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Industrial emissions and risks of preterm and small-for-gestational-age birth

A population-based cohort study in Quebec, Canada

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Background: Ambient air pollution has been linked to adverse birth outcomes, but the role of industrial emissions remains understudied. We examined the association between maternal exposure to industrial air pollutants during pregnancy and the risk of preterm birth (PTB) and small-for-gestational-age (SGA) birth.

Methods: We conducted a retrospective cohort study of 1,199,516 singleton live births in Quebec, Canada, from 2002 to 2016. Exposure to $PM_{2.5}$, NO_2, and SO_2 emitted by industries within 7.5 km of the maternal residence was estimated using an indicator combining residential proximity, emissions, and wind data. Logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for PTB and SGA comparing exposed to unexposed individuals. We assessed the modifying effects of maternal comorbidities using subgroup analyses.

Results: The cohort comprised 71,699 PTB and 105,894 SGA cases. Compared with unexposed participants, exposure to industrial air pollutants during pregnancy increased the risk of extreme and very PTB and SGA. For extreme PTB, adjusted ORs (95% CI) comparing exposed with unexposed were 1.08 (1.00, 1.17) for $PM_{2.5}$, 1.11 (1.03, 1.19) for NO_2, and 1.05 (0.98, 1.12) for SO_2. For SGA, the corresponding values were 1.03 (1.02, 1.05) for $PM_{2.5}$, 1.03 (1.02, 1.04) for NO_2, and 1.05 (1.04, 1.06) for SO_2. Exposure to NO_2 was associated with a higher risk of extreme and very PTB among mothers with preeclampsia (OR: 1.26; 95% CI: 1.12, 1.42) compared with no preeclampsia (OR:1.07; 95% CI: 1.01, 1.12).

Conclusion: Exposure to industrial air emissions during pregnancy may increase the risk of extreme and very PTB and SGA, especially among women with preeclampsia.

Keywords: Air pollution; Industrial emissions; Preterm birth; Small-for-gestational-age birth

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Introduction

Preterm birth (PTB) and small-for-gestational-age (SGA), commonly used as a proxy for intrauterine growth restriction, remain major global public health concerns. Each year, an estimated 15 million infants are born prematurely before 37 completed weeks of gestation, representing nearly one in 10 live births.[1] Additionally, approximately one in five live births are SGA, representing over 20 million births globally.[1–3] PTB and SGA are leading causes of neonatal and under-five mortality, as well as important risk factors for long-term morbidity.[4,5] Globally, over 80% of neonatal deaths are associated with low birth weight, with two-thirds of cases occurring in preterm and one-third in SGA births.[6,7] Together, these outcomes contribute substantially to the global burden of disease, accounting for more than 170 million disability-adjusted life

What this study adds

In the context of low pollution levels, this large population-based cohort study provides new evidence that prenatal exposure to industrial emissions is associated with increased risks of preterm birth, particularly extreme and very preterm birth, and small-for-gestational-age birth. By using a source-specific, wind-weighted exposure indicator, this study advances prior research that has largely relied on nonsource-specific air pollution measures. The findings also highlight maternal comorbidities as a risk modifier. Together, these findings underscore the need for public health and clinical strategies to better protect pregnant women and their offspring, especially those with comorbidities living in areas with higher emissions.

years globally.[2] In Canada, these adverse birth outcomes have increased in recent years. In 2023, PTB accounted for 8.3% of all births, one of the highest recorded in the past 50 years.[8] Similarly, the proportion of SGA rose from 7.2% in 2000 to 8.0% in 2016.[9] These proportions are generally comparable to those reported in other high-income countries, although some variations exist across settings.[10] For instance, approximately 10.4% of live births in the United States are preterm, while 11.1% are SGA.[11]

While a wide range of genetic, maternal, social, and environmental determinants have been established as risk factors for adverse birth outcomes,[12,13] evidence is accumulating that maternal exposure to air pollutants during pregnancy is associated with an increased risk of PTB and SGA.[14,15] Biological mechanisms potentially underlying these effects include systemic inflammation, oxidative stress, endothelial dysfunction, and metabolic disturbances occurring in the mother, which may impair placental function and the transport of oxygen and nutrients to the fetus.[16,17] In addition, some pollutants or their constituents may cross the placenta and reach the fetal circulation, suggesting potential direct effects on fetal development.[18,19]

Despite growing evidence, findings across studies remain heterogeneous, with some reporting null or weak associations.[20] Most studies have examined overall ambient concentrations of pollutants, such as fine particulate matter (<2.5 μm; $PM_{2.5}$) from all sources, or nitrogen dioxide (NO_2) commonly used as a marker of road traffic pollution. However, industries have received relatively little attention despite being major contributors to air pollution. In contrast to urban or traffic-related pollution, industrial emissions can contain higher concentrations of heavy metals (e.g., lead, cadmium, arsenic) and other highly toxic compounds (e.g., sulfur dioxide, volatile organic compounds), potentially conferring distinct toxicological properties and enhancing oxidative stress, systemic inflammation, and endothelial dysfunction.[21,22] Recent studies suggest a plausible link between specific industrial air pollutant emissions and the risk of adverse birth outcomes.[23,24] A systematic review conducted in 2022 also supports that industrial air pollution, particularly from power plants and petrochemical facilities, may be an important risk factor for PTB and SGA.[25] A main limitation of previous studies is the reliance on residential proximity as a proxy of exposure, without accounting for the magnitude of emissions and factors influencing the dispersion of pollutants, which may lead to substantial exposure misclassification.[26,27] Additionally, few studies have examined the role of maternal health, although there is suggestive evidence that certain pre-existing health conditions or pregnancy complications may heighten the risk of adverse birth outcomes and the effects of ambient air pollution.[28,29]

In this study, our objective was to assess the associations between maternal exposures to industrial air pollutant emissions during pregnancy and the risks of PTB and SGA in a large population-based cohort of newborns in Quebec, Canada, a setting characterized by low ambient air pollution levels and stringent environmental regulation compared with many countries, particularly emerging ones. Nonetheless, important industrial activities, including metal smelting, mining, petrochemical production, pulp and paper industries, and other manufacturing sectors, remain present in different regions of the province and contribute to local air pollution exposures. Evaluating associations in such a setting may help determine whether adverse birth outcomes can occur even at low levels of industrial air pollution exposure and inform environmental and public health policies. As a secondary objective, we explored whether certain maternal characteristics, including pre-existing comorbidities and socioeconomic status (SES), modify these associations to identify subgroups potentially more susceptible to the effects of industrial air pollution during pregnancy.

Methods

Study Design and Population

This retrospective cohort study included all live births in Quebec hospitals from 2002 to 2016. Data were extracted from the Maintenance and Use of Data for the Study of Hospital Clientele (MED-ECHO system), a previously described provincial health administrative database.[30,31] The database contains detailed maternal and perinatal information, including maternal age, parity, and comorbidities coded using the Canadian version of the International Classification of Diseases, Ninth and Tenth Revisions (Table S1, https://links.lww.com/EE/A447). Perinatal data include gestational age, birth weight, and the vital status of the newborn (live birth or stillbirth). The six-digit residential postal code at the time of delivery is also recorded and used to assign exposure and socioeconomic indicators. It represents a block face (i.e., one side of a street between two intersections) in the core of urban areas but may cover much larger areas in rural settings. Postal codes were obtained at delivery, and year-specific geographic coordinates were used to assign pollution levels. We restricted the cohort to singleton births with complete data on exposure to industrial air emissions. Multiple births were excluded due to their distinct pathophysiological mechanisms and inherently higher risk of preterm birth and low birth weight,[32] both of which could complicate the interpretation of associations with air pollution.[33]

Birth Outcomes

We examined two outcomes: PTB and SGA. PTB was defined as delivery before 37 completed weeks of gestation. The date of birth and gestational age in completed weeks were documented on the infant chart. To calculate the date of conception, we subtracted the gestational age from the date of birth and added 2 weeks to account for the timing of ovulation after the last menstrual period. Gestational age was determined by dating ultrasounds in the first trimester. In addition to overall preterm birth, we considered the following categories of severity: extremely preterm (less than 28 weeks), very preterm (28–<32 weeks), and moderate to late preterm (32–<37 weeks).[34]

We also examined SGA, which is commonly used as a proxy for intrauterine growth restriction. Although SGA is not equivalent to fetal growth restriction, as some infants may be constitutionally small, it is widely considered a more accurate indicator of fetal growth restriction than birth weight alone.[35] SGA was defined as birth weight below the 10th percentile for gestational age, based on the sex-specific Canadian fetal growth reference.[36]

Air pollution exposure

We examined three pollutants predominantly emitted by major industrial sectors in Canada[21]: $PM_{2.5}$, NO_2, and SO_2. After previous work,[37,38] we constructed an exposure indicator that integrates residential proximity, quantities of industrial air pollutant emissions, and local wind patterns. Specifically, for each postal code and year, we identified all industrial sources within a 7.5 km radius. This buffer was selected for consistency with previous studies[37,39,40] and because contributions from more distant sources are minimal under the following inverse distance–weighted approach. Annual emissions from these sources were then weighted by the inverse of the distance to the postal code centroid and the percentage of time the postal code was downwind of the emitter. Weighted emissions were summed separately for each pollutant to generate annual exposure indicators. Data on annual emissions (in tons) from industrial facilities

across Canada were extracted from the National Pollutant Release Inventory.[41] Hourly wind direction data were obtained from the National Climatic Data Access Integration using the Weathercan package in R.[42]

These exposure indicators were generated separately for each pollutant and assigned to newborns according to their mother's residential postal code in the year of birth. For pregnancies spanning two calendar years, we calculated a weighted average based on the number of gestational days occurring in each year. Pregnant women with no industry within a 7.5 km radius of their residential postal code were considered unexposed and assigned an exposure value of zero.

Statistical analysis

For each air pollutant, we used logistic regression models to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the associations between maternal exposure to industrial emissions during pregnancy and the risks of PTB and SGA. Given that preterm birth is a heterogeneous outcome with distinct underlying etiologies,[43] we also estimated associations specific to each PTB category (moderate to late, very and extreme PTB) to capture potential differences in susceptibility across gestational age categories. To address the zero-inflated nature of the exposure (28–52% had no industry within 7.5 km), we used a two-stage approach. We first dichotomized the exposure variable and estimated ORs comparing exposed to unexposed participants. Second, we categorized exposed individuals into quartiles and estimated ORs for each quartile of exposure relative to no exposure.

We also estimated associations using an alternative regression approach in which we simultaneously included a binary term (exposed vs. not exposed) and a continuous term centered at the median value among exposed individuals, while keeping a zero value for unexposed individuals.[37,44] This approach handles bias that could result from modeling continuous exposures with many zeros. The binary term provides the risk for individuals exposed at the median relative to those not exposed, whereas the continuous term characterizes the concentration–response relationship among the exposed. The continuous term was fitted using natural cubic splines with three degrees of freedom to account for potential nonlinearity.

All models were adjusted for newborn sex, maternal age at delivery (<20, 20–24, 25–29, 30–34, 35–39, and ≥40 years), parity (0, 1, ≥2), place of residence (urban or rural), and neighborhood material deprivation index (quintiles).[12,45,46] The material deprivation index is based on average personal income, employment rate, and the proportion of individuals without a high school degree, measured from data in Canada's Census of Population.[47] The index is constructed at the level of dissemination areas, which are small geographic units that may encompass several postal codes[48]; accordingly, each postal code was assigned the deprivation value of its corresponding dissemination area. Furthermore, we controlled for potential time-related unmeasured confounding by including month and year of conception as stratification variables in the regression models, thereby contrasting newborns conceived within the same month and year. We further considered adjustment for maternal comorbidities (yes or no), including epilepsy and mood disorders, pre-existing obesity, pre-existing diabetes, hypertension, anemia or other blood disorders, and substance use disorders (tobacco, alcohol, illicit drugs) (see Table S1, https://links.lww.com/EE/A447 for diagnostic codes used). In addition to being potential confounders, these conditions are common causes of both fetal loss and adverse birth outcomes; therefore, adjusting for them may help mitigate selection bias related to the restriction to live births.[49] We did not adjust for preeclampsia, as it may lie on the causal pathway between prenatal exposure to industrial air pollution and adverse birth outcomes.

We performed subgroup analyses to explore the potential modifying effects of maternal comorbidities listed earlier, as well as preeclampsia, which have been associated with PTB and SGA.[50–52] We also examined effect modification by neighborhood material deprivation level, used as a proxy for SES. We used Cochran's Q test to evaluate heterogeneity across subgroups.[53]

Finally, in complementary analysis to logistic regression, we used multinomial regression to simultaneously estimate associations across PTB categories. All statistical analyses were performed using R software (version 4.4.1; R Development Core Team).

Results

Description of the cohort

A total of 103,961 births were excluded because exposure estimates could not be assigned, with no evidence of differential exclusion by SES or place of residence. As a result, the analytical cohort included 1,199,516 single live births, of which 71,699 were preterm (**Table 1**). The majority were moderate or late preterm (87%), while 7% were very preterm and 6% were extremely preterm. For the SGA analysis, 1077 births were excluded due to gestational age values below 22 weeks or above 43 weeks, ranges for which standardized growth curves are not available. Of the remaining 1,198,439 births, 8.8% were classified as SGA. PTB was more frequent among mothers under age 20 or over 40 years, those with comorbidities, in lower socioeconomic quintiles, and among male newborns. Similarly, SGA was more common among mothers under age 20 years, primiparous women, and those with comorbidities.

Table 2 describes the distribution of the exposure indicators developed for industrial $PM_{2.5}$, NO_2, and SO_2 emissions (exposure distributions by PTB category are provided in Table S2, https://links.lww.com/EE/A447). The exposure distributions were skewed to the right, with a relatively large proportion of participants unexposed. Depending on the pollutant, between 28% and 52% of participants had no industrial sources within 7.5 km of their residence and were therefore classified as unexposed. The correlation across the indicators for the three pollutants was high (Spearman r = 0.78–0.86; Table S3, https://links.lww.com/EE/A447).

Associations between PTB and exposure to industrial emissions

We found no evidence that exposed individuals were at increased risk of overall PTB compared with no exposure (**Table 3**); adjusted ORs were 0.98 (95% CI: 0.96, 0.99) for $PM_{2.5}$ and 0.99 (95% CI: 0.98, 1.01) for both NO_2 and SO_2. However, analyses by PTB category revealed increased risks of extreme and very PTB among exposed compared with unexposed individuals. For example, for extreme PTB, ORs were 1.08 (95% CI: 1.00, 1.17), 1.11 (95% CI: 1.03, 1.19), and 1.05 (95% CI: 0.98, 1.12) for $PM_{2.5}$, NO_2, and SO_2 emissions, respectively. Consistent results were obtained using multinomial regression analyses (Table S4, https://links.lww.com/EE/A447) and in sensitivity analyses excluding adjustment for maternal comorbidities (Table S5, https://links.lww.com/EE/A447).

Estimated ORs for each quartile of exposure relative to no exposure are presented in Figure 1 and Table S6, https://links.lww.com/EE/A447. For very PTB, associations were positive in the second, third, and fourth exposure quartiles, with no evidence of increasing risk across these higher quartiles. Similarly, for extreme PTB, associations with $PM_{2.5}$ and SO_2 were positive in the second, third, and fourth exposure quartiles, with no evidence of increasing risk across these quartiles. Positive associations were observed for NO_2 across all exposure quartiles, with no clear exposure–response trend.

Table 1.

Descriptive maternal and newborn characteristics of the study cohort, Quebec, 2002–2016 (newborns, N = 1,199,516; preterm, N = 71,699; small-for-gestational-age, N = 105,894)

Characteristics	Total births n (%)	Not preterm n (%)	Preterm n (%)	Not SGA n (%)	SGA n (%)
Child sex*					
Male	615,054 (51.3%)	575,938 (51.0%)	39,116 (54.6%)	560,511 (51.3%)	54,021 (51.0%)
Female	584,388 (48.7%)	551,817 (49.0%)	32,571 (45.4%)	532,034 (48.7%)	51,873 (49.0%)
Parity at child's birth					
0	596,346 (49.7%)	557,324 (49.4%)	39,022 (54.4%)	529,195 (48.4%)	66,614 (63.0%)
1	415,522 (34.7%)	394,516 (35.0%)	21,006 (29.3%)	387,894 (35.6%)	27,263 (25.7%)
2+	187,648 (15.6%)	175,977 (15.6%)	11,671 (16.3%)	175,456 (16.0%)	12,017 (11.3%)
Mother's age at delivery, years					
<20	31,607 (2.6%)	29,125 (2.6%)	2,482 (3.5%)	27,917 (2.6%)	3,664 (3.5%)
20–24	175,920 (14.6%)	164,216 (14.6%)	11,704 (16.3%)	157,400 (14.4%)	18,394 (17.4%)
25–29	403,807 (33.7%)	380,604 (33.7%)	23,203 (32.4%)	368,229 (33.7%)	35,261 (33.3%)
30–34	386,920 (32.3%)	365,883 (32.4%)	21,037 (29.3%)	355,339 (32.5%)	31,285 (29.5%)
35–39	168,188 (14.0%)	157,535 (14.0%)	10,653 (14.8%)	153,752 (14.1%)	14,205 (13.4%)
≥40	33,074 (2.8%)	30,454 (2.7%)	2,620 (3.7%)	29,908 (2.7%)	3,085 (2.9%)
Socioeconomic status quintile					
1—Low deprivation	213,147 (17.8%)	201,804 (17.9%)	11,343 (15.8%)	195,451 (17.9%)	17,509 (16.5%)
2	233,872 (19.5%)	220,767 (19.6%)	13,105 (18.3%)	213,968 (19.6%)	19,686 (18.6%)
3	231,658 (19.3%)	217,639 (19.3%)	14,019 (19.6%)	211,320 (19.3%)	20,129 (19.0%)
4	233,300 (19.5%)	218,949 (19.4%)	14,351 (20.0%)	211,782 (19.4%)	21,297 (20.1%)
5—High deprivation	244,048 (20.3%)	227,783 (20.2%)	16,265 (22.7%)	220,535 (20.2%)	23,299 (22.0%)
Unknown	43,491 (3.6%)	40,875 (3.6%)	2,616 (3.6%)	39,489 (3.6%)	3,974 (3.8%)
Place of residence					
Urban	962,978 (80.3%)	906,100 (80.3%)	56,878 (79.4%)	876,603 (80.2%)	85,485 (80.7%)
Rural	222,549 (18.5%)	208,477 (18.5%)	14,072 (19.6%)	203,128 (18.6%)	19,247 (18.2%)
Unknown	13,989 (1.2%)	13,240 (1.2%)	749 (1.0%)	12,814 (1.2%)	1,162 (1.1%)
Any maternal comorbidity†	158,394 (13.2%)	140,495 (12.4%)	17,899 (25.0%)	139,936 (12.8%)	18,300 (17.3%)
Epilepsy and mood disorders	6,650 (0.6%)	6,043 (0.5%)	607 (0.8%)	5,973 (0.5%)	674 (0.6%)
Obesity	26,260 (2.2%)	24,468 (2.2%)	1,792 (2.5%)	24,668 (2.3%)	1,579 (1.5%)
Diabetes	9,342 (0.8%)	7,723 (0.7%)	1,619 (2.3%)	8,791 (0.8%)	541 (0.5%)
Hypertension	13,336 (1.1%)	11,407 (1.0%)	1,929 (2.7%)	11,564 (1.1%)	1,757 (1.7%)
Preeclampsia	40,468 (3.4%)	31,774 (2.8%)	8,694 (12%)	33,232 (3.0%)	7,227 (6.8%)
Anemia and other blood disorders	61,194 (5.1%)	55,476 (4.9%)	5,718 (8.0%)	56,208 (5.1%)	4,885 (4.6%)
Substance use (smoking, drug, alcohol)	21,799 (1.8%)	19,533 (1.7%)	2,266 (3.2%)	17,379 (1.6%)	4,403 (4.2%)

*For child sex, 74 cases with imprecise data were excluded from the calculation of percentages comparing male and female infants in the "Total births" column. These included 62 from the "No preterm" group and 12 from the "Preterm" group.

†"Any maternal comorbidity" was coded as "yes" if the participants had one or more of the listed comorbidities: epilepsy and mood disorders, obesity, diabetes, hypertension, preeclampsia, anemia and other blood disorders, or substance abuse. Because participants may have multiple comorbidities, the total count for "Any maternal comorbidity" does not correspond to the sum of the counts for each individual comorbidity.

Table 2.

Distribution of the indicators of prenatal exposure to industrial $PM_{2.5}$, NO_2, and SO_2 emissions among 1,199,516 newborns in Quebec (Canada), 2002–2016

				Percentiles of the exposure distribution among exposed							
	Industrial pollutant	Unexposed newborns, n (%)	Mean (SD)	Min	25th	50th	75th	90th	95th	99th	Max
Not preterm	$PM_{2.5}$	329,852 (29.2%)	0.47 (1.92)	0.00	0.02	0.07	0.30	0.93	1.90	6.99	161.14
	NO_2	445,483 (39.5%)	4.03 (16.95)	0.00	0.16	0.87	3.52	9.57	17.72	45.10	6,014.0
	SO_2	582,235 (51.6%)	11.98 (56.20)	0.00	0.13	0.99	5.80	26.67	55.77	169.39	4,835.17
Preterm	$PM_{2.5}$	21,490 (30%)	0.51 (1.97)	0.00	0.02	0.08	0.33	1.02	2.05	7.38	119.37
	NO_2	28,382 (39.6%)	4.16 (14.81)	0.00	0.16	0.92	3.68	9.94	18.37	47.34	2,036.17
	SO_2	37,070 (51.7%)	13.63 (69.69)	0.00	0.15	1.07	6.28	28.01	60.76	195.99	5,415.37
SGA	$PM_{2.5}$	29,858 (28.2%)	0.49 (1.91)	0.00	0.02	0.08	0.32	0.98	1.96	6.89	159.59
	NO_2	40,179 (38%)	4.06 (12.65)	0.00	0.17	0.92	3.62	9.51	17.54	45.77	844.81
	SO_2	52,287 (49.4%)	12.06 (64.37)	0.00	0.14	1.02	5.68	23.61	54.65	174.39	4,477.25

Max., maximum; Min., minimum.

Exposure distributions were similar between SGA and non-SGA infants; therefore, only the SGA group is presented.

In the spline-based analysis, the estimated ORs for the binary exposure term comparing median versus no exposure were null (Table S7, https://links.lww.com/EE/A447). Figure 2A shows the exposure–response functions for the continuous terms for exposure. Curves may appear compressed at lower concentrations due to the highly right-skewed exposure distribution. Plots were truncated at the 99th percentile to improve interpretability while retaining observations corresponding to individuals exposed to higher levels. For all three pollutants, the curves showed monotonically positive associations with steeper slopes at lower exposure levels (up to approximately the 80th percentile), after which associations attenuated but remained positive.

Table 3.

Adjusted odds ratios (and 95% CIs) for preterm birth and small-for-gestational-age birth comparing newborns exposed versus unexposed to prenatal industrial air emissions

	Adjusted ORs (95% CIs) for exposed versus unexposed				
Industrial emissions	**All PTB (n = 71,699)**	**Moderate/Late (n = 62,209)**	**Very PTB (n = 5,066)**	**Extremely PTB (n = 4,424)**	**SGA (n = 105,894)**
$PM_{2.5}$	0.98 (0.96, 0.99)	0.97 (0.95, 0.99)	1.04 (0.97, 1.11)	1.08 (1.00, 1.17)	1.03 (1.02, 1.05)
NO_2	0.99 (0.98, 1.01)	0.98 (0.97, 1.00)	1.07 (1.00, 1.14)	1.11 (1.03, 1.19)	1.03 (1.02, 1.04)
SO_2	0.99 (0.98, 1.01)	0.99 (0.97, 1.01)	1.05 (0.98, 1.11)	1.05 (0.98, 1.12)	1.05 (1.04, 1.06)

$PM_{2.5}$, fine particulate matter of aerodynamic diameter <2.5 μm; NO_2, nitrogen dioxide; SO_2, sulfur dioxide.

Models examining PTB categories included 1,199,516 births, whereas models examining SGA included 1,198,439 births. Logistic regression models were stratified by year and month of conception and adjusted for child sex, maternal age, parity, neighborhood socioeconomic status, and rural/urban residence. Moderate/late preterm birth was defined as 32–<37 weeks of gestation, very preterm birth as 28–<32 weeks, and extremely preterm birth as <28 weeks.

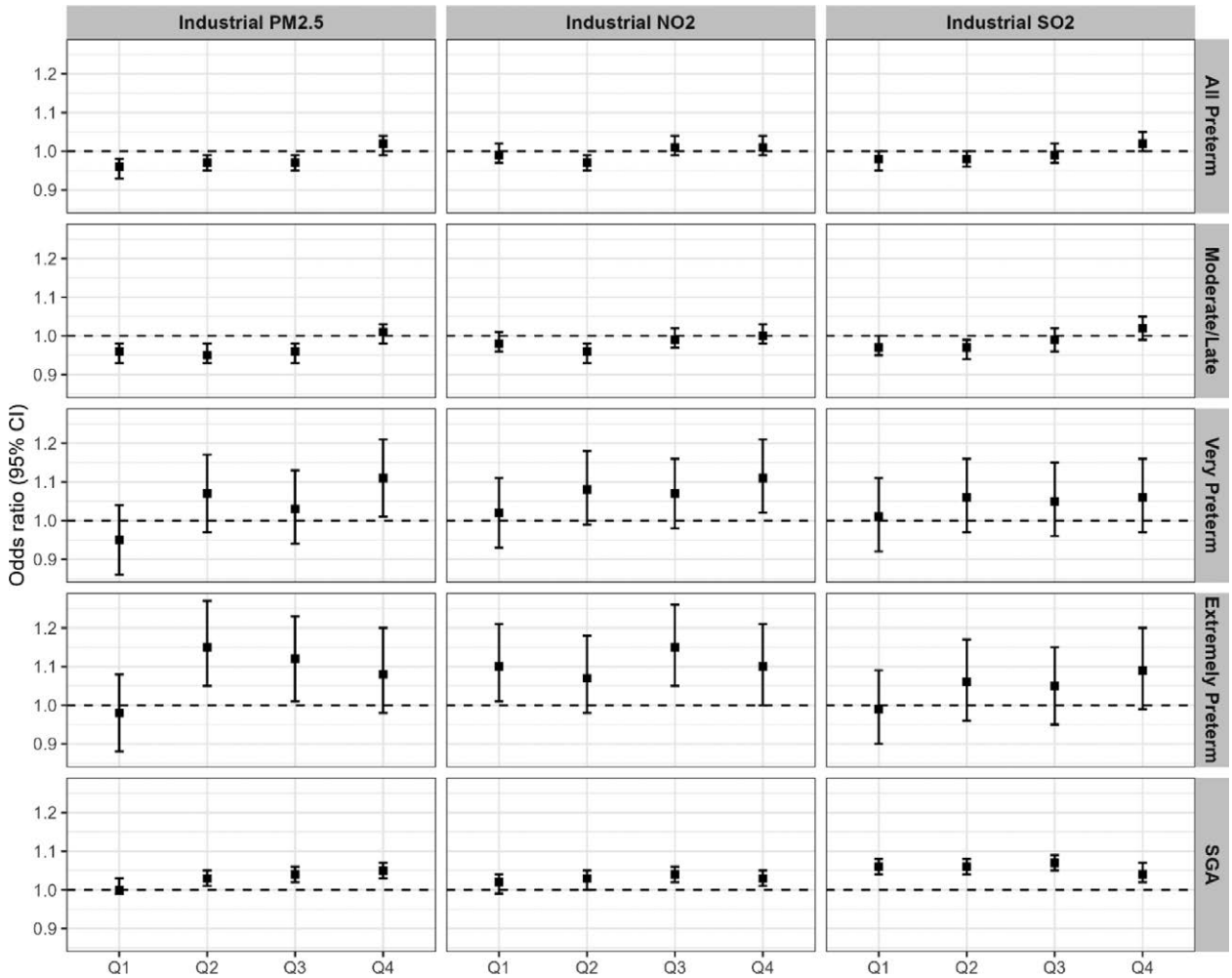

Figure 1. Adjusted odds ratio (OR) for preterm birth and small-for-gestational-age birth (SGA) across quartiles of prenatal exposure to industrial air pollutant emissions, with unexposed individuals as the reference group. The horizontal axis shows exposure quartiles (Q1–Q4), ranging from the lowest (Q1, ≤25th percentile) to the highest exposure levels (Q4, >75th percentile). Each square represents the adjusted mean OR for a given exposure quartile relative to those not exposed, with whiskers indicating the 95% confidence intervals (CIs). Models were stratified by month and year of conception and adjusted for child's sex, maternal age, parity, neighborhood socioeconomic status, rural versus urban residence, and maternal comorbidity. Numerical values for ORs and 95% CIs, as well as the number of cases and the exposure ranges for each quartile, are provided in Table S6, https://links.lww.com/EE/A447.

Associations between SGA and exposure to industrial emissions

Prenatal exposure to industrial air pollutant emissions was associated with an increased risk of SGA (**Table 3**). The adjusted ORs comparing exposed to unexposed individuals were 1.03 (95% CI: 1.02, 1.05) for $PM_{2.5}$, 1.03 (95% CI: 1.02, 1.04) for NO_2, and 1.04 (95% CI: 1.04, 1.06) for SO_2. For $PM_{2.5}$, no increased risk of SGA was observed in the lower exposure group (first quartile), whereas other quartiles supported a trend of increasing risk with higher exposure (Figure 1 and Table S6, https://links.lww.com/EE/A447). For NO_2 and SO_2, all exposure quartiles were associated with an increased risk compared with no exposure; however, there was no clear evidence of an exposure–response trend.

In the spline-based analysis, the estimated ORs for the binary term of exposure were all positive (Table S6, https://links.lww.com/EE/A447).

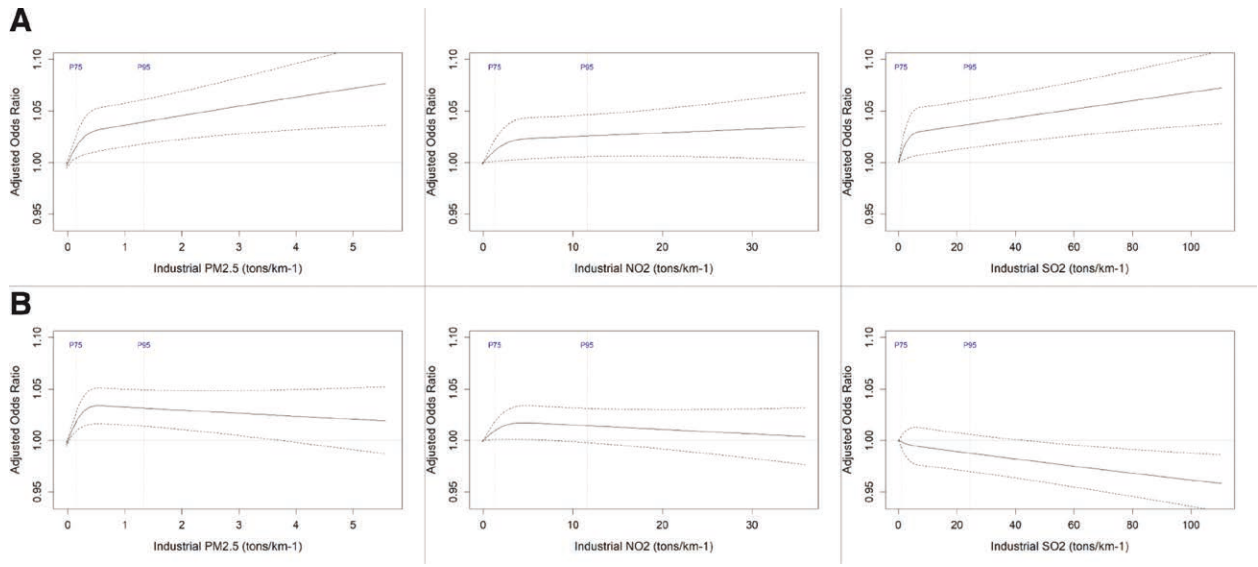

Figure 2. Adjusted exposure–response functions for the association between exposure to industrial air emissions and the odds of (A) preterm birth and (B) small-for-gestational-age birth. The horizontal axis represents the wind- and inverse distance–weighted emissions (tons/km) centered at the median exposure among newborns who were exposed. The vertical axis represents the odds ratio (OR) using children with median exposure as the reference (i.e., OR = 1.0). Solid lines represent the mean OR from the nonlinear function fitted using restricted cubic splines with three degrees of freedom, with the dashed lines representing the 95% confidence interval. ORs were estimated from a single pollutant logistic regression model stratified by year and month of conception and adjusted for parity, maternal age, infant sex, neighborhood socioeconomic status, rural/urban residence, and maternal comorbidity. Vertical dashed lines indicate the 75th (P75) and 95th (P95) percentiles of the exposure distribution. The exposure–response functions are truncated at the 99th percentile to improve interpretability given the highly skewed exposure distribution.

Among the exposed, the response functions for $PM_{2.5}$ and NO_2 were positive up to approximately the 80th percentile, after which the slope attenuated and appeared to become slightly negative at higher exposure levels (Figure 2B); however, estimates in this range were less precise due to the smaller number of observations. For SO_2, although the OR for the binary exposure term was positive (OR= 1.07; 95% CI: 1.05, 1.08), the exposure–response curve among exposed individuals showed a generally negative slope.

Modifying effects of maternal comorbidities and SES

Estimated ORs from subgroup analyses comparing exposed with unexposed individuals by maternal comorbidities are presented in Figure 3 (numeric values are provided in Tables S8, https://links.lww.com/EE/A447, for PTB and in Table S9, https://links.lww.com/EE/A447 for SGA).

For PTB, the association with industrial $PM_{2.5}$ was elevated among mothers with pre-existing obesity (OR: 1.12; 95% CI: 0.98, 1.27), but not among mothers without obesity (OR: 0.98; 95% CI: 0.96, 0.99) (Cochran's Q P = 0.04). For all three industrial pollutants, and particularly for $PM_{2.5}$, elevated associations were observed among mothers with pre-eclampsia. These associations were especially pronounced for very and extremely preterm births, with ORs of 1.18 (95% CI: 1.03, 1.34; Cochran's Q P = 0.11), 1.26 (95% CI: 1.12, 1.42; Cochran's Q P = 0.01), and 1.14 (95% CI: 1.02, 1.27; Cochran's Q P = 0.13) for $PM_{2.5}$, NO_2, and SO_2, respectively. Associations with NO_2 and SO_2 for overall PTB, as well as for very and extremely preterm births, appeared elevated in mothers with epilepsy and mood disorders as compared with mothers without these conditions. Specifically, among the subgroup of mothers with epilepsy and mood disorders, adjusted ORs for very and extremely preterm births were 1.62 (95% CI: 0.95, 2.75; Cochran's Q P = 0.14) for NO_2 and 1.69 (95% CI: 1.03, 2.77; Cochran's Q P = 0.06) for SO_2; however, CIs were wide owing to the small number of cases. All three pollutants were associated with lower risk of PTB among mothers with anemia and other blood disorders (e.g., OR for $PM_{2.5}$ = 0.91; 95% CI: 0.85, 0.98; Cochran's Q P < 0.01), and possibly among mothers with pre-existing diabetes, but CIs were wide. No evidence of effect modification was found for pre-existing maternal hypertension.

For SGA, we found evidence of effect modification for all three pollutants, with a lower risk of SGA in mothers with diabetes (Cochran's Q P ranging from <0.01 to 0.07) (Figure 3, Table S9, https://links.lww.com/EE/A447). Notably, the adjusted ORs for exposure to industrial NO_2 emissions were 0.79 (95% CI: 0.65, 0.96) and 1.03 (95% CI: 1.02, 1.05) in mothers with and without diabetes, respectively. There was no evidence of effect modification for SGA with other comorbidities examined.

Findings of effect modification according to SES are presented in Table S10, https://links.lww.com/EE/A447. Industrial NO_2 (OR = 1.23; 95% CI: 1.06, 1.44; Cochran's Q P = 0.15) and SO_2 (OR = 1.16; 95% CI: 1.00, 1.34; Cochran's Q P = 0.08) appeared more strongly associated with extreme PTB among the lower SES group, although differences were not statistically significant. For SGA, there was no evidence of effect modification with SES.

Discussion

In this population-based study conducted in a low ambient air pollution setting, maternal exposure to industrial emissions of $PM_{2.5}$, NO_2, and SO_2 during pregnancy was associated with SGA but not PTB overall; however, when examining PTB categories, we identified elevated risks for the most severe categories, namely extreme and very PTB. Findings were broadly consistent across spline- and quartile-based analyses, which increases confidence in the robustness of the observed associations, although direct comparisons should be interpreted cautiously because the continuous spline term characterized the exposure–response relationship only among exposed individuals. Given the highly right-skewed exposure distribution, spline models provided a better characterization of the exposure–response relationship than quartile-based analyses, which rely on arbitrary cut-points and may mask heterogeneity at higher

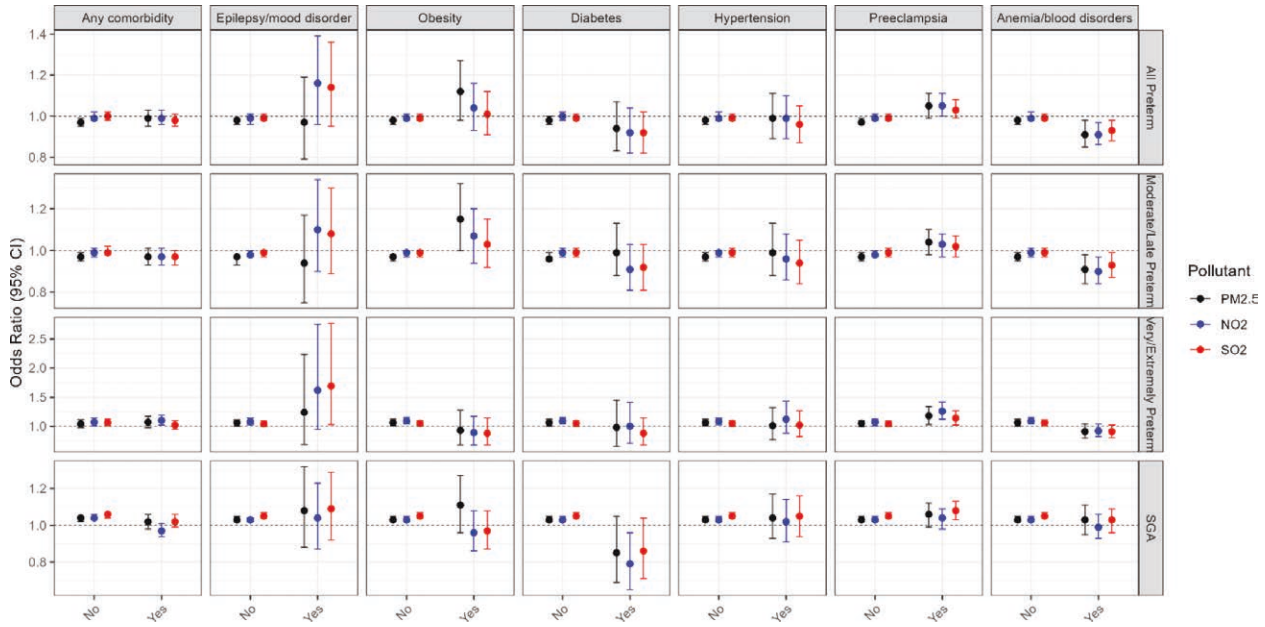

Figure 3. Adjusted odds ratio (OR) for preterm birth categories and small-for-gestational-age birth (SGA) associated with prenatal exposure to industrial air pollutant emissions, according to maternal comorbidity. Dots represent the adjusted mean OR for exposed relative to not exposed, and bars indicate the corresponding 95% confidence intervals (CIs). Models were stratified by month and year of conception and adjusted for child's sex, maternal age, parity, neighborhood socioeconomic status, and rural or urban residence. Numerical values for ORs and 95% CIs, as well as the number of cases in each subgroup and *P* value of Cochran Q tests, are provided in Tables S8 and S9 https://links.lww.com/EE/A447.

exposure levels. This is especially relevant because the highest exposures, although relatively uncommon, correspond to individuals residing in close proximity to major industries and are therefore of particular public health interest. The fact that associations were not limited to the highest exposure levels suggests the potential for a substantial public health burden, given the high prevalence of exposure in the population. Our findings also suggest that maternal comorbidities may be an effect modifier, with preeclampsia, epilepsy, and mood disorders, or pre-existing obesity appearing to increase susceptibility to the adverse effects of industrial emissions. Together, these findings raise the possibility that current regulatory standards may not be sufficiently protective against adverse birth outcomes and support the need for interventions aimed at reducing exposure to industrial air pollution, as well as enhanced clinical monitoring for women at higher risk, especially those with comorbidities.

Several epidemiological studies have examined associations between industrial air pollution and preterm birth, mostly reporting positive associations. However, comparisons across studies remain challenging because of substantial contextual and methodological differences, particularly in terms of exposure assessment methods. Many studies relied on binary proximity-based indicators[54–56] or ecological exposure metrics,[57,58] generally comparing populations residing in industrial areas with control populations or using varying distance thresholds (e.g., within 0–2 km,[59] within 0–5 km, or within 5–10 km[60]) to classify exposure. Such approaches may introduce substantial exposure misclassification and limit the identification of specific pollutants or emission sources. By contrast, our study employed an exposure indicator integrating industrial emission magnitude, residential proximity, and wind direction, thereby enabling a more refined characterization of potential prenatal exposure. To our knowledge, no previous studies have used a similar exposure indicator to examine associations with adverse birth outcomes.

We nevertheless identified two studies with methodologies more comparable to ours, as they evaluated the same industrial pollutants using dispersion models that incorporated meteorological information rather than relying solely on residential proximity. One cross-sectional study of 4488 singleton live births conducted in a highly industrialized region of the Netherlands reported positive associations between PTB and industrial nitrogen oxides (NO_x) and SO_2 exposures, estimated using dispersion modeling at maternal residential addresses.[61] The reported ORs were 1.14 (95% CI: 1.01, 1.29) per 1.16 μg/m^3 increase in NO_x and 1.19 (95% CI: 1.00, 1.41) per 0.42 μg/m^3 increase in SO_2. The other study, conducted in Estonia, examined $PM_{2.5}$ exposure from oil shale industries using combined data from monitoring stations, dispersion models, and residential proximity.[23] Analyses based on $PM_{2.5}$ concentrations estimated using an Eulerian air quality dispersion model (1 × 1 km resolution) showed no association during the first trimester but suggested a positive association during the third trimester (OR per 10 μg/m^3 = 1.30; 95% CI: 0.95, 1.79). In our study, emissions data were available on an annual basis, which limited our ability to capture seasonal or monthly variability in emissions and to assess exposure precisely during pregnancy. This temporal aggregation precluded the assessment of trimester-specific associations, potentially masking critical exposure windows. In contrast with the Estonian study, our results for industrial $PM_{2.5}$ exposure across pregnancy and overall PTB suggested a slightly protective association (OR = 0.98; 95% CI: 0.96, 0.99); this finding is not biologically plausible and should therefore be interpreted cautiously, as it may reflect residual confounding, selection bias related to restriction to live births, or competing risks as further discussed later. Differences in exposure assessment methods, in the composition and intensity of industrial emissions across settings, as well as the fact that our exposure indicator aggregated emissions across multiple industrial sectors, whereas the Dutch and Estonian studies were conducted in more specific industrial contexts, may also partly explain the discrepancies between our findings and those of these two studies.

One key feature of the present study is the examination of PTB severity, which revealed positive associations for extreme and very PTB that were initially masked when considering PTB overall. This is clinically important, as infants born before 32 weeks face significantly higher risks of complications such as respiratory problems, feeding difficulties, infections, and brain

bleeds compared with infants born moderate to late preterm.[34] Few previous studies have examined industrial air pollution in relation to PTB severity, with inconsistent findings.[57,62] A cohort study conducted in the United States, which used residential proximity to power plants as a proxy for $PM_{2.5}$ exposure, reported a 2.2% increase in the odds of very preterm birth (95% CI: 1.0%, 3.4%) for each 5 km decrease in distance to the nearest power plant.[62] In Spain, a municipal level ecological study based on residential proximity to industrial facilities (within 3.5 km) found no overall association with very or moderate to late PTB when all industrial sectors were combined[57]; however, sector-specific analyses suggested an increased risk of very PTB near pharmaceutical plants (RR = 1.10, 95% CI: 1.00, 1.20), and of moderate to late PTB near galvanization industries (RR = 1.10, 95 % CI: 1.00, 1.21) and hazardous waste facilities (RR = 1.08, 95 % CI: 1.00, 1.17). Overall, these findings suggest that aggregating PTB into a single outcome may obscure associations specific to gestational age subgroups and that stratified analyses by PTB severity may provide a more clinically and etiologically informative assessment of risk.[43]

The few studies that examined SGA in relation to industrial air pollution have provided mixed results. Our positive findings appear consistent with a previous exploratory study from Alberta, Canada, that used spatial data mining and geographical information systems to generate hypotheses about specific mixtures of industrial pollutants potentially associated with SGA.[63] All the identified mixtures (e.g., PM combined with volatile organic compounds and carbon monoxide) were associated with an increased SGA risk, with adjusted ORs ranging from 1.23 to 1.42. The study also reported a positive association for PM ($PM_{2.5}$/PM_{10}) alone (OR = 1.22, 95% CI: 1.17, 1.28), which was a common component in all mixtures. Another Canadian study[64] using geographic information-based exposure assessment identified a weak positive association between NOx exposure and SGA in Quebec. In contrast, the study from the Netherlands[61] found no association between exposure to industrial SO_2 or NO_x and the risk of SGA. Taken together, these findings suggest that associations with SGA may be more sensitive to pollutant mixtures, local industrial context, and exposure assessment approaches.

Another key contribution is the evaluation of maternal comorbidities as potential modifiers of the associations between industrial air pollution and adverse birth outcomes. Yet, few studies[65–69] have addressed this question in relation to ambient air pollution, and to our knowledge, none has specifically examined industrial emissions. Our results suggest that preeclampsia may increase susceptibility to PTB associated with industrial air pollutant exposure, particularly for very and extreme PTB. Although not specific to industrial emissions, a similar effect modification by preeclampsia on PTB risk has been reported in previous studies from Ontario, Canada,[59] and China.[67] One plausible mechanism is that air pollutant exposure may further impair placental vascularization and maternal endothelial function, both already compromised in preeclampsia,[70] thereby accelerating inflammatory disturbances that trigger PTB.[71] In contrast, studies from Taiwan[66] and Australia[68] found no evidence of effect modification by preeclampsia on the associations between ambient $PM_{2.5}$, NO_2, or O_3 exposure and PTB. These discrepancies may relate to differences in exposure levels, pollutant composition and toxicity, population characteristics, and the detection and clinical management of preeclampsia. Importantly, preeclampsia may also lie on the causal pathway between air pollution exposure and PTB, suggesting a potential mediating role that warrants further investigation in future studies.

Our findings regarding epilepsy and mood disorders should be considered more exploratory, given the relatively small number of cases (n = 607). To our knowledge, this finding is novel, although pregnant women with epilepsy are known to be at increased risk of PTB and SGA, potentially driven by prenatal anti-seizure medication exposure.[72,73] While some previous studies have reported stronger associations between ambient $PM_{2.5}$, NO_2, SO_2, or O_3 and SGA in diabetic women,[29,68] our associations appeared protective in diabetic than in nondiabetic mothers. As with the findings for preeclampsia, differences in population characteristics, exposure profiles, and clinical contexts may explain these inconsistencies. Diabetic pregnancies are typically associated with a higher risk of macrosomia or large for gestational age[74,75] which may also represent another possible explanation for the lower observed SGA risk. We also found an apparent protective effect of anemia or other blood disorders on associations with PTB. This was unexpected, given that anemia has been identified as a key contributor to PTB clinical subtypes in Quebec.[51] Overall, further research is needed to support these findings and clarify the role of maternal comorbidities.

Our study has several strengths, notably its large population-based cohort, including all newborns delivered in hospitals, providing high coverage of adverse birth outcomes and sufficient statistical power to enable robust stratified analyses. However, we did not have data for miscarriages, terminations, or stillbirths; this may have introduced selection bias, likely attenuating associations, if exposure to industrial air pollutants increases the risk of fetal loss. The cohort included detailed maternal and infant information, enabling adjustment for several potential confounders, though some residual confounding may remain. Individual-level SES was not available and may contribute to residual confounding, despite adjustment for neighborhood-level SES. Other factors, such as ethnicity and family history, may influence birth outcomes but are less likely to be associated with industrial air pollution. Additional unmeasured factors, including traffic-related pollution, occupational exposures, and psychosocial stress, may also contribute to residual confounding.

Our exposure indicator improved over previous studies relying on proximity-based measures by incorporating emissions and wind data. However, as an indicator of relative exposure rather than absolute concentrations, it may be less directly interpretable for policy-relevant metrics. We also did not account for some meteorological or topographical factors that may influence pollutant dispersion. Emissions data were available on an annual basis, which limited our ability to capture seasonal or monthly variability in emissions and to assess exposure precisely for the period of pregnancy. This temporal aggregation precluded the assessment of trimester-specific associations, potentially masking critical exposure windows and attenuating observed associations. Additionally, data on residential mobility and time–activity patterns during pregnancy were not available. Previous research suggests that only about 10% of pregnant women relocate during pregnancy, and most of these moves occur within the same municipality.[65] Assuming residential mobility is not systematically related to adverse birth outcomes and that annual exposures correlate with pregnancy exposure, misclassification is expected to be largely nondifferential, thus attenuating our findings toward the null.

Conclusion

In this population-based study, maternal exposure to industrial emissions during pregnancy was associated with increased risks of extreme and very PTB, as well as SGA birth. These associations appeared stronger among women with certain maternal comorbidities, particularly preeclampsia. Further large-scale cohort studies are needed to investigate potential effect modification by maternal comorbidities and to identify critical windows of vulnerability during pregnancy. Such research would help clarify underlying mechanisms and inform targeted prevention strategies to better protect pregnant women at elevated risk of PTB and SGA. Future research should also aim to improve exposure assessment by incorporating concentration-based exposure estimates, along with higher spatial and temporal resolution data. Examining specific particulate components and

industry types may help identify the pollutants driving these associations and guide protective interventions.

Conflicts of interest statement

The authors declare that they have no conflicts of interest with regard to the content of this report.

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