lencar *et al.* 2008). Examining time spent at the reference location (e.g. place of residence) compared to other locations (such as the workplace) is also important to minimise possible exposure misclassification. However, obtaining detailed time-activity information for large study populations may significantly increase the financial, staff and time costs of the study. The validity of investigating exposure at the residential address is supported by data that suggest that pregnant women spend most of their time at home, particularly in the latter stages of pregnancy (Nethery, Brauer *et al.* 2009), and that outdoor measurements of traffic-related air pollutants are associated with personal exposure (Nethery, Teschke *et al.* 2008). The only reviewed study that stratified analysis by time spent at home or outdoors reported a 77g decrease in birth weight for an interquartile increase in BTEX over pregnancy among women who spent less than 2 hours a day outdoors (Aguilera, Guxens *et al.* 2009). Although statistically non-significant, the authors also reported that the effect estimates for BTEX were more pronounced among women who spent more time at home, compared with the whole cohort. Women may also be more likely to move house during pregnancy, indicating that spatially derived exposures will need to consider implications in relation to exposure misclassification. The study conducted in Vancouver updated exposures according to changes in residential postal codes and weighted exposure by time spent in multiple residences (Brauer, Lencar *et al.* 2008). This post code information was obtained from provincial health registration and health care contact records. The completeness of such databases also requires consideration.

4.10 BIOLOGICAL MECHANISMS

There is an accumulating body of knowledge regarding plausible biological mechanisms by which exposure to traffic emissions may lead to adverse pregnancy outcomes. Much of this evidence is derived from tobacco research or broader air pollution studies (Albuquerque, Smith *et al.* 2004; Zdravkovic, Genbacev *et al.* 2005; Ziaei, Nouri *et al.* 2005). Few studies have specifically investigated traffic emissions and therefore many more are required (Tsukue, Tsubone *et al.* 2002; Takeda, Tsukue *et al.* 2004; Rocha e Silva, Lichtenfels *et al.* 2008; Veras, Damaceno-Rodrigues *et al.* 2009). This recommendation parallels a previous suggestion that further animal studies are required to inform important mechanistic research gaps in relation to more general air pollution exposure (Woodruff, Parker *et al.* 2009). In general, the effects of the constituents of traffic emissions on pregnancy outcomes may manifest through the cardiovascular mechanisms of oxidative stress, inflammation, coagulation, endothelial function, and hemodynamic responses (Kannan, Misra *et al.* 2006). Adverse pregnancy outcomes may be influenced by a variety of factors, including abnormality of the biological clock, abnormal implantation, and infection (Mattison, Wilson *et al.* 2003).

Moreover, maternal exposure has been correlated with that of the fetus (Perera, Deliang *et al*. 2004), which may be even more susceptible to such insults (Perera, Jedrychowski *et al*. 1999).

Exposure to diesel exhaust (Tsukue, Tsubone *et al*. 2002) and other traffic emissions (Rocha e Silva, Lichtenfels *et al*. 2008) have been shown to restrict fetal growth in mice. Diesel exhaust contains PM with adsorbed PAH (Schauer, Kleeman *et al*. 1999; Schauer, Kleeman *et al*. 2002; Oberdorster, Oberdorster *et al*. 2005). Such PAH exposure has been associated with restricted fetal growth among non-smoking and non-occupationally exposed African-American and Caucasian Polish women (Hyunok, Jedrychowski *et al*. 2006). Exposure to the carcinogenic fraction of PAH has also been linked to restricted fetal growth (Dejmek 2000). These results have been supported by research that has shown that higher than median PAH-DNA adducts in newborns born to Polish women is associated with decreased birth length, birth weight and head circumference (Perera, Whyatt *et al*. 1998). The adverse effect of PAH was also observed among infants born to African-American women, but not Hispanic women (Perera, Rauh *et al*. 2003) or among a population in Manhattan, New York (Perera, Deliang *et al*. 2005) possibly indicative of more susceptible populations. There is also evidence which suggests that maternal exposure to traffic-generated PM prior to conception can negatively affect fetal birth weight (Veras, Damaceno-Rodrigues *et al*. 2009), indicating an exposure period that can be investigated in future observational studies.

The biological mechanisms by which air pollution, such as that arising from traffic emissions, may lead to PTD are not as well understood (Xu and Hui 1995). However, it is known that PTD can result in part from infection caused by genital tract bacteria (Gibbs, Romero *et al*. 1992), and it has been suggested that air pollution can lead to increased susceptibility to such infection (Slama, Darrow *et al*. 2008). Air pollution may cause PTD by interfering with placental development (Dejmek 2000) and through an abnormal production or an early activity of cytokines favouring inflammation, which are a part of the body's preparation for parturition (Keelan, Blumenstein *et al*. 2003; Engel, Erichsen *et al*. 2005).

A decrease in fetal survival of rats was demonstrated for exposure to benzo(a)pyrene, which belongs to the PAH group (Archibong, Inyang *et al*. 2002). Spontaneous abortion are more likely to occur with chromosomal anomalies (Byrne, Warburton *et al*. 1985) which may be adversely affected by air pollution. Sperm quality can be impeded by exposure to traffic-related air pollution (Selevan 2000; De Rosa, Zarrilli *et al*. 2003) while a higher rate of spontaneous abortion has been associated with fathers whose sperm had elevated levels of DNA fragmentation (Evenson and Wixon 2005).

5 CONCLUSION

Most of the studies that have investigated the localised spatial variability in traffic emissions have done so in relation to its influence on gestational duration and intrauterine growth. The evidence to date suggests an adverse effect was consistently reported for gestational duration and less consistently reported yet plausible for intrauterine growth. However, the small number of studies, the possibility of publication bias and the limited research conducted on biological mechanisms precluded more formal statements on the existence of an effect. Few studies have investigated mortality or pregnancy complications, and no study has investigated the influence of this exposure on the risk of congenital anomalies, all of which are areas for potential future research.

The methods that have been used to capture the localised spatial variability in traffic emissions were: simple distances, annually averaged daily traffic counts, distance-weighted traffic density, dispersion models, and land-use regression models. The construction of these exposure models requires expertise in geography (GIS) or environmental science (air pollution monitoring and modelling), while analysis interpretation also requires knowledge of the periods of biological susceptibility. Our review also noted the potential influence of spatial gradients in socioeconomic status and the particular vulnerability of certain population groups, which adds a social science context to the topic. Finally, although a formal review of potential biological mechanisms was beyond the scope of this review we noted the plausibility of an association and that further toxicological research is required that specifically focuses on the constituents of traffic emissions.

The ubiquity of motor vehicle traffic emissions, the biological vulnerability of the fetus, and the adverse associations detected among many of the reviewed studies motivates a multi-disciplinary collaborative effort toward further research on the topic.

Table 1. Characteristics of the studies included in review

Author, year, location (study period)	Design	Health outcome		Cases	Total
Aguilera *et al* 2009 Barcelona (Apr 2004 - Mar 2006)	Prospective cohort	BW	570	570	NO_2 (LUR) BTEX (LUR)
Brauer *et al* 2008 Vancouver (1999 - 2002)	Retrospective cohort	SGA Term LBW	6,939 894	70,249	<150m of hwy, <50m of major road <50m of hwy <150m of hwy <50m of major road <150m of major road $PM_{2.5}$ (LUR) $PM_{2.5}$ absorbance (LUR) NO (LUR) NO_2 (LUR)
De Medeiros *et al* 2009 Sao Paulo, Brazil (Aug 2000 - Jan2001)	Case-control	Perinatal mortality	631	318	DWTD quartiles
Généreux *et al* 2008 Montreal (1997 - 2001)	Retrospective cohort	PTD SGA LBW	6,248 9,116 4,562	99,178 99,087 99,180	<200m of hwy
Green *et al* 2009 California (1990 - 1991)	Prospective cohort	Spontaneous abortion	479	4,979	Maximum AADT <50m from residence <100m from residence <150m from residence Distance to nearest arterial Highest AADT weighted by distance
Ponce *et al* 2005 Los Angeles (1994 - 1996)	Case-control	PTD	13,394	37,347	DWTD<20th percentile DWTD>80th percentile by SES area and Season
Slama *et al* 2007 Munich (Jan 1998 – Jan 1999)	Retrospective cohort	Term BW (2.5-3kg)	142	1016	$PM_{2.5}$ (LUR) $PM_{2.5}$ absorbance (LUR) NO_2 (LUR)
Van den Hooven *et al* 2009 Rotterdam (Apr 2002 – Jan 2006)	Prospective cohort	BW SGA (<-2 SD birth weight) PTD Hypertension (Pre-)eclampsia/HELLP Gestational diabetes	7288 257 406 250 144 50	7288 7278 7337 7108 7108 7068	DWTD quartiles Distance to nearest major road: >200m 150-200m 100-150m 50-100m 0-50m
Wilhelm & Ritz 2003 Los Angeles (1994 - 1996)	Case-control	PTD Term LBW PTD and LBW	13,464 3,771 3,509	34,588 30,122 24,633	Freeway in buffer (152.4m radius) DWTD quintiles
Wu *et al* 2009 Los Angeles (1997 - 2006)	Retrospective cohort	Pre-eclampsia PTD Moderate PTD (<35wk) Very PTD (<30wk)	2,442 6,712 2,749 775	81,186	NOx (Dispersion) PM2.5 (Dispersion)
Yang *et al* 2003 Kaohsiung, Taiwan (Jan 1992 – Dec 1997)	Retrospective cohort	PTD	294	6,251	500-1500m of freeway <500m of freeway
Zeka *et al* 2008 Eastern Massachusetts (Jan 1996 – Dec 2002)	Retrospective cohort / case-control	BW SGA PTD	425,751 42,109 33,184	425,751	Cumulative AADT Distance to nearest major highway

Table 2. Characteristics controlled for in the reviewed studies by adjustment, restriction, matching or stratification

Characteristic	Aguilera	Brauer	de Medeiros	Généreux	Green	Ponce	Slama	van den Hooven	Wilhelm	Wu	Yang	Zeka
Infant Characteristics												
Birth weight / IUGR							•					•
Congenital anomaly			•									
Gestational duration	•	•					•	•	•			•
Live-birth								•			•	•
Sex	•	•	•	•		•	•	•	•		•	•
Singleton		•		•		•	•	•	•	•	•	•
Maternal/Paternal Characteristics												
Ethnicity/Race		•		•	•	•		•	•	•		•
History of stillbirth				•								
Housing type / crowding			•									
Income			•		•							
Insurance						•				•		
Interval since previous live birth						•			•			
Marital status / duration of union			•	•							•	
Maternal age		•	•	•	•	•		•	•	•	•	•
Maternal/paternal education	•		•	•		•	•	•	•		•	•
Maternal/paternal height	•						•					
Maternal occupation/employment			•		•							
Maternal number of stressful life events					•							
Parity	•	•	•	•		•	•	•	•	•	•	
Previous infant weighing 4000g or more												•
Previous LBW or preterm infant			•			•			•			•
Pregnancy and Labour Characteristics												
Alcohol consumption before/during pregnancy			•					•				
Ectopic pregnancy					•							
Exposure during other trimesters (NO2, BTEX)	•											
Hypertension during pregnancy			•									•
Maternal weight/BMI before/during pregnancy	•						•	•				
Maternal diabetes			•							•		•
Molar pregnancy					•							
Prenatal care / initiation time			•			•			•	•		•
Problems during delivery / eclampsia/haemorrhage			•									
Renal / lung disease												•
Time-activity / time at home	•											
Tobacco smoke - maternal	•		•		•		•	•				•
Tobacco smoke - environmental		•										
Urinary tract infection(s)										•		
Vaginal bleeding during pregnancy			•									•
Temporal characteristics												
Date, month or year of birth		•		•		•		•				•
Season of birth/trimester/conception	•								•	•	•	
Area derived characteristics												
Age of home									•			
Background pollutant (CO, NO_2, O_3, PM_{10})					•	•			•			
Education		•		•								
Freeways present in buffer									•			
Home value									•			
Income		•		•		•			•			•
Poverty						•				•		
Rent									•			
Unemployment						•						

Table 3. Adjusted risk estimates for PTD

Study author, year, location	Health outcome	Exposure Type	Exposure	Relative Risk	95% CI
Généreux *et al*	PTD	SD	>200m of highway	1	Referent
2008 Montreal			<200m of highway	1.14	(1.02, 1.27)
Ponce *et al*	PTD	DWTD	1st quintile	1	Referent
2005 Los Angeles			*Low SES area, 3rd trim Summer months* 5th quintile (>24,711 veh/day)	0.93	(0.76, 1.13)
			Low SES area, 3rd trim Winter months 5th quintile (>24,711 veh/day)	1.30	(1.07, 1.58)
			Mid SES area, 3rd trim Summer months 5th quintile (>24,711 veh/day)	1.19	(0.99, 1.43)
			Mid SES area, 3rd trim Winter months 5th quintile (>24,711 veh/day)	1.18	(0.99, 1.41)
			High SES area, 3rd trim Summer months 5th quintile (>24,711 veh/day)	0.93	(0.80, 1.09)
			High SES area, 3rd trim Winter months 5th quintile (>24,711 veh/day)	1.00	(0.85, 1.17)
Van den Hooven *et al*	PTD	DWTD	1st quartile (<159 veh.m/day)	1	Referent
2009 Rotterdam			2nd quartile (159-547 veh.m/day)	1.37	(1.02, 1.84)
			3rd quartile (547-1,235 veh.m/day)	1.33	(0.98, 1.79)
			4th quartile (>1,235 veh.m/day)	1.18	(0.87, 1.59)
		SD	*Distance to major road (m)*		
			>200m	1	Referent
			150-200m	1.09	(0.79, 1.50)
			100-150m	1.13	(0.84, 1.52)
			50-100m	1.08	(0.80, 1.45)
			0-50m	1.15	(0.84, 1.58)
Wilhelm & Ritz	PTD	DWTD	1st quartile (<1,537 veh/day)	1	Referent
2003 Los Angeles			2nd quartile (1,537-5,338 veh/day)	0.98	(0.92, 1.04)
			3rd quartile (5,339-11,722 veh/day)	1.02	(0.95, 1.08)
			4th quartile (11,723-24,711 veh/day)	1.06	(0.99, 1.12)
			5th quintile (>24,711 veh/day)	1.08	(1.01, 1.15)
			One or more freeways in buffer	0.96	(0.90, 1.02)
			3rd trimester in Winter months		
			1st quintile (<1,537 veh/day)	1	Referent
			2nd quintile (1,537-5,338 veh/day)	0.97	(0.89, 1.06)
			3rd quintile (5,339-11,722 veh/day)	1.04	(0.95, 1.13)
			4th quintile (11,723-24,711 veh/day)	1.08	(0.99, 1.18)
			5th quintile (>24,711 veh/day)	1.15	(1.05, 1.26)
	PTD & LBW	DWTD	1st quintile (<1,537 veh/day)	1	Referent
			2nd quintile (1,537-5,338 veh/day)	0.98	(0.87, 1.11)
			3rd quintile (5,339-11,722 veh/day)	1.03	(0.91, 1.17)
			4th quintile (11,723-24,711 veh/day)	1.12	(0.99, 1.26)
			5th quintile (>24,711 veh/day)	1.12	(0.98, 1.27)
		SD	One or more freeways in buffer	1.00	(0.89, 1.12)
		DWTD	*3rd trimester in Winter months*		
			1st quintile (<1,537 veh/day)	1	Referent
			2nd quintile (1,537-5,338 veh/day)	0.93	(0.78, 1.11)
			3rd quintile (5,339-11,722 veh/day)	0.98	(0.82, 1.17)
			4th quintile (11,723-24,711 veh/day)	1.11	(0.93, 1.33)
			5th quintile (>24,711 veh/day)	1.24	(1.03, 1.48)

Table 3 continue on next page

Wu *et al*	PTD	Dispersion	*NO_x IQR (5.65ppb)*		
2009 Los Angeles			Pregnancy	1.06	(1.03, 1.09)
			1st trimester	1.05	(1.02, 1.08)
			2nd trimester	1.06	(1.03, 1.09)
			$PM_{2.5}$ IQR (1.35 µgm^{-3})		
			Pregnancy	1.03	(1.01, 1.06)
			1st trimester	1.03	(1.01, 1.06)
			2nd trimester	1.04	(1.01, 1.07)
	MPTD	Dispersion	*NO_x IQR (5.65ppb)*		
			Pregnancy	1.13	(1.09, 1.18)
			1st trimester	1.12	(1.07, 1.17)
			2nd trimester	1.13	(1.08, 1.17)
			$PM_{2.5}$ IQR(1.35 µgm^{-3})		
			Pregnancy	1.07	(1.03, 1.12)
			1st trimester	1.08	(1.03, 1.12)
			2nd trimester	1.08	(1.04, 1.12)
	VPTD	Dispersion	*NO_x over whole pregnancy*		
			1st quartile (NA)	1	Referent
			4th quartile (NA)	2.28	(2.15, 2.42)
			IQR (5.65ppb)	1.25	(1.17, 1.33)
			NO_x IQR (5.65ppb)		
			1st trimester	1.21	(1.13, 1.30)
			2nd trimester	1.24	(1.15, 1.32)
			$PM_{2.5}$ over whole pregnancy		
			1st quartile (NA)	1	Referent
			4th quartile (NA)	1.81	(1.71, 1.92)
			IQR (1.35 µgm^{-3})	1.18	(1.10, 1.26)
			$PM_{2.5}$ IQR (1.35 µgm^{-3})		
			1st trimester	1.17	(1.09, 1.26)
			2nd trimester	1.18	(1.10, 1.27)
Yang *et al*	PTD	SD	500-1500m of freeway	1	Referent
2003 Kaohsiung, Taiwan			<500m of freeway	1.30	(1.03, 1.65)
Zeka *et al*	PTD	AADT	Cumulative traffic density (veh.km/day)	1.00	(0.98, 1.01)
2008 Eastern Massachusetts		SD	Distance to nearest major highway (m)	1.00	(0.98, 1.01)

Table 4. Adjusted risk estimates for indicators of IUGR

Study author, year, location	Health outcome	Exposure Type	Exposure	Relative Risk	95% CI
Aguilera *et al* 2009 Barcelona	BW	LUR	*All women (N=570):*		
			NO_2 over whole pregnancy IQR (9.51 μgm^{-3})	8.8	(-23.8, 41.5)
			1st trimester NO_2 IQR (12.27 μgm^{-3})	3.3	(-33.2, 39.7)
			2nd trimester NO_2 IQR (12.00 μgm^{-3})	3.7	(-31.1, 38.4)
			3rd trimester NO_2 IQR (12.47 μgm^{-3})	16.8	(-18.8, 52.4)
			All women (N=570):		
			BTEX over whole pregnancy IQR (8.42 μgm^{-3})	-7.6	(-54.9, 39.8)
			1st trimester BTEX IQR (9.79 μgm^{-3})	-12.0	(-62.0, 38.0)
			2nd trimester BTEX IQR (10.04 μgm^{-3})	-13.3	(-65.1, 38.4)
			3rd trimester BTEX IQR (9.72 μgm^{-3})	2.5	(-45.3, 50.4)
			At least 15h/day at home (N=276):		
			NO_2 over whole pregnancy IQR (9.51 μgm^{-3})	8.6	(-37.9, 55.2)
			1st trimester NO_2 IQR (12.27 μgm^{-3})	9.8	(-43.2, 62.9)
			2nd trimester NO_2 IQR (12.00 μgm^{-3})	-1.5	(-50.9, 47.9)
			3rd trimester NO_2 IQR (12.47 μgm^{-3})	15.8	(-35.1, 66.6)
			At least 15h/day at home (N=276):		
			BTEX over whole pregnancy IQR (8.42 μgm^{-3})	-13	(-79.3, 53.3)
			1st trimester BTEX IQR (9.79 μgm^{-3})	-16.3	(-87.8, 55.2)
			2nd trimester BTEX IQR (10.04 μgm^{-3})	-22.5	(-95.1, 50.0)
			3rd trimester BTEX IQR (9.72 μgm^{-3})	-1.4	(-68.8, 66.0)
			Less than 2h/day outdoors (N=259):		
			NO_2 over whole pregnancy IQR (9.51 μgm^{-3})	-18.6	(-66.3, 29.1)
			1st trimester NO_2 IQR (12.27 μgm^{-3})	4.2	(-49.3, 57.6)
			2nd trimester NO_2 IQR (12.00 μgm^{-3})	-42.3	(-92.1, 7.4)
			3rd trimester NO_2 IQR (12.47 μgm^{-3})	-9.0	(-60.5, 42.6)
			Less than 2h/day outdoors (N=259)		
			BTEX over whole pregnancy IQR (8.42 μgm^{-3})	-76.6	(-146.3, -7.0)
			1st trimester BTEX IQR (9.79 μgm^{-3})	-52.5	(-125.8, 20.8)
			2nd trimester BTEX IQR (10.04 μgm^{-3})	-101.9	(-176.2, -27.6)
			3rd trimester BTEX IQR (9.72 μgm^{-3})	-59.7	(-130.9, 11.5)
Brauer *et al* 2008 Vancouver	SGA	SD	<150m of hwy, <50m of major road	0.99	(0.92, 1.06)
			<50m of hwy	1.26	(1.07, 1.49)
			<150m of hwy	0.93	(0.83, 1.03)
			<50m of major road	1.03	(0.95, 1.12)
			<150m of major road	1.04	(0.98, 1.11)
		LUR	NO (10 μgm^{-3})	1.02	(1.00, 1.04)
			NO_2 (10 μgm^{-3})	0.99	(0.96, 1.02)
			$PM_{2.5}$ absorbance (10-5 m-1)	1.01	(0.99, 1.03)
	Term LBW	SD	<150m of hwy, <50m of major road	0.95	(0.79, 1.13)
			<50m of hwy	1.22	(0.81, 1.87)
			<150m of hwy	1.01	(0.76, 1.33)
			<50m of major road	0.96	(0.77, 1.18)
			<150m of major road	0.94	(0.79, 1.10)
		LUR	NO (10 μgm^{-3})	1.01	(0.96, 1.07)
			NO_2 (10 μgm^{-3})	0.97	(0.89, 1.05)
			$PM_{2.5}$ absorbance (10-5 m-1)	1.00	(0.95, 1.07)
Généreux *et al* 2008 Montreal	SGA	SD	>200m of highway	1	Referent
			<200m of highway	1.06	(0.96, 1.17)
	LBW	SD	>200m of highway	1	Referent
			<200m of highway	1.17	(1.04, 1.33)

Table 4 continue on next page

Slama *et al*	Term BW	LUR	*$PM_{2.5}$ absorbance ($10^{-5}m^{-1}$) over whole pregnancy*		
2007 Munich	(2.5-3kg)		1st quartile (1.29-1.61)	1	Referent
			2nd quartile (1.61-1.72)	1.21	(0.73, 1.97)
			3rd quartile (1.72-1.89)	1.63	(0.98, 2.57)
			4th quartile (1.89-3.10)	1.78	(1.10, 2.70)
			Increase of 0.5x10-5 m-1	1.45	(1.06, 1.87)
			1st trimester $PM_{2.5}$ absorbance ($10^{-5}m^{-1}$)		
			1st quartile (1.29-1.61)	1	Referent
			2nd quartile (1.61-1.72)	1.15	(0.73, 1.80)
			3rd quartile (1.72-1.89)	1.01	(0.61, 1.53)
			4th quartile (1.89-3.10)	1.04	(0.70, 1.57)
			Increase of 0.5x10-5 m-1	1.03	(0.82, 1.28)
			2nd trimester $PM_{2.5}$ absorbance ($10^{-5}m^{-1}$)		
			1st quartile (1.29-1.61)	1	Referent
			2nd quartile (1.61-1.72)	1.33	(0.85, 2.22)
			3rd quartile (1.72-1.89)	1.76	(1.07, 2.91)
			4th quartile (1.89-3.10)	1.83	(1.11, 2.81)
			Increase of 0.5x10-5 m-1	1.27	(1.04, 1.54)
			3rd trimester $PM_{2.5}$ absorbance ($10^{-5}m^{-1}$)		
			1st quartile (1.29-1.61)	1	Referent
			2nd quartile (1.61-1.72)	1.30	(0.85, 2.09)
			3rd quartile (1.72-1.89)	0.92	(0.55, 1.50)
			4th quartile (1.89-3.10)	1.50	(1.00, 2.27)
			Increase of 0.5x10-5 m-1	1.20	(0.98, 1.44)
			NO_2 (μgm^{-3}) over whole pregnancy		
			1st quartile (23.6-32.7)	1	Referent
			2nd quartile (32.7-35.8)	0.80	(0.52, 1.28)
			3rd quartile (35.8-39.0)	1.32	(0.86, 2.09)
			4th quartile (39.0-60.8)	1.16	(0.71, 1.71)
			Increase of 10 μgm^{-1}	1.21	(0.86, 1.68)
Van den Hooven *et al*	SGA	DWTD	1st quartile (<159 veh.m/day)	1	Referent
2009 Rotterdam			2nd quartile (159-547 veh.m/day)	0.94	(0.65, 1.36)
			3rd quartile (547-1,235 veh.m/day)	0.99	(0.69, 1.43)
			4th quartile (>1,235 veh.m/day)	1.12	(0.78, 1.59)
		SD	Distance to major road (m)		
			>200m	1	Referent
			150-200m	1.00	(0.67, 1.49)
			100-150m	1.01	(0.69, 1.48)
			50-100m	1.12	(0.78, 1.62)
			0-50m	1.14	(0.77, 1.68)
	BW	DWTD	1st quartile (<159 veh.m/day)	1	Referent
			2nd quartile (159-547 veh.m/day)	-20	(-47, 8)
			3rd quartile (547-1,235 veh.m/day)	-9	(-37, 18)
			4th quartile (>1,235 veh.m/day)	6	(-21, 34)
		SD	Distance to major road (m)		
			>200m	1	Referent
			150-200m	-21	(-52, 9)
			100-150m	-41	(-69, -12)
			50-100m	8	(-20, 37)
			0-50m	-6	(-36, 24)
Wilhelm & Ritz	Term LBW	DWTD	1st quintile (<1,524 veh/day)	1	Referent
2003 Los Angeles			2nd quintile (1,524-5,266 veh/day)	1.10	(0.98, 1.24)
			3rd quintile (5,267-11,568 veh/day)	1.17	(1.04, 1.32)
			4th quintile (11,569-24,579 veh/day)	1.16	(1.02, 1.31)
			5th quintile (>24,579 veh/day)	1.14	(1.00, 1.29)
			One or more freeways in buffer	1.00	(0.89, 1.12)
			3rd trimester in Winter months		
			1st quintile (<1,524 veh/day)	1	Referent
			2nd quintile (1,524-5,266 veh/day)	1.20	(1.01, 1.43)
			3rd quintile (5,267-11,568 veh/day)	1.36	(1.14, 1.62)
			4th quintile (11,569-24,579 veh/day)	1.35	(1.13, 1.61)
			5th quintile (>24,579 veh/day)	1.39	(1.16, 1.67)
Zeka *et al*	SGA	AADT	Cumulative traffic density (veh.km/day)	1.02	(1.00, 1.03)
2008 Eastern Massachusetts		SD	Distance to nearest major highway (m)	0.99	(0.97, 1.00)
	BW	AADT	Cumulative traffic density (veh.km/day)	-0.4	(-2.0, 1.3)
		SD	Distance to nearest major highway (m)	3.8	(1.9, 5.7)

Table 5. Adjusted risk estimates for mortality

Study author, year, location	Health outcome	Exposure Type	Exposure	Relative Risk	95% CI
Green *et al*	Spontaneous	Max AADT	*All women: Max AADT< 50m from residence*		
2009 California	abortion		<75th percentile	1	Referent
			75-89th percentile	0.91	(0.68, 1.21)
			>89th percentile	1.18	(0.87, 1.60)
			All women: Max AADT<100m from residence		
			<50th percentile	1	Referent
			50-74th percentile	0.97	(0.76, 1.24)
			75-89th percentile	1.10	(0.84, 1.46)
			>89th percentile	1.11	(0.80, 1.54)
			All women: Max AADT<150m from residence		
			<50th percentile	1	Referent
			50-74th percentile	1.02	(0.80, 1.29)
			75-89th percentile	0.88	(0.66, 1.18)
			>89th percentile	0.99	(0.71, 1.38)
			All women:		
			Max AADT<150m from resid. distance-weighted	1	Referent
			<75th percentile	1.07	(0.85, 1.36)
			75-89th percentile	1.05	(0.79, 1.40)
			>89th percentile	1.08	(0.78, 1.50)
			African American (N=314):		
			Max AADT< 50m from residence		
			<75th percentile	1	Referent
			75-89th percentile	0.92	(0.31, 2.74)
			>89th percentile	3.11	(1.26, 7.66)
			Non-Hispanic white (N=3,275):		
			Max AADT< 50m from residence		
			<75th percentile	1	Referent
			75-89th percentile	0.86	(0.61, 1.25)
			>89th percentile	1.16	(0.79, 1.71)
			Non-smokers (N=4,056):		
			Max AADT< 50m from residence		
			<75th percentile	1	Referent
			75-89th percentile	1.09	(0.80, 1.49)
			>89th percentile	1.47	(1.07, 2.04)
			Smokers (N=907):		
			Max AADT< 50m from residence		
			<75th percentile	1	Referent
			75-89th percentile	0.41	(0.19, 0.86)
			>89th percentile	0.36	(0.14, 0.93)
		SD	*All women: Distance to nearest arterial (m)*		
			0-50	1.00	(0.74, 1.34)
			51-100	0.93	(0.68, 1.26)
			101-200	0.89	(0.67, 1.18)
			201-300	1.00	(0.75, 1.35)
			>300	1	Referent
De Medeiros *et al*	Early neonatal	DWTD	1st quartile (0-6.0 veh/day)	1	Referent
2009 Sao Paulo, Brazil	mortality		2nd quartile (6.0-45.3 veh/day)	1.46	(0.67, 3.18)
	(0-28 days)		3rd quartile (45.3-370.2 veh/day)	2.82	(1.32, 6.03)
			4th quartile (370.2-10,810.9 veh/day)	1.47	(0.69, 3.19)
	Fetal mortality		1st quartile (0-6.0 veh/day)	1	Referent
			2nd quartile (6.0-45.3 veh/day)	1.06	(0.57, 1.96)
			3rd quartile (45.3-370.2 veh/day)	0.92	(0.48, 1.77)
			4th quartile (370.2-10,810.9 veh/day)	1.20	(0.65, 2.24)

Table 6. Adjusted risk estimates for pregnancy complications

Study author, year, location	Health outcome	Exposure Type	Exposure	Relative Risk	95% CI
Van den Hooven *et al* 2009 Rotterdam	Pre-eclampsia Eclampsia HELLP	DWTD	1st quartile (<159 veh.m/day)	1	Referent
			2nd quartile (159-547 veh.m/day)	0.94	(0.57, 1.55)
			3rd quartile (547-1,235 veh.m/day)	1.12	(0.70, 1.79)
			4th quartile (>1,235 veh.m/day)	1.14	(0.71, 1.82)
		SD	Distance to major road (m)		
			>200m	1	Referent
			150-200m	0.74	(0.42, 1.29)
			100-150m	0.96	(0.59, 1.56)
			50-100m	0.85	(0.52, 1.38)
			0-50m	1.03	(0.63, 1.69)
	Pregnancy-induced hypertension	DWTD	1st quartile (<159 veh.m/day)	1	Referent
			2nd quartile (159-547 veh.m/day)	1.00	(0.69, 1.45)
			3rd quartile (547-1,235 veh.m/day)	0.90	(0.62, 1.30)
			4th quartile (>1,235 veh.m/day)	1.07	(0.75, 1.53)
		SD	Distance to major road (m)		
			>200m	1	Referent
			150-200m	0.88	(0.57, 1.36)
			100-150m	0.94	(0.64, 1.39)
			50-100m	1.07	(0.75, 1.54)
			0-50m	1.08	(0.74, 1.60)
	Gestational diabetes	DWTD	1st quartile (<159 veh.m/day)	1	Referent
			2nd quartile (159-547 veh.m/day)	0.69	(0.30, 1.57)
			3rd quartile (547-1,235 veh.m/day)	1.07	(0.51, 2.23)
			4th quartile (>1,235 veh.m/day)	0.79	(0.35, 1.81)
		SD	Distance to major road (m)		
			>200m	1	Referent
			150-200m	1.07	(0.47, 2.44)
			100-150m	0.77	(0.32, 1.88)
			50-100m	1.13	(0.51, 2.50)
			0-50m	0.68	(0.25, 1.86)
Wu *et al* Los Angeles	Pre-eclampsia	Dispersion	NO_x over whole pregnancy		
			1st quartile (NA)	1	Referent
			4th quartile (NA)	1.33	(1.18–1.49)
			IQR (5.65ppb)	1.11	(1.06, 1.16)
			NO_x over 1st trimester		
			IQR (5.65ppb)	1.09	(1.05, 1.15)
			NO_x over 2nd trimester		
			IQR (5.65ppb)	1.10	(1.06, 1.15)
			NO_x over 3rd trimester		
			IQR (5.65ppb)	1.11	(1.06, 1.16)
			$PM_{2.5}$ over whole pregnancy		
			1st quartile (NA)	1	Referent
			4th quartile (NA)	1.42	(1.26, 1.59)
			IQR (1.35 μgm^{-3})	1.11	(1.06, 1.15)
			$PM_{2.5}$ over 1st trimester		
			IQR (1.35 μgm^{-3})	1.10	(1.06, 1.15)
			$PM_{2.5}$ over 2nd trimester		
			IQR (1.35 μgm^{-3})	1.12	(1.07, 1.16)
			$PM_{2.5}$ over 3rd trimester		
			IQR (1.35 μgm^{-3})	1.10	(1.06, 1.15)

References

Aguilera, I., M. Guxens, et al. (2009). "Association between GIS-Based Exposure to Urban Air Pollution during Pregnancy and Birth Weight in the INMA Sabadell Cohort." Environmental Health Perspectives 117(8): 1322-1327.

Albuquerque, C. A., K. R. Smith, et al. (2004). "Influence of maternal tobacco smoking during pregnancy on uterine, umbilical and fetal cerebral artery blood flows." Early Human Development 80(1): 31-42.

Archibong, A. E., F. Inyang, et al. (2002). "Alteration of pregnancy related hormones and fetal survival in F-344 rats exposed by inhalation to benzo(a)pyrene." Reproductive Toxicology 16(6): 801-808.

Bostrom, C. E., P. Gerde, et al. (2002). "Cancer risk assessment, indicators, and guidelines for polycyclic aromatic hydrocarbons in the ambient air." Environmental Health Perspectives 110 Suppl 3: 451-88.

Brauer, M., G. Hoek, et al. (2003). "Estimating Long-Term Average Particulate Air Pollution Concentrations: Application of Traffic Indicators and Geographic Information Systems." Epidemiology 14(2): 228.

Brauer, M., C. Lencar, et al. (2008). "A cohort study of traffic-related air pollution impacts on birth outcomes." Environmental Health Perspectives 116(5): 680-686.

Briggs, D. J., C. de Hoogh, et al. (2000). "A regression-based method for mapping traffic-related air pollution: application and testing in four contrasting urban environments." Science of the Total Environment 253(1-3): 151-67.

Byrne, J., D. Warburton, et al. (1985). "Morphology of early fetal deaths and their chromosomal characteristics." Teratology 32(2): 297-315.

Cox, L. H. (2000). "Statistical issues in the study of air pollution involving airborne particulate matter." EnvironMetrics(London, Ont.) 11(6): 611-626.

Cyrys, J., M. Hochadel, et al. (2005). "GIS-Based Estimation of Exposure to Particulate Matter and NO_2 in an Urban Area: Stochastic versus Dispersion Modeling." Environmental Health Perspectives 113(8): 987.

de Medeiros, A., N. Gouveia, et al. (2008). "Traffic-Related Air Pollution and Perinatal Mortality: A Case-Control Study." Environ Health Perspect 117(1).

De Rosa, M., S. Zarrilli, et al. (2003). "Traffic pollutants affect fertility in men." Hum. Reprod. 18(5): 1055-1061.

Dejmek, J. (2000). "The impact of polycyclic aromatic hydrocarbons and fine particles on pregnancy outcome." Environmental Health Perspectives 108(12): 1159.

Department of Environmental Protection. (2000). "Air Pollution and You." Retrieved 12 April 2008], from http://portal.environment.wa.gov.au/pls/portal/docs/PAGE/DOE_ADMIN/TECH_REPORTS_REPOSITORY/TAB1019688/AIR_POLLUTION.PDF.

Engel, S. A. M., H. C. Erichsen, et al. (2005). "Risk of spontaneous preterm birth is associated with common proinflammatory cytokine polymorphisms." Epidemiology 16(4): 469.

Evenson, D. P. and R. Wixon (2005). "Environmental toxicants cause sperm DNA fragmentation as detected by the Sperm Chromatin Structure Assay (SCSA®)." Toxicology and Applied Pharmacology 207(2, Supplement 1): 532-537.

Finkelstein, M. M., M. Jerrett, et al. (2005). "Environmental inequality and circulatory disease mortality gradients." Journal of Epidemiology & Community Health 59(6): 481-7.

Flachsbart, P. G. (1995). "Long-term trends in United States highway emissions, ambient concentrations, and in-vehicle exposure to carbon monoxide in traffic." J Expo Anal Environ Epidemiol 5(4): 473-95.

Généreux, M., N. Auger, et al. (2008). "Neighbourhood socioeconomic status, maternal education and adverse birth outcomes among mothers living near highways." Journal of Epidemiology & Community Health 62(8): 695-700.

Gibbs, R. S., R. Romero, et al. (1992). "A review of premature birth and subclinical infection." American journal of obstetrics and gynecology 166(5): 1515-1528.

Gilbert, N. L., S. Woodhouse, et al. (2003). "Ambient nitrogen dioxide and distance from a major highway." The Science of The Total Environment 312(1-3): 43-46.

Glinianaia, S. V., J. Rankin, et al. (2004). "Particulate air pollution and fetal health: a systematic review of the epidemiologic evidence." Epidemiology 15(1): 36-45.

Green, R. S., B. Malig, et al. (2009). "Residential Exposure to Traffic and Spontaneous Abortion." Environmental Health Perspectives 117(12): 1939.

Hansen, C., A. Neller, et al. (2006). "Low levels of ambient air pollution during pregnancy and fetal growth among term neonates in Brisbane, Australia." Environmental Research 103(3): 383-389.

Hansen, C. A., A. G. Barnett, et al. (2009). "Ambient air pollution and birth defects in brisbane, australia." PLoS ONE [Electronic Resource] 4(4): e5408.

Hansen, C. A., A. G. Barnett, et al. (2008). "The effect of ambient air pollution during early pregnancy on fetal ultrasonic measurements during mid-pregnancy." Environmental Health Perspectives 116(3): 362-9.

Hoek, G., R. Beelen, et al. (2008). "A review of land-use regression models to assess spatial variation of outdoor air pollution." Atmospheric environment 42(33): 7561.

Hoek, G., G. Kos, et al. (2009). "A Land Use Regression Model for Ultrafine Particles in Amsterdam." Epidemiology(Supplement): S76.

Hyunok, C., W. Jedrychowski, et al. (2006). "International Studies of Prenatal Exposure to Polycyclic Aromatic Hydrocarbons and Fetal Growth." Environmental Health Perspectives 114(11): 1744-1750.

Hyunok, C., V. Rauh, et al. (2008). "Prenatal Exposure to Airborne Polycyclic Aromatic Hydrocarbons and Risk of Intrauterine Growth Restriction.. (cover story)." Environmental Health Perspectives 116(5): 658-665.

Janssen, N. A. H., P. H. N. van Vliet, et al. (2001). "Assessment of exposure to traffic related air pollution of children attending schools near motorways." Atmospheric Environment 35(22): 3875-3884.

Jensen, S. S. (1998). "Mapping human exposure to traffic air pollution using GIS." Journal of Hazardous Materials 61(1-3): 385-392.

Kannan, S., D. P. Misra, et al. (2006). "Exposures to Airborne Particulate Matter and Adverse Perinatal Outcomes: A Biologically Plausible Mechanistic Framework for Exploring Potential Effect Modification by Nutrition." Environmental Health Perspectives 114(11): 1636.

Kaufman, J. S. (2009). "Interaction Reaction." Epidemiology 20(2): 159.

Keelan, J. A., M. Blumenstein, et al. (2003). "Cytokines, Prostaglandins and Parturition - A Review." Placenta 24(Supplement 1): S33-S46.

Kramer, M. S., R. W. Platt, et al. (2001). "A New and Improved Population-Based Canadian Reference for Birth Weight for Gestational Age." Pediatrics 108(2): e35-.

Lajinian, S., S. Hudson, et al. (1997). "An association between the heat-humidity index and preterm labor and delivery: a preliminary analysis." American Journal of Public Health 87(7): 1205.

Lipfert, F. W., R. E. Wyzga, et al. (2006). "Traffic density as a surrogate measure of environmental exposures in studies of air pollution health effects: Long-term mortality in a cohort of US veterans." Atmospheric Environment 40(1): 154-169.

Maisonet, M., A. Correa, et al. (2004). "A review of the literature on the effects of ambient air pollution on fetal growth." Environmental Research 95(1): 106-15.

Mattison, D. R., S. Wilson, et al. (2003). The Role of Environmental Hazards in Premature Birth: Workshop Summary.

Morgenstern, V., A. Zutavern, et al. (2007). "Respiratory health and individual estimated exposure to traffic-related air pollutants in a cohort of young children." Occup Environ Med 64(1): 8-16.

Murray, L. J., D. P. J. O'Reilly, et al. (2000). "Season and outdoor ambient temperature: effects on birth weight." Obstetrics and gynecology 96(5 Part 1): 689.

Nethery, E., M. Brauer, et al. (2009). "Time-activity patterns of pregnant women and changes during the course of pregnancy." Journal of Exposure Science & Environmental Epidemiology 19(3): 317-24.

Nethery, E., K. Teschke, et al. (2008). "Predicting personal exposure of pregnant women to traffic-related air pollutants." Science of the Total Environment 395(1): 11-22.

Noller, K. L., L. J. Resseguie, et al. (1996). "The effect of changes in atmospheric pressure on the occurrence of the spontaneous onset of labor in term pregnancies." American journal of obstetrics and gynecology 174(4): 1192.

Oberdorster, G., E. Oberdorster, et al. (2005). "Nanotoxicology: An Emerging Discipline Evolving from Studies of Ultrafine Particles." Environmental Health Perspectives 113(7): 823-839.

Pearson, R. L., H. Wachtel, et al. (2000). "Distance-weighted traffic density in proximity to a home is a risk factor for leukemia and other childhood cancers." Journal of the Air & Waste Management Association 50(2): 175-80.

Pereira, G., A. J. B. M. De Vos, et al. (2009). "Residential traffic exposure and children's emergency department presentation for asthma: a spatial study." International Journal of Health Geographics 8: 63-72.

Perera, F. P., T. Deliang, et al. (2005). "Relationships among Polycyclic Aromatic Hydrocarbon--DNA Adducts, Proximity to the World Trade Center, and Effects on Fetal Growth." Environmental Health Perspectives 113(8): 1062-1067.

Perera, F. P., T. Deliang, et al. (2004). "Biomarkers in Maternal and Newborn Blood Indicate Heightened Fetal Susceptibility to Procarcinogenic DNA Damage." Environmental Health Perspectives 112(10): 1133-1136.

Perera, F. P., W. Jedrychowski, et al. (1999). "Molecular epidemiologic research on the effects of environmental pollutants on the fetus." Environmental Health Perspectives 107 Suppl 3: 451-60.

Perera, F. P., V. Rauh, et al. (2003). "Effects of Transplacental Exposure to Environmental Pollutants on Birth Outcomes in a Multiethnic Population." Environmental Health Perspectives 111(2): 201.

Perera, F. P., R. M. Whyatt, et al. (1998). "Recent Developments in Molecular Epidemiology: A Study of the Effects of Environmental Polycyclic Aromatic Hydrocarbons on Birth Outcomes in Poland." Am. J. Epidemiol. 147(3): 309-314.

Ponce, N. A., K. J. Hoggatt, et al. (2005). "Preterm birth: the interaction of traffic-related air pollution with economic hardship in Los Angeles neighborhoods." American Journal of Epidemiology 162(2): 140-8.

Rankin, J., T. Chadwick, et al. (2009). "Maternal exposure to ambient air pollutants and risk of congenital anomalies." Environmental Research 109(2): 181-7.

Ritz, B. and M. Wilhelm (2008). "Ambient Air Pollution and Adverse Birth Outcomes: Methodologic Issues in an Emerging Field." Basic and Clinical Pharmacology and Toxicology 102: 182-190.

Ritz, B., M. Wilhelm, et al. (2007). "Ambient air pollution and preterm birth in the environment and pregnancy outcomes study at the University of California, Los Angeles." American Journal of Epidemiology 166(9): 1045-52.

Ritz, B., F. Yu, et al. (2002). "Ambient Air Pollution and Risk of Birth Defects in Southern California." American Journal of Epidemiology 155(1): 17.

Rocha e Silva, I. R., A. J. F. C. Lichtenfels, et al. (2008). "Effects of ambient levels of air pollution generated by traffic on birth and placental weights in mice." Fertility and sterility 90(5): 1921-1924.

Schauer, J. J., M. J. Kleeman, et al. (1999). "Measurement of Emissions from Air Pollution Sources. 2. C1 through C30 Organic Compounds from Medium Duty Diesel Trucks." Environmental Science & Technology 33(10): 1578-1587.

Schauer, J. J., M. J. Kleeman, et al. (2002). "Measurement of Emissions from Air Pollution Sources. 5. C1âˆ'C32 Organic Compounds from Gasoline-Powered Motor Vehicles." Environmental Science & Technology 36(6): 1169-1180.

Selevan, S. G. (2000). "Semen Quality and Reproductive Health of Young Czech Men Exposed to Seasonal Air Pollution." Environmental Health Perspectives 108(9): 887.

Shemin, D. and D. Rittenberg (1946). "The life span of the human red blood cell." The Journal of biological chemistry 166(62): 7.

Slama, R., L. Darrow, et al. (2008). "Meeting report: atmospheric pollution and human reproduction." Environmental Health Perspectives 116(6): 791-8.

Slama, R., V. Morgenstern, et al. (2007). "Traffic-related atmospheric pollutants levels during pregnancy and offspring's term birth weight: a study relying on a land-use regression exposure model." Environmental Health Perspectives 115(9): 1283-92.

Slama, R. m., L. Darrow, et al. (2008). "Meeting Report: Atmospheric Pollution and Human Reproduction." Environmental Health Perspectives 116(6): 791-798.

Sram, R. J., B. Binkova, et al. (2005). "Ambient air pollution and pregnancy outcomes: a review of the literature." Environmental Health Perspectives 113(4): 375-82.

Stroup, D. F. (2000). "Meta-analysis of observational studies in epidemiology: a proposal for reporting." JAMA 283(15): 2008.

Takeda, K., N. Tsukue, et al. (2004). "Endocrine-disrupting activity of chemicals in diesel exhaust and diesel exhaust particles." Environmental sciences 11(1): 33-45.

Tsukue, N., H. Tsubone, et al. (2002). "Diesel exhaust affects the abnormal delivery in pregnant mice and the growth of their young." Inhalation Toxicology 14(6): 635-651.

van den Hooven, E., V. Jaddoe, et al. (2009). "Residential traffic exposure and pregnancy-related outcomes: a prospective birth cohort study." Environmental Health 8(1): 59.

Veras, M. M., N. R. Damaceno-Rodrigues, et al. (2009). "Chronic exposure to fine particulate matter emitted by traffic affects reproductive and fetal outcomes in mice." Environmental Research 109(5): 536-543.

Wilhelm, M. and B. Ritz (2003). "Residential proximity to traffic and adverse birth outcomes in Los Angeles County." Environmental Health Perspectives 111: 207-216.

Wilhelm, M. and B. Ritz (2005). "Local variations in CO and particulate air pollution and adverse birth outcomes in Los Angeles County, California, USA." Environmental Health Perspectives 113(9): 1212-21.

Woodruff, T. J., J. D. Parker, et al. (2009). "Methodological issues in studies of air pollution and reproductive health." Environmental Research 109(3): 311-320.

Wu, J., C. Ren, et al. (2009). "Association between Local Traffic-Generated Air Pollution and Preeclampsia and Preterm Delivery in the South Coast Air Basin of California." Environmental Health Perspectives 117(11): 1773-1779.

Xu, X. and D. Hui (1995). "Acute effects of total suspended particles and sulfur dioxides on preterm delivery: A community." Archives of Environmental Health 50(6): 407.

Yackerson, N., B. Piura, et al. (2008). "The influence of meteorological factors on the emergence of preterm delivery and preterm premature rupture of membrane." Journal of Perinatology 28(10): 707.

Yang, C. Y., C. C. Chang, et al. (2003). "Evidence for increased risks of preterm delivery in a population residing near a freeway in Taiwan." Archives of Environmental Health 58(10): 649-54.

Zdravkovic, T., O. Genbacev, et al. (2005). "The adverse effects of maternal smoking on the human placenta: A review." Placenta 26(Supplement 1): S81-S86.

Zeka, A., S. Melly, et al. (2008). "The effects of socioeconomic status and indices of physical environment on reduced birth weight and preterm births in Eastern Massachusetts." Environmental Health 7(1): 60.

Zhu, Y., W. C. hinds, et al. (2002). "Concentration and Size Distribution of Ultrafine Particles Near a Major Highway." Journal of the Air & Waste Management Association (1995) 52(9): 1-2.

Ziaei, S., K. Nouri, et al. (2005). "Effects of carbon monoxide air pollution in pregnancy on neonatal nucleated red blood cells." Paediatric & Perinatal Epidemiology 19(1): 27-30.