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evidence review

Exposure to Traffic-Related Air Pollution and Perinatal Health

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Summary

- The period between conception and early childhood when vital organs are forming and rapidly developing is the most vulnerable of life stages to the effects of toxic environment exposures, including traffic-related air pollution (TRAP).
- Epidemiologic studies on preterm birth have consistently shown elevated risks with a number of measures of TRAP, including distance of residence from traffic corridors, traffic volume, air pollution surrogates, particularly $PM_{2.5}$, and modeled estimates.
- Fetal exposure to traffic-related pollutants is not consistently associated with indicators of fetal growth, including low birth weight, small for gestational age, and intrauterine growth restriction.
- There is very limited evidence of weak associations between TRAP and perinatal mortality and congenital abnormalities.
- Further research on the potential for perinatal health effects due to exposure to TRAP is warranted, given that TRAP is a common exposure, and that there are long-term health implications associated with poor perinatal health.

Background

Perinatal health

The stage between conception and birth is one of the most vulnerable life stages because it represents a phase of great maturation and change in organ development. It is recognized that exposures to toxic substances in fetal life and early childhood may result in disease and dysfunction throughout life.[1] The developing fetus has an immature immune system and is less proficient at eliminating air pollutants, and there is heightened susceptibility to infections during early childhood.[2]

The World Health Organization defines the perinatal period from 22 completed weeks (or 154 days) gestation to seven days following birth.[3] In recent years, perinatal health has become a major focus for public health practitioners and health policymakers in Canada. A 2007 report by the Canadian Institutes for Health Research identified the need to study the "effects of low-level exposure to a wide range of environmental toxicants on

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the development of the embryo and fetus (including the risks of birth defects, miscarriage, stillbirth, preterm birth, and growth restriction)".[4] Researching birth outcomes, such as prematurity, low birth weight, and intrauterine growth retardation is an emerging field of environmental epidemiology.[5] Not only are these important indicators of newborn and infant health, they can influence the development of chronic disease in adulthood.[6,7]

The existing Canadian Perinatal Surveillance System presents trends in perinatal health and specific determinants that influence health status.[8] However, the effects of exposure to environmental contaminants have not yet been addressed.[9]

Traffic-Related Air Pollution (TRAP)

TRAP refers to air pollutants emitted from motor vehicles, including carbon monoxide (CO), carbon dioxide (CO_2), hydrocarbons, particulate matter (PM), nitrogen oxides (NO and NO_2), as well as mobile source air toxics, such as benzene, formaldehyde, acetaldehyde and 1,3-butadiene.[10] Growing car and large truck vehicle fleets and increasing traffic congestion and urbanization have amplified concerns about exposures to poor quality air from traffic sources.[10]

Individuals typically spend more than 80% of their time at home.[11,12] Given the duration of time spent at home, and the ease of measuring the proximity of homes to major roads and highways, residential location can be used as a proxy for exposure.[13] Traffic-related emission gradients exist up to 300–500 metres from major roadways,[10,14] and in Canada, nearly one-third of the population resides within 100 metres of a major road or 500 metres of a highway.[13]

Another proxy for exposure is the use of specific air pollutants as surrogates that represent TRAP, although a limitation of this approach is that the pollutants are not unique to traffic emissions. The most commonly used surrogates of TRAP include: NO_2, ultrafine particles, fine particles ($PM_{2.5}$), black carbon (specific to diesel exhaust), CO, and benzene.[10]

In epidemiological studies, land-use regression (LUR) modeling is also a common method for estimating TRAP.[15] These models use existing parameters such as traffic intensity, road type, and land cover to predict pollutant concentrations across an urban environment.[16] To date, air pollution researchers have constructed LUR models for nine Canadian cities.[13]

Purpose

The objective of this review is to provide Canadian public health practitioners with an assessment of the relationship between exposure to TRAP and specific perinatal health outcomes.

Methods

A literature search of article keywords, titles, and abstracts was conducted using terms uniquely focused on TRAP, combined with terms for perinatal health. Four databases (Ovid Medline; Web of Science; Google Scholar; and EBSCO Databases) were used to search for academic articles and abstracts, as well as grey literature that pertained to TRAP and the following perinatal health outcomes: (a) mortality of fetuses and newborns (i.e., perinatal or intrauterine mortality); (b) low full-term birth weight (LBW), small for gestational age (SGA), and intrauterine growth restriction (IUGR); (c) premature (or preterm) births (PTB); and (d) congenital (or birth) defects (or anomalies). Studies where the time periods of the outcomes overlapped the perinatal period (such as the neonatal period from birth to 28 days) were included.

Full details of the literature search strategy and literature organization can be found in Appendix 1.

The review is structured to include an assessment of the effects of individual traffic-surrogate air pollutants followed by evidence relating to TRAP as defined by the proximity of residences near major roads or through modeling approaches.

Results and Discussion

Perinatal mortality

Perinatal mortality is defined as fetal deaths beginning at 22 completed weeks, or 154 days gestation, and live-birth deaths within the first seven days following delivery.[17]

In a systematic review of 15 studies published between 1966 and 2003 there was inconsistent evidence of an association between PM air pollution total suspended particles (TSP), PM_{10}, and $PM_{2.5}$, and neonatal mortality.[18] Two studies on intrauterine mortality (stillbirth after 28 weeks gestation) were described in a comprehensive review by Lacasana and colleagues.[19] The time-series analysis of data from São Paulo, Brazil, showed a strong association between intrauterine mortality and NO_2, while links with PM_{10}, SO_2, and CO were inconsistent.[20] No association between air pollutants (TSP, SO_2, and NO_X) and intrauterine mortality was found in the Czech Republic study.[21]

A case-control study in São Paulo, Brazil,[22,23] estimated exposure to TRAP using distance-weighted traffic density, based on the mother's residential address, the distance to neighboring streets, and overall traffic flow in these streets.[24] The study showed a gradient of elevated risk of early neonatal death and TRAP. For mothers exposed to the highest exposure category, compared with those less exposed, the odds ratio for neonatal deaths was elevated but non-statistically significant (OR 1.47; 95% CI, 0.67–3.19).[24]

Measures of fetal growth

Birth weight is a common measure of fetal growth as data are widely available through medical registers. Low birth weight refers to a birth of less than 2,500 grams; below this weight, infant mortality begins to rise dramatically.[17] Intrauterine growth restriction (IUGR) is a non-specific condition in which the fetus fails to reach its expected size at a given gestational age, manifesting as low birth weight.[17] IUGR is associated with chronic disease in adulthood, such as coronary heart disease and hypertension.[5] Small (or short) for gestational age applies to all newborns with a birth weight (or length) below the 10th percentile at any given gestational age.

There is conflicting evidence on the relationship between TRAP and birth weight, although the majority of studies imply an association. In a systematic review and meta-analysis, Stieb and colleagues[25] reviewed 62 studies of air pollution and pregnancy outcome, with the majority of studies reporting reduced birth weight and increased odds of low birth weight as a result of exposure to CO, NO_2 or PM. Pooled estimates of decrease in birth weight for estimated exposures over the entire pregnancy varied from 11.4 g (95% CI, 6.9–29.7 g) per 1 ppm increase in CO to 28.1 g (11.5–44.8 g) per 20 ppb increase in NO_2. Pooled odds ratios based specifically on third trimester exposures were low, but statistically significant, at 1.04 (1.02–1.06) per 1 ppm increase in CO to 1.06 (1.03–1.11) per 20 $\mu g/m^3$ increase in PM_{10} exposure.

Two of 10 selected studies in a systematic review[26] reported an association between exposure to specific pollutants and birth weight, while the remaining eight studies reported no relationship. The first study by Salam and colleagues determined that a 12 parts per billion (ppb) increase in 24-hour ozone exposure averaged over the entire pregnancy was associated with a 47.2 g reduced birth weight (95% CI, 27.4–67.0 g), and this association was even stronger for exposures during the second and third trimesters in the perinatal period.[27] The second study to show a relationship reported an interquartile increase in gestational exposure to NO_2, CO, PM_{10}, or $PM_{2.5}$ reduced birth weight by 8.9 grams (95% CI, 7.0–10.8 g), 16.2 g (95% CI, 12.6–19.7 g), 8.2 g (95% CI, 5.3–11.1 g), and 14.7 g (95% CI, 12.3–17.1 g), respectively.[28]

Adverse fetal growth indicators have been linked to traffic proximity and density. In a Californian cohort of 237,031 singleton births, higher traffic density was associated with increased probability of full-term LBW. While the results did not show clearly an exposure-response relationship across the traffic density exposure quartiles, significant differences in the probability of LBW were shown between the highest and lowest quartiles.[29] For pregnant women living near a high-volume freeway, the estimated probability of term low-birth weight was slightly increased at 2.27% (95% CI, 2.16–2.38), as compared with 2.02% (95% CI, 1.90–2.12) for someone living near a smaller local road.[29]

In North Carolina, a large sample of women who lived within 250 metres of a roadway were at 3 to 5% increased odds of LBW, preterm birth, and late preterm birth compared to those living further away ($p<0.05$).[30] However, birth weight, birth weight percentile for gestational age, and small-for-gestational age were not associated with road proximity. Montreal mothers living within 200 metres of highways had odds of 1.17 (95% CI, 1.04–1.33) of giving birth to a child with LBW, compared to mothers who did not live near busy roadways. For mothers residing in wealthy neighbourhoods, proximity to a highway was associated with even higher odds of LBW (OR 1.81, 95% CI, 1.36–2.41).[31]

A study in Vancouver, British Columbia, found that SGA was associated with average exposure to $PM_{2.5}$, NO_2, and NO over the full gestation period and with living within 50 metres of highways where a "highway" was defined as an expressway averaging about 114,000 vehicles per day, or a main highway averaging approximately 21,000 motor vehicles each day. Mothers residing within 50 metres of highways had a 26% increased risk of their newborn being SGA (95% CI, 1.07–1.49), and an 11% increased risk of LBW (95% CI, 1.01–1.23) in newborns.[32]

In contrast to the positive findings in the above studies, a recent meta-analyses by Sapkota and colleagues[33] concluded that the association between $PM_{2.5}$ and PM_{10} with low birth weight was inconclusive. This review identified 20 peer-reviewed articles and found heterogeneity in exposure made it difficult to pool studies to establish an overall risk estimate.[33]

Racial or ethnicity differences in the relationship between perinatal health outcomes and air pollution have been observed but not explained. For example, the effect estimates are stronger between exposure to CO and LBW in African American infants[34] and of exposure to polycyclic aromatic hydrocarbons with head circumference and birth weight among African American women.[35]

Appendix 2, Table 1 summarizes the reviewed studies on the association of TRAP exposure with the fetal growth indices of LBW, SGA, and IUGR.

Preterm births (PTB)

PTB refers to delivery before 37 weeks, or less than 259 days, of gestation.[17] In a systematic review, exposures to sulphur dioxide and $PM_{2.5}$ were associated with PTB.[26] In their meta-analysis, Sapkota and colleagues calculated a 15% increase in risk of PTB associated with a 10 µg/m^3 increase in $PM_{2.5}$ (combined OR, 1.15; 95% CI, 1.14–1.16).[33] The magnitude of risk associated with PM_{10} exposure was less (2% per 10-µg/m3 increase) and was not statistically significant.[33] A study in Los Angeles and Orange County showed elevated risks for very preterm birth (VPTB) associated with maternal exposure to traffic-generated nitrogen oxides and $PM_{2.5}$. Women in the highest $PM_{2.5}$ and nitrogen oxides exposure quartiles had an 81% (OR 1.81, 95% CI, 1.71–1.92) and 128% (OR 2.28, 95% CI, 2.15–2.42) increased risk for VPTB, respectively.[36] In Vancouver, average $PM_{2.5}$ exposure during pregnancy was associated with PTB, as determined in two periods (less than 35 and 30 weeks). There was no association between road proximity and PTB less than 37 weeks.[32]

However, proximity to major roads has been consistently associated with PTB. A study from Taiwan showed that the prevalence of PTB was significantly higher among mothers who resided within 500 metres of a freeway relative to mothers who lived 500 to 1,500 metres away.[37] Mothers living in wealthy neighbourhoods in Montreal and situated within 200 metres of a busy highway had elevated odds of PTB (OR 1.58, 95% CI, 1.23–2.04). A study from Shizuoka, Japan, found an association between proximity to major roads and PTB at different gestational ages.[38] In this study, researchers found that living within 200 metres of a major road increased the risk of births before 28 weeks by 1.8 times (95% CI, 1.0–3.2), births before 32 weeks by 1.6 times (1.1–2.4), and births before 37 weeks by 1.5 times (1.2–1.8). A recent systematic review corroborated the relationship between PTB and TRAP indices including residential exposure to TRAP as estimated by proximity (e.g., distance to major road), an indication for traffic volume (e.g., vehicle kilometres travelled), and a modeled traffic pollutant or measured pollutant at the maternal residential address. Although effect estimates were elevated, not all were statistically significant.[39]

Appendix 2, Table 2 summarizes results on the association of TRAP exposure with preterm births.

Congenital (birth) defects

Congenital or birth defects/anomalies can be defined as structural or functional anomalies (including metabolic disorders) which are present at birth.[3] A limited number of studies have examined associations between exposure to ambient air pollution, as determined by air quality measurements from fixed monitoring stations, and the risk of congenital defects.[5,19]

In a recent systematic review and meta-analysis of studies evaluating the risk of congenital anomalies due to air pollution, exposures to NO_2, SO_2, and PM_{10} were each associated with a slight increased risk of at least one cardiac anomaly.[40] The reviewed studies were based on registry information, with air quality measurements based on residential addresses available only at birth. Exposure to NO_2 was associated with increases of coarctation (abnormal narrowing) of the aorta; and SO_2 was associated with tetralogy of Fallot (a common form of cyanotic heart defect), pulmonary stenosis, right ventricular hypertrophy and an overriding aorta; and PM_{10} exposure was associated with an increased risk of atrial septal defects (a congenital heart defect that enables the flow of blood between the left and right atria).[40] The review[40] identified one study[41] that used a model for maternal exposure to black smoke as a surrogate of TRAP and showed a weak association with congenital cardiac malformations when using exposure as a continuous variable but no association when exposure was treated as a categorical variable.[41]

A French retrospective cohort study of the risk of congenital anomalies related to residential traffic density found associations with cardiac anomalies but also with skin anomalies and obstructive uropathies.[42]

Knowledge Gaps and Challenges

Three meta-analyzes on air pollution and perinatal health have helped to elucidate the relationship between a host of air pollutants and specific adverse health outcomes.[25,33,40] While results were not always statistically significant, maternal residence near major roads and highways (a simple proxy for exposure to TRAP) was related to LBW,[31,32,43] SGA,[32] and PTB.[31,37,38,43] However, it is unknown whether socioeconomic variables, which may be related to residence near roadways, were adequately taken into account. The majority of reviewed studies adjusted for pregnancy, child, and maternal characteristics in their analyses, but comparatively few controlled for the confounding effects of environmental tobacco smoke or maternal smoking during pregnancy. According to Pereira et al., information on personal exposures is seldom available from sizeable population data sources.[44]

The biological route and mechanisms of effect remain unknown. Exposure to $PM_{2.5}$ has been demonstrated to elevate oxidative stress,[45] and elevated oxidative stress has then been linked to PTB.[46] A Czech Republic study found exposure to $PM_{2.5}$ is associated with increased T cells (CD3+ and CD4+ lymphocytes), as well as decreased B cells (CD19+) and natural killer cell percentages in placental blood.[47] The shifts in cord blood lymphocyte distributions initiated by increased $PM_{2.5}$ exposure may in turn influence fetal immune development.[47] The lack of research conducted on the biological mechanisms precludes more formal statements of the deleterious effect of maternal exposure to TRAP during the perinatal period.[39]

Better exposure assessment of TRAP should not rely on maternal residence as the exposure metric, or as the basis for modeled exposure to air pollutants. Error in measurements can lead to an underestimation of the association. As well, assessment for a variety of outcomes related to perinatal health can suggest significance due to multiple comparisons in the analysis. Publication bias would emphasize positive studies, which seems less likely due to contradictory findings.

Conclusion

In the 2010 Health Effects Institute's report, *Traffic-Related Air Pollution: A Critical Review of the Literature on Emissions, Exposure, and Health Effects*, only four studies of TRAP exposure and perinatal outcomes[32,43,48,49] were identified.[10] The small number of studies and their narrow geographic coverage led the review panel to conclude that there is "inadequate and insufficient" evidence to infer causality.[10] Since the HEI report was released, Pereira et al.[39] found 12 studies which focused on the relationship between TRAP and adverse birth outcomes, and a number of newer studies have confirmed a relationship between exposure to TRAP and adverse birth outcomes.[29,30,44]

In general, the evidence on perinatal health effects related to TRAP is still relatively sparse, with the exception of the relatively consistent findings of an elevated risk of premature births related to exposure to different metrics of TRAP. Findings on the fetal growth indices, such as low birth weight, are contradictory and relatively few studies have investigated the effect of TRAP on perinatal mortality. Furthermore, the plausibility of the relationship of TRAP and perinatal health needs to be addressed through a better understanding of the toxicologically relevant constituents and underlying mechanisms.

Adverse perinatal outcomes are a major public health concern. Because exposure to TRAP is common and effects on fetal growth and development can have critical consequences on health throughout life, further investigations of the effects of TRAP on perinatal health are important. Exposure to TRAP through proximity of residents to major roads suggests opportunities for urban design approaches to mitigate exposures and ultimately prevent adverse health outcomes.

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Appendix 1

Databases and search tools: The literature search employed the following databases and indices:

- **Ovid Medline:** http://www.ovid.com
- **Web of Science:** Citation Index; https://apps.isiknowledge.com
- **Google Scholar:** http://scholar.google.com
- **EBSCO Databases:** http://www.ebsco.com/

Search criteria: Text word searches of article titles and abstracts using the search tools listed above were conducted using search terms related to traffic-related air pollution and perinatal health. Combinations of the following primary keywords were used in the searches:

traffic	*air pollution*	*pregnancy*	*perinatal*
perinatal care	*perinatal mortality*	*postnatal*	*vehicle emissions*
traffic-related air pollution	*environmental exposure*	*carbon monoxide*	*nitrogen dioxide*
reproductive	*birth*	*particulate matter*	*black carbon*

The literature search was conducted in January 2013 and updated through to the end of March 2013. There was no restriction of searches to specific time/date ranges, but greater emphasis was placed on articles that have been published since 2004 and where the research relates to a Canadian or North American context.

Inclusion and exclusion criteria: A total of 176 abstracts/articles were compiled using the search tools and keywords discussed above and were subsequently screened and restricted further according to their specific relevance to traffic-related air pollution and perinatal health. References where the "traffic" and "perinatal" components were absent were generally excluded. Studies examining exclusively the postnatal, neonatal, and postneonatal periods were not included. Initial review of searched articles yielded additional references – including grey literature – that was used to supplement the original search. In general, we sought English-language literature and categorized the search results according to the birth outcomes listed below. Several studies examined two or more of these outcomes:

a) Mortality of fetuses and newborns;
b) Low full-term birth weight (LBW), small for gestational age (SGA), and intrauterine growth restriction (IUGR)
c) Premature (preterm) births (i.e., prematurity);
d) Congenital (birth) defects.

Literature organization: Bibliographic data and relevant references (in PDF format) from the electronic and print literature obtained through the above methods were entered and stored into *Papers2* – an online citation management database and centralized electronic repository (http://www.mekentosj.com/papers/).

Appendix 2

Table 1. Studies of exposure to traffic-related air pollution, low birth weight (LBW), small for gestational age (SGA), or intrauterine growth restriction

Reference /Location	Study Design Year of Study (N = live births)	Exposure Metric	Summary of Results
Padula et al., (2012)[29] San Joaquin Valley, United States	**Cohort study** 2000–2006 **(329,362)**	Traffic density, per quartile.	**LBW**: Full-term births results showed no clear exposure-response relation across the quartiles of traffic density. For a pregnant woman living near a high-volume freeway, the estimated probability of term low birth weight would be 2.27% (95% CI, 2.16–2.38) as compared with 2.02% (95% CI, 1.90–2.12) for someone living near a smaller local road.
Wilhelm et al., (2012)[50] Los Angeles County, United States	**Cohort** 2004–2006 **(220,528)**	Air toxics (including PAHs) and source-specific $PM_{2.5}$ estimated based on (1) a chemical mass balance model; (2) criteria air pollutants from government monitoring data; (3) land use regression estimates for residential NO, NO_2, and nitrogen oxides concentrations (LUR previous developed by (51)).	**Term LBW**: approximately 5% increase in the odds of term LBW per interquartile range increase in entire pregnancy averages of nitrogen oxides, nitrogen oxide, and NO_2 (as estimated by LUR, elemental carbon, and $PM_{2.5}$ from diesel and gasoline exhaust and paved road dust.
Yorifuji et al., (2012)[38] Shizuoka, Japan	**Cohort** 1997–2008 **(14,189)**	Proximity to major roads (residing within 200 m of a major road).	**Placenta and birth weight**: Residential proximity to major roads was associated with higher placenta/birth weight ratio. Residing within 200 m of a major road increased the ratio by 0.48% (95% CI, 0.15–0. 80), after adjusting for potential confounders (e.g. maternal occupation and smoking status). Residing within close proximity to major roads was associated with lower placenta weight and birth weight.
Kashima et al., (2011)[51] Shizuoka, Japan	**Cohort** 1997–2008 **(16,311)**	Three traffic-based exposure indicators: (1) distance to a major road; (2) distance-weighted traffic density; (3) estimated concentration of NO_2 by land use regression.	**Birth weight/term LBW/SGA**: No clear associations between the three markers of TRAP and birth weight related outcomes.
Gehring et al., (2011)[52] Amsterdam, The Netherlands	**Prospective cohort** 2003–2004 **(7,600)**	Temporally adjusted land-use regression model for NO_2 at maternal residence during entire pregnancy and trimesters.	**Birth weight**: No indication of an adverse effect of TRAP exposure on term birth weight. Furthermore, no indication of a harmful effect of NO_2 as a marker for TRAP exposure over varying periods of pregnancy on term birth weight.

Gehring et al., (2011)[53] Amsterdam, The Netherlands	**Cohort** 1996–1997 **(3,853)**	Temporally adjusted land-use regression model for NO_2, $PM_{2.5}$, and ''soot'' at birth address of each participant during pregnancy (entire pregnancy, first trimester, and last month).	**Term birth weight**: Maternal exposure to TRAP during pregnancy not associated with term birth weight.
Malmqvist et al., (2011)[54] Scania, Sweden	**Cohort** 1999–2005 **(81,110)**	(1) proximity to roads with differing traffic density; (2) modeled exposure data at residence for nitrogen oxides.	**LBW**: Individually modeled nitrogen oxide levels and traffic density were not associated with the risk of having a child with LBW. **SGA**: Increased risk for SGA babies when comparing residences in the highest vs. lowest nitrogen oxides quartiles, adjusting for maternal age, year of birth, sex, and smoking (upon adjusting for confounders with the greatest impact on SGA, parity, and maternal country of origin – which were highly intercorrelated; the increased risk was not statistically significant). In subgroup analyzes, an increased risk for SGA among girls was still observed for the noted quartiles [odds ratio (OR) = 1.12; 95% confidence interval (CI), 1.01–1.24)].
Barnett et al., (2011)[55] Logan, Australia	**Prospective cohort** 2007–2008 **(970)**	(1) residential distance to nearest road (freeways, highways, main roads); (2) number of roads around the home (in radii from 50–500 m).	**LBW / Birth length / head circumference**: No negative impacts after adjusting for gestation.
Miranda et al., (2010)[30] North Carolina, United States	**Cohort** 2004–2008 **(531,385)**	TRAP exposure during pregnancy characterized by the linear distance between residential address at delivery and nearest major roadway.	**LBW**: Women living within 250 m of a major roadway were at 3–5% increased odds of LBW compared with women living beyond 250 m ($p<0.05$). Birth weight, birth weight percentile for gestational age, gestational hypertension, and SGA were not associated with road proximity.
Ballester et al., (2010)[56] Valencia, Spain	**Cohort** 2003–2005 **(785)**	Land use regression used to assess exposure to ambient NO_2, spatially adjusted to correspond to relevant periods during pregnancy.	**Birth length and weight**: NO_2 exposure >40 μg/m^3 during the first trimester associated with a change in birth weight of -40.3 grams (-96.3 to 15.6) and with a change in birth length of -0.27 cm (95% CI, -0.51 to -0.03). After adjusting for confounders, a 10 μg/m^3 increase in NO_2 during the second trimester associated with SGA-weight [odds ratio (OR): 1.37 (1.01–1.85)] and with SGA-length [OR: 1.42 (0.89–2.25)].
Aguilera et al., (2010)[57] Catalonia, Spain	**Prospective cohort** 2004–2006 **(562 pregnant mothers/1,692 ultrasound measurements)**	Temporally adjusted land-use regression to estimate exposures to NO_2 and benzene, toluene, ethylbenzene, m/p-xylene, and o-xylene.	**Fetal growth** (using ultrasound for measurements): Exposure to BTEX during early pregnancy was negatively associated with growth in biparietal diameter (out of five fetal growth characteristics). Other fetal growth parameters were not associated with exposure to air pollution during pregnancy. For women who spent < 2 hr/day in nonresidential outdoor locations, effect estimates were statistically significant (p,0.05) for the association between NO_2 and growth in head circumference during weeks 12–20, and growth in biparietal diameter, abdominal circumference, and estimated fetal weight between weeks 20-32.

Brauer et al., (2008)[32] Vancouver, Canada	**Retrospective cohort** 1999–2002 **(70,249)**	(1) inverse-distance weighted CO, NO, NO_2, ozone, sulphur dioxide, $PM_{2.5}$, and PM_{10} measured at regulatory monitoring sites; (2) modeled black carbon, nitrogen oxide, NO_2, and $PM_{2.5}$ from measurement at multiple monitoring points and LUR-based on roads within residential buffers; (3) measures of distance from roadways.	**SGA**: Mothers residing within 50 m of highways had an average of a 26% increased risk of their newborn being SGA (95% CL, 1.07–1.49). Exposure to air pollutants with the exception of O_3 was associated with SGA, with comparable odds ratios (ORs) for LUR and monitoring estimates. For example: LUR: OR 1.02; 95% CI, 1.00–1.04; IDW: OR 1.05; 95% CI, 1.03–1.08 per 10-μg/m^3 increase in NO. **LBW**: Mothers residing within 50 m of highways had an average of an 11% increase in LBW (95% CI, 1.01–1.23).
Généreux et al., (2008)[31] Montreal, Quebec	**Retrospective cohort** 1997–2001 **(99,819)**	Residential proximity within 200 m of highway (i.e., major road having a maximum speed limit of ≥ 70 km/h with no stop signs or traffic lights).	**LBW**: Mothers residing within 200 m of highway had a 17% increased odds of LBW (OR 1.17, 95% CI, 1.04–1.33) compared to mothers residing farther away from highways. For mothers living in wealthy neighbourhoods, proximity to highway was associated with even higher odds.
Généreux et al., (2008)[31] Montreal, Quebec	**Retrospective cohort** 1998–1999 **(1,016)**	Exposure estimated from LUR • 40 sites • measures of road density, Per quartile of exposure range, for NO_2, and $PM_{2.5}$.	**LBW**: The prevalence ratios of birth weight less than 3,000 g associated with the highest quartile were 1.2 for NO_2 (95% CI, 0.7–1.7), 1.7 for $PM_{2.5}$ (95% CI, 1.2–2.7), and 1.8 for $PM_{2.5}$ absorbance (95% CI, 1.1–2.7) [the lowest quartile of exposure during pregnancy used as reference]. The prevalence ratio associated with an increase of 1 μg/m^3 in $PM_{2.5}$ levels was 1.13 (95% CI, 1.00–1.29).
Slama et al., (2007)[48] Munich, Germany	**Case-control** 1994–1996 **(50,933)**	Distance-weighted traffic density.	**LBW**: Elevated risks for LBW for women residing in the highest distance-weighted traffic density area and whose third trimester fell during winter months [OR for term LBW = 1.39, 95% CI, 1.16–1.67)].

Abbreviations:
LUR – land use regression; PM – particulate matter; NO_x – nitrogen oxides; SO_2 – sulphur dioxide; CI – confidence interval; SGA – small for gestational age

Table 2. Studies of exposure to traffic-related air pollution and preterm births (PTB)

Reference /Location	**Study Design** Year of Study **(N = live births)**	**Exposure Metric**	**Summary of Results**
Miranda et al., (2013)[30] North Carolina, United States	**Cohort** 2004–2008 **(531,385)**	TRAP exposure (during pregnancy) characterized by the linear distance between residential address at delivery and nearest major roadway.	**PTB and late PTB**: Women living within 250 m of a major roadway were at 3-5% increased odds of PTB and late PTB, compared with women living beyond 250 m ($p<0.05$).
Malmqvist et al., (2011)[54] Scania, Sweden	**Cohort** 1999–2005 **(81,110)**	(1) Proximity to roads with differing traffic density; (2) modeled exposure data at residence for nitrogen oxides.	**PTB**: Risk of PTB was lower in the three higher NO_2 exposure quartiles compared with reference category. For traffic density, no statistically significant associations were observed.
Barnett et al., (2011)[55] Logan, Australia	**Prospective cohort** 2007–2008 **(970)**	(1) residential distance to nearest road (freeways, highways, main roads); (2) number of roads around the home (in radii from 50–500 m).	**Shorter gestation time**: No associations with distance to road, however a greater number of main roads and freeways surrounding home were associated with a shorter gestation time (for every 10 extra main roads within 400 m of home, gestation time decreased by 1.1% (95% CI, -1.7 – -0.5; p-value = 0.001].
Yorifuji et al., (2011)[38] Shizuoka, Japan	**Cohort** 1997–2008 **(14,226)**	Proximity to major roads.	**PTB**: Positive associations between proximity to major roads and preterm births at all gestational ages. Living within 200 m increased the risk of births before 28 weeks by 1.8 times (95% CI, 1.0–3.2), birth before 32 weeks by 1.6 times (95% CI, 1.1–2.4), and births before 37 weeks by 1.5 times (95% CI, 1.2–1.8).
Wilhelm et al., (2011)[58] Los Angeles County, United States	**Case-control** 2004–2006 **(112,915)**	Pregnancy period exposure averages were estimated for the following: (1) polycyclic aromatic hydrocarbons and $PM_{2.5}$ via a Chemical Mass Balance model; (2) criteria air pollutants based on government monitoring data; and (3) land use regression estimates for NOx.	**PTB**: Odds of PTB increased between 6 and 21% per inter-quartile range increase in entire pregnancy exposures to elemental carbon, organic carbon, benzene, and $PM_{2.5}$ (attributed to biomass burning, ammonium nitrate and diesel). $PM_{2.5}$. Thirty percent per inter-quartile increase in polycyclic aromatic hydrocarbons. Weak associations with LUR exposure metrics (3 to 4% per inter-quartile range increase).
Wu et al., (2009)[36] Los Angeles and Orange Counties, United States	**Retrospective cohort** 1997–2006 **(81,186)**	Line-source dispersion model for traffic-generated $PM_{2.5}$ and NOx across entire pregnancy.	**PTB and VPTB**: Elevated risks for preterm birth from maternal exposure to local traffic-generated nitrogen oxides and $PM_{2.5}$. The risk of VPTB increased 81% (OR 1.81, 95% CI, 1.71–1.92) and 128% (OR 2.28, 95% CI, 2.15–2.42) for women in the highest $PM_{2.5}$ and NOx exposure quartiles, respectively.
van den Hooven et al., (2009)[59] Rotterdam, The Netherlands	**Prospective cohort** 2002–2006 **(7,339)**	(1) Distance-weighted traffic density quartiles; (2) Distance to nearest road.	**PTB**: No substantial differences in traffic exposure between cases and non-cases of PTB.

Généreux et al., (2008)[31] Montreal, Quebec	**Retrospective cohort** 1997–2001 **(99,819)**	Residential proximity within 200 m of highway (i.e., major road having a maximum speed limit of ≥ 70 km/h with no stop signs or traffic lights).	**PTB**: Mothers residing within 200 m of a highway had a 14% increased odds of preterm birth (OR 1.14, 95% CI, 1.02–1.27).
Brauer et al., (2008)[32] Vancouver, Canada	**Retrospective cohort** 1999–2002 **(70,249)**	(1) inverse-distance weighted CO, NO, NO_2, ozone, SO_2, $PM_{2.5}$, and PM_{10} measured at regulatory monitoring sites; (2) modeled BC, NO, NO_2, and $PM_{2.5}$ from measurement at multiple monitoring points and LUR-based on roads within residential buffers; (3) measures of distance from roadways.	**PTB**: No significant associations were detected for those living in close proximity to traffic. Associations were observed with $PM_{2.5}$ for births < 37 weeks gestation, as well as for other pollutants at < 30 weeks. Authors note that no consistent patterns suggested exposure windows of greater significance.
Ritz et al., (2007)[60] Los Angeles County, United States	**Case-control** 2003 **(2,543)**	Mother's residence (at time of delivery) linked to air quality monitoring station that provided mean pollutant measures for CO, NO_2 and ozone, and near daily measurements for $PM_{2.5}$. Three gestational periods: (a) entire pregnancy; (b) first trimester; (c) last 6 weeks prior to delivery.	**PTB**: Odds of PTB increased with increasing high CO and $PM_{2.5}$ exposure levels, pre- and post-adjustment, during the first-trimester. Maternal exposure to CO above 0.91 ppm during last 6 weeks of pregnancy also experienced increased odds of PTB.
Ponce et al., (2005)[49] Los Angeles County, United States	**Case-control** 1994–1996 **(37,347)**	Distance-weighted traffic density <20th percentile; Distance-weighted traffic density >80th percentile by season and SES area.	**PTB**: Highest percentage of PTB was among mothers residing in low socioeconomic status neighbourhoods. TRAP in low socioeconomic status neighborhoods in the winter was associated with the highest proportion of preterm births.
Wilhelm & Ritz, (2003)[43] Los Angeles County, United States	**Case-control** 1994–1996 **(50,933)**	Distance-weighted traffic density.	**PTB**: An 8% increase in risk of PTB observed for infants in the highest distance-weighted traffic density quintile, after adjustment for all covariates, background air pollution concentrations, and socioeconomic status variables (RR of 1.08; 95% CI, 1.01–1.15).

Abbreviations:
LUR – land use regression; PM – particulate matter; NOx – nitrogen oxides; SO_2 – sulphur dioxide; CI – confidence interval

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