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Critical Time Windows for Air Pollution Exposure and Birth Weight in a Multicity Canadian Pregnancy Cohort

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Background: Maternal prenatal exposure to air pollution has been associated with adverse birth outcomes. However, previous studies focused on *a priori* time intervals such as trimesters reported inconsistent associations.

Objectives: We investigated time-varying vulnerability of birth weight to fine particulate matter ($PM_{2.5}$) and nitrogen dioxide (NO_2) using flexible time intervals.

Methods: We analyzed 1,300 live, full-term births from Maternal–Infant Research on Environmental Chemicals, a Canadian prospective pregnancy cohort spanning 10 cities (2008–2011). Daily $PM_{2.5}$ and NO_2 concentrations were estimated from ground-level monitoring, satellite models, and land-use regression, and assigned to participants from pre-pregnancy through delivery. We developed a flexible two-stage modeling method—using a Bayesian Metropolis–Hastings algorithm and empirical density threshold—to identify time-dependent vulnerability to air pollution without specifying exposure periods *a priori*. This approach identified critical windows with varying lengths (2–363 days) and critical windows that fell within, or straddled, predetermined time periods (i.e., trimesters). We adjusted the models for detailed infant and maternal covariates.

Results: Critical windows associated with reduced birth weight were identified during mid- to late-pregnancy for both $PM_{2.5}$ and NO_2: –6 g (95% credible interval: –11, –1 g) and –5 g (–10, –0.1 g) per μg/m^3 $PM_{2.5}$ during gestational days 91–139 and 249–272, respectively; and –3 g (–5, –1 g) per ppb NO_2 during days 55–145.

Discussion: We used a novel, flexible selection method to identify critical windows when maternal exposures to air pollution were associated with decrements in birth weight. Our results suggest that air pollution impacts on fetal development may not be adequately captured by trimester-based analyses.

Keywords: Air pollution; Birth weight; Critical time interval; Fine particulate matter; Maternal exposures; Metropolis-Hastings method; Nitrogen dioxide; Pregnancy cohort

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Exposure to ambient air pollution has been associated with a variety of adverse birth outcomes including preterm birth, decreased and low birth weight, growth restriction, and neonatal mortality.[1–7] Adverse birth outcomes have consistently ranked in the top ten global causes for disability-adjusted life years,[8–10] with low birth weight, small for gestational age, and preterm birth linked to increased risk of infant mortality as well as developmental, cardiovascular, and respiratory health problems in childhood and adulthood.[4,11–14]

Time-dependent vulnerability to air pollution persists as a critical research priority that needs to be addressed to elucidate the full impact of air pollution on fetal development and birth outcomes.[1,3,6,15–20] Literature reviews have cited the need for examining progressively smaller critical time windows during pregnancy for air pollution exposure.[7,21] Most previous studies have examined relatively large, predetermined exposure periods—for example, total-pregnancy, trimester-specific, or first and last month of pregnancy average.[7,21] The primary limitation with *a priori* selection of critical time periods is that this approach may not identify true critical exposure windows that straddle two predetermined periods selected for analysis. Trimester-based or weekly analyses also assume that all critical windows are the same

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duration. Finally, comparing trimester averages can lead to biased estimates; for example, when estimating the association between a trimester average exposure and the outcome without controlling for other trimesters, seasonal variations in air pollution can act as unmeasured confounders.[22]

Recent studies linking air pollution with birth outcomes have used distributed lag nonlinear models to examine smaller time intervals. This method addresses some of the limitations associated with trimester average exposures,[22] assuming a nonlinear shape via. smoothing over the lags. However, the models are highly sensitive to the specification of lag distribution—specifically, degrees of freedom (df) and smoothing function[23,24]—and selection of df and smoothing method can introduce bias due to mis-specification.[25]

To address these issues, we developed a novel two-stage modeling method[26]—using a Bayesian Metropolis–Hastings (M-H) algorithm coupled with an empirical density threshold—to identify critical time windows without relying on predetermined time intervals (e.g., trimesters) or distributional assumptions (e.g., distributed lag nonlinear model time lags). This approach allowed us to identify critical periods with varying lengths (i.e., 2 or 200 days) and critical periods that fell within, or straddled, predetermined time periods such as trimesters. We applied this flexible method to identify critical windows from pre-pregnancy through delivery when maternal exposures to ambient air pollution ($PM_{2.5}$, NO_2) disproportionately affected fetal growth and development (birth weight) in a Canadian prospective pregnancy cohort spanning 10 cities.

MATERIALS AND METHODS

Study Population

The Maternal–Infant Research on Environmental Chemicals (MIREC) Study,[27] a Canadian prospective pregnancy cohort, provided data for women in 10 cities from 2008 to 2011. Participants were recruited during the first trimester of pregnancy and provided information on: demographics, socioeconomic status, behavior, residential location, reproductive history, and maternal/infant clinical data. We obtained approval to conduct the research from Research Ethics Boards at Health Canada and Hospital Sainte Justine, as well as the MIREC biobank.

Starting with 1983 MIREC participants, analyses were restricted to live, singleton, full-term births because stillbirth (n = 80), nonsingleton (n = 49), and preterm (n = 116) births are strongly associated with low birth weight. To reduce potential exposure misclassification in temporal data, participants with >25% of their daily concentrations missing during the study period were excluded from $PM_{2.5}$ (n = 184) and NO_2 (n = 228) analyses. We also excluded participants with missing residential (n = 50), BMI (n = 64), income (n = 62), education (n = 2), infant sex (n = 1), and alcohol consumption during pregnancy (n = 1) data. Finally, to reduce spatial exposure misclassification, we excluded participants living in large (>20 × 20 km) forward sortation areas (see the section on Air Pollution) from $PM_{2.5}$ (n = 40) and NO_2 (n = 38) analyses. A total of 1,334 and 1,305 mother-baby pairs were analyzed for $PM_{2.5}$ and NO_2, respectively. Exclusions are illustrated in eFigure A1 in eAppendix; http://links.lww.com/EDE/B865.

We applied an advanced method to impute missing daily air pollution concentrations. We did not apply imputation to the small number of missing covariates due to the nature of the missing data—specifically, daily air pollution data have periodic structure characterized by a weekly pattern, while the other covariates were socioeconomic or health-related variables without specific patterns.

Birth Weight

The objective of this study was to identify specific periods when maternal exposures to ambient air pollution may disproportionately affect birth weight; therefore, we modeled birth weight as a continuous variable rather than a binary variable based on low birth weight.

Air Pollution

For each participant, we generated air pollution concentrations for each day spanning from pre-pregnancy (day –90) through delivery. We estimated the beginning of pregnancy (day 0) based on last menstrual period and early ultrasound (see eAppendix; http://links.lww.com/EDE/B865 for details). We estimated daily concentrations of $PM_{2.5}$ and NO_2 by applying the relative daily variation observed at ground-level monitoring sites under Canada's National Air Pollution Surveillance (NAPS) program to long-term, spatially refined concentrations from land-use regression[28] and satellite-derived models.[29] This hybrid approach[30] combined the enhanced spatial scale of land-use regression and satellite-derived data with daily temporal resolution provided by NAPS measurements. Estimation of daily and long-term $PM_{2.5}$ and NO_2 data is described in eAppendix (eFigure A2 and A3; http://links.lww.com/EDE/B865).

Daily concentrations were missing for 1.5% ($PM_{2.5}$) and 1.2% (NO_2) of the study period, mainly due to missing hourly NAPS data (Table 1). We imputed missing daily values using a multistage approach that combined classical prediction techniques with phase- and frequency-fitting tools via. the multitaper method; see eAppendix for further details (eFigure A4 (a) and (b); http://links.lww.com/EDE/B865).[31,32] We limited imputation to participants with at least 75% of daily air pollution data during the study period (pre-pregnancy through pregnancy). We excluded participants with less than 75% of daily data.

We linked daily $PM_{2.5}$ and NO_2 concentrations to each participant based on residential location (forward sortation area) at birth. Forward sortation areas consist of the first three characters of the Canadian postal code and can range from small sizes in urban areas (<2 × 2 km), to large sizes in rural areas (>40 × 40 km). We excluded participants living in large forward sortation areas (>20 × 20 km) from the analyses to reduce potential exposure misclassification (eTable A1; http://

TABLE 1. Descriptive Statistics for Daily $PM_{2.5}$ and NO_2

	$PM_{2.5}$ (μg/m³)		NO_2 (ppb)	
	All Daily Values (n = 1,334 Participants)	**Unimputed Only (n = 1,324 Participants)**	**All Daily Values (n = 1,305 Participants)**	**Unimputed Only (n = 1,096 Participants)**
Nonmissing daily concentrations: N (%)[a]	481,450 (99%)	473,289 (99%)	471,682 (100%)	392,913 (99%)
Missing daily concentrations: n (% missing)[b]	2,792 (1%)	7,323 (2%)	2,033 (0%)	4,935 (1%)
Mean	8.8	8.8	16.4	18.5
Standard deviation (SD)	7.6	7.6	13.7	13.7
Median	6.6	6.7	12.6	15.9
Min	<0.001	0.05	<0.001	<0.001
Max	226.3	226.3	119.4	118.1
Coefficient of variation[c]	0.86	0.86	0.84	0.74

[a]N = number of MIREC participants × sum of all nonmissing gestational + pre-pregnancy days for each participant (i.e., for $PM_{2.5}$, N = 1,334 participants × a maximum of 363 days per participant).
[b]% nonmissing = nonmissing values/maximum possible daily values × 100 (i.e., for $PM_{2.5}$, the maximum % nonmissing = 481,450/484,242 × 100).
[c]Coefficient of variation (CV) = standard deviation/mean.

links.lww.com/EDE/B865). See eAppendix; http://links.lww.com/EDE/B865 for further description.

We estimated associations between air pollution and birth weight based on average exposure for each randomly selected time interval (the selection method is described further in the next section). We generated daily concentrations during each time interval using a log-normal distribution based on the estimated daily concentrations and number of days within the interval. This approach is more appropriate for assigning average exposure to intervals with varying lengths and is more robust to missing data, because the variance of the exposure depends on the number of nonmissing days.[26] Briefly, the average exposure for a time interval with a small number of days has a larger variance than that of a wider interval with a greater number of days. Using a log-normal distribution rather than calculating the average exposure as the mean or median concentration for the nonmissing days addresses this issue.

Statistical Analyses

We employed a data-driven time interval selection method which examined flexible (versus predetermined) exposure periods. eFigure A5; http://links.lww.com/EDE/B865 outlines the selection process in five steps, which are described in detail below. All statistical analyses and computations were conducted using R 3.5.3[33] and SAS 9.4.[34]

(1) Generate random time intervals: We labeled each day based on the beginning of pregnancy (day 0). Time intervals were identified through random selection of start-end day pairs between day –90 (90 days before pregnancy) and delivery, using a Bayesian Metropolis-Hastings (M-H) algorithm.[25] Three chains with 100,000 iterations and a burn-in of 1,000 iterations returned 300,000 intervals, which comprised the randomly generated start-end day pairs selected through the comparisons in step 2. This approach facilitated identification of multiple critical periods if more than one interval met the inclusion threshold and was not limited to uniform-length time intervals; specifically, time intervals ranged from 2 to 363 days.

(2) Select time intervals with better fit: For each time interval (the random start–end day pairs generated in step 1), we estimated the likelihood for a multiple linear regression model [1] relating birth weight with air pollution exposure during the selected time interval. We then compared each interval with subsequent time intervals based on their estimated likelihoods. Time intervals with better likelihood were retained, and those with lower likelihood were discarded. This process was repeated until we obtained the 300,000 intervals summarized in step 1.

[Model 1] **birth weight ~ exposure (average exposure during the selected time interval)** + gestational age at birth (days) + infant sex + smoking + education + marital status + income + parity + ethnicity + alcohol use + season of birth + maternal age + maternal pre-pregnancy BMI + error (where the error term has a normal distribution with mean zero).

Covariate specification is described in a directed acyclic graph for the direct effect of ambient air pollution exposure on birth weight (eFigure A6; http://links.lww.com/EDE/B865). There were 10 potential confounders and ancestors of the outcome (gestational age and infant sex), which were causally linked with the outcome but not the exposure. Air pollution exposure was the only time-varying variable; the 12 covariates were fixed across exposure intervals.

(3) Calculate empirical density based on selected time intervals: The M-H algorithm[35] in steps 1 to 2 allowed for the selection of overlapping time intervals. Therefore, we proposed a new approach to identify potential critical

periods. We calculated the selection density for each day within the study period based on the frequency with which that day occurred in the time intervals selected in steps 1 and 2. Higher frequency resulted in higher density, indicating critical exposure timing. This new approach for generating an empirical density for the study period is a simplification of the bivariate normal distribution assumption for the start-end intervals.[26]

(4) Identify potential critical exposure periods: Each day during the study period was ranked from the lowest to highest based on the density calculated in step 3. Those days with higher density demonstrated better fit for model 1, and thus higher rank, while those days with low density reflected poorer fit and lower rank. We introduced thresholds to determine which days appeared frequently enough to be considered important. We identified days that fell in the 75th percentile (i.e., the top 25%) as critical exposure periods.

(5) Estimate associations between air pollution and birth weight: We fit model [1] using noninformative priors (mean zero and variance 100) to estimate the change in birth weight per unit change in air pollution exposure during the critical time periods identified in step 4. We set up three chains with 10,000 samples for each chain, which resulted in 30,000 samples for the posterior distribution of each parameter. We reported 95% credible intervals in this article.

Sensitivity Analyses

We conducted sensitivity analyses to (1) examine the implications of using alternative thresholds (90th and 50th percentiles of selection density) to identify critical exposure periods; (2) examine the influence of imputed concentrations on identification of critical exposure periods; (3) compare associations between air pollution and birth weight for randomly selected versus predetermined exposure periods including pre-pregnancy (T_0), individual trimesters (T_1, T_2, T_3), total-pregnancy (T_4, T_1–T_3), and pregnancy plus pre-pregnancy (T_5, T_0–T_3); (4) compare our flexible selection method with distributed lag nonlinear models; and (5) examine the influence of excluding large forward sortation areas. See eAppendix; http://links.lww.com/EDE/B865 for additional details.

RESULTS

Selected Participants and Study Time Span

As described earlier, our analyses included 1,334 participants for $PM_{2.5}$ and 1,305 for NO_2. Because the number of women delivering after day 272 was limited, we examined the period from day –90 to 272 to maintain at least 1,000 participants for each day.

Maternal and Infant Characteristics

Table 2 summarizes maternal and infant characteristics for participants included in $PM_{2.5}$ and NO_2 analyses, versus all participants with live, singleton births. Most participants were married or in long-term partnerships (>1 year), and were highly educated, with high household incomes. Few participants smoked (4.3%) or consumed alcohol (20.2%) during pregnancy. However, 42% of pregnant women in this study were ≥35 years old, compared with 19.4% of pregnant women ≥35 years in the general population.[36]

Maternal and infant characteristics were comparable for participants included in $PM_{2.5}$ and NO_2 analyses (Table 1). Birth weight had a symmetric distribution with mean 3,511 g and SD 458 g among participants (n = 1,541) without missing air pollution data (not shown). The mean birth weight was slightly higher for participants included in $PM_{2.5}$ and NO_2 analyses compared with the full cohort due to the exclusion of nonsingleton and preterm birth, but similar among participants in the $PM_{2.5}$ and NO_2 analyses. Other maternal and infant characteristics were similar between participants included and excluded from the analyses, providing assurance that differential exclusion based on data availability introduced little bias.

Air Pollution Concentrations

Table 1 summarizes daily ambient $PM_{2.5}$ and NO_2 concentrations. Mean daily concentrations were 8.8 μg/m^3 (SD = 7.6) for $PM_{2.5}$ and 16.4 ppb (SD = 13.7) for NO_2. The distribution of daily concentrations was similar for $PM_{2.5}$, with or without imputed data, whereas mean concentrations without imputed data were lower, with slightly less variation for NO_2 (based on the coefficient of variation, a ratio of SD to mean). This suggests that imputed data provided more daily variation, which could better support the detection of critical exposure periods. Graphical summaries are provided for daily concentrations for T_0–T_3 (eFigures A7 to A10; http://links.lww.com/EDE/B865).

Critical Exposure Periods

We identified three critical periods for $PM_{2.5}$ based on the 75th percentile of the selection density (Figure 1) during: pre-pregnancy (days –90 to –75), mid-pregnancy (days 91–139), and late-pregnancy (days 249–272). For NO_2, we identified only one critical period during mid-pregnancy (days 55–145) (Figure 2).

Associations Between Air Pollution and Birth Weight

Maternal exposures to air pollution were associated with decreased birth weight (Figure 3A,B; eTables A2 to A3; http://links.lww.com/EDE/B865). $PM_{2.5}$ was associated with reductions in birth weight of –6 g (–11 g, –1 g) and –5 g (–10 g, –0.1 g) per 1 μg/m^3 increase in $PM_{2.5}$ during mid-pregnancy (days 91–139) and late-pregnancy (days 249–272), respectively. NO_2 during mid-pregnancy (days 55–145) was associated with –3 g (–5 g, –1 g) reduction in birth weight per 1 ppb increase in NO_2.

Figure 4 shows a timeline of critical exposure periods for $PM_{2.5}$ and NO_2 by gestational age, with corresponding milestones in fetal development. Associations between the

TABLE 2. Descriptive Statistics for Maternal and Infant Characteristics

	$PM_{2.5}$ (n = 1,334)[a]		NO_2 (n = 1,305)[a]		MIREC Live, Singleton Births (N = 1,854)[b]	
Maternal characteristics						
Age (total N = 1,854)	**n**	**%**	**n**	**%**	**n**	**%**
<20	2	0.1	2	0.2	51	3
20–24	50	4	47	4	81	4
25–29	243	18	220	17	341	18
30–34	479	36	461	35	638	34
≥35	560	42	575	44	743	40
Parity (previous live birth) (total N = 1,854)	728	55	732	56	1,045	56
Alcohol during pregnancy (total N = 1,805)	269	20	258	20	343	19
Smoked during pregnancy (total N = 1,805)	57	4	57		94	5
Household income (>$50,000) (total N = 1,778)	1,152	86	1,086	83	1,466	82
Education (university degree) (total N = 1,804)	1,234	93	1,203	92	1,647	91
Married or long-term partner (total N = 1,854)	1,277	96	1,250	96	1,767	95
Ethnicity (White) (total N = 1,854)	1,152	86	1,115	85	1,548	86
Pre-pregnancy BMI						
Underweight (total N = 1,716)	33	3	32	3	49	3
Normal (total N = 1,716)	824	62	809	62	1,041	61
Overweight (total N = 1,716)	289	22	282	22	369	22
Obese (total N = 1,716)	188	14	182	14	257	1
Infant characteristics						
	n	**%**	**n**	**%**	**n**	**%**
Infant sex (girl) (total N = 1,853)	623	47	616	47	873	47
Birth season (warm: April–September) (total N = 1,854)	694	52	697	53	960	52
	mean (SD)	**range**	**mean (SD)**	**Range**	**mean (SD)**	**Range**
Gestational age (weeks) (total N = 1,854)	39 (1.3)	37–42	39 (1.2)	37–42	39 (1.8)	21–42
Birth weight (g) (total N = 1,852)	3,508 (453)	1,765–5,620	3,510 (452)	1,765–5,620	3,452 (532)	651–5,620

[a]Preterm excluded (n = 116).
[b]Preterm included.

12 covariates and birth weight are summarized in eTable A4; http://links.lww.com/EDE/B865.

Sensitivity Analysis Results

(1) Selection thresholds: Critical periods identified for $PM_{2.5}$ were more robust to selection threshold—i.e., 50th or 90th versus 75th percentile—compared with NO_2 (Figures 1 and 2, eTables A2 to A3; http://links.lww.com/EDE/B865). The analyses identified several time-varying critical periods for $PM_{2.5}$, which were similar across selection thresholds, whereas NO_2 had just one critical period, which was narrower when we applied more conservative selection thresholds.

(2) Imputed data: Inclusion of imputed data had minimal influence on associations between air pollution and birth weight for both $PM_{2.5}$ and NO_2 (eFigures A11 to A12; http://links.lww.com/EDE/B865). Associations between $PM_{2.5}$ and birth weight were nearly identical for models including and excluding imputed data. For NO_2, associations were similar but slightly weaker in magnitude for models excluding imputed data, because there were 209 fewer participants and less variation in NO_2 concentrations when imputed data were excluded.

(3) Randomly selected versus predetermined exposure periods: Estimates of association for $PM_{2.5}$ and NO_2 during critical periods identified in this study were comparable in magnitude with effect estimates for predetermined time periods, specifically, T_1–T_5 (Figure 6A,B). However, the critical periods identified by the flexible selection method did not align with the fixed trimesters; specifically, the mid-pregnancy critical period for $PM_{2.5}$ (days 91–139) did not align perfectly with T_2 (days 91–174). For NO_2, exposures across predetermined time periods were consistently associated with reduced birth weight, while the random selection method identified a single critical period from late-T_1 to mid-T_2.

(4) Bayesian random selection method versus distributed-lag nonlinear models: For distributed lag models, we defined lag0 as the first day of the study period (day –90) and used Akaike information criterion to choose the best fit. Among the 19 values (df = 2 to 20), df = 4 was optimal for $PM_{2.5}$ and df = 2 for NO_2 (eTable A5; http://links.lww.com/EDE/B865).

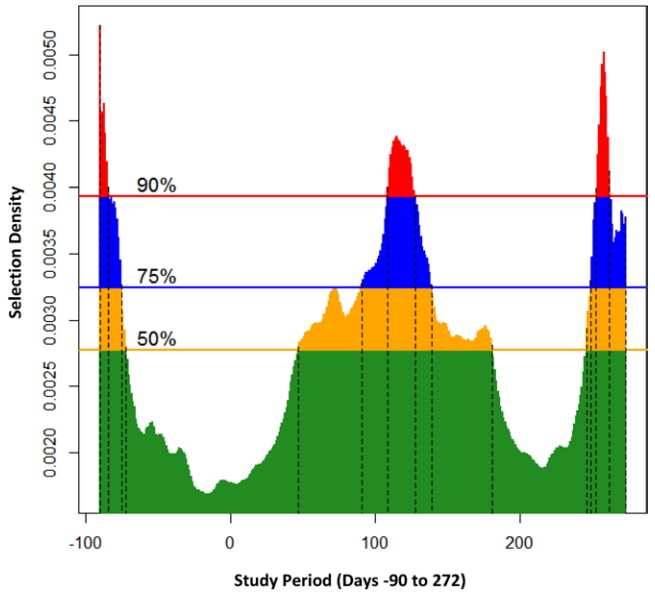

FIGURE 1. Critical periods for $PM_{2.5}$ (n = 1,334) at selected density levels: (A) 50% (yellow): (–90, –72), (47, 181), and (246, 272); (B) 75% (blue): (–90, –75), (91, 139), and (249, 272); and (C) 90% (red): (–90, –84), (109, 128), and (253, 262). The vertical dotted lines indicate the start-end pair days of critical periods.

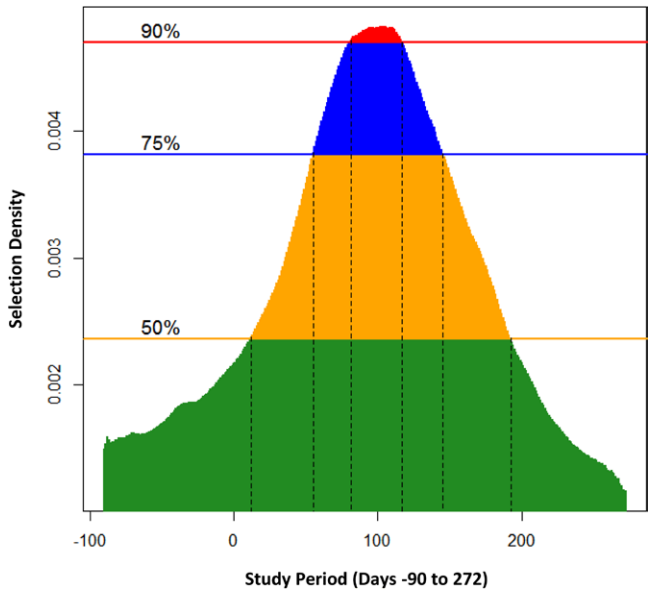

FIGURE 2. Critical periods for NO_2 (n = 1,305) at selected density levels: (A) 50% (yellow): (12, 192); (B) 75% (blue): (55, 145); and (C) 90% (red): (81, 117). The vertical dotted lines indicate the start-end pair days of critical periods.

eFigure A13; http://links.lww.com/EDE/B865 displays the lag distributions along with the critical periods obtained by the Bayesian random selection method. For $PM_{2.5}$ and NO_2, distributed lag nonlinear models and Bayesian methods returned consistent results on the number of inflection points (knots) but at different locations (lags).

(5) Large forward sortation areas: Due to the small number of participants living in large forward sortation areas, the inclusion of large forward sortation areas did not change the critical periods identified in the analyses, or the associations between birth weight and exposure during those critical periods (eTable A6; http://links.lww.com/EDE/B865, eFigures A14 to A15; http://links.lww.com/EDE/B865; http://links.lww.com/EDE/B865).

DISCUSSION

We investigated time-varying vulnerability of birth weight to maternal air pollution exposure using a novel, flexible selection method to identify critical exposure periods. Maternal exposures to both $PM_{2.5}$ and NO_2 during pregnancy were associated with decreased birth weight in the MIREC cohort. $PM_{2.5}$ displayed stronger time-dependent variation compared with NO_2 (Figure 4A,B), with two critical exposure periods during mid-pregnancy and late-pregnancy. NO_2 associations varied less by the timing of exposure, with a single critical exposure period during mid-pregnancy.

Time-Dependent Associations Between Air Pollution and Birth Outcomes

Recent reviews and meta-analyses have examined critical exposure periods for air pollution and birth outcomes during pregnancy. However, results varied significantly between studies, possibly due to lack of consistency in methods—particularly exposure estimation, time periods, analytical approach, and model specification—as well as variation between pollutant species, regional PM composition, birth outcomes, and study populations.[1,3,6,37,38] Despite differences in methodologies, overall associations and critical periods identified in the current study were generally consistent with previous research.

In a meta-analysis of 32 studies, $PM_{2.5}$ exposures in T_2 and T_3 were associated with reduced birth weight and low birth weight,[39] which was consistent with the mid- and late-pregnancy critical periods we observed for $PM_{2.5}$. Other reviews and meta-analyses found that effect estimates relating air pollution in late-pregnancy with low birth weight and preterm birth were more precise than effect estimates for early-, mid- or total-pregnancy.[3,7] However, results from individual studies varied.[2,7]

While most studies focused on trimester-level exposure, a few examined shorter time intervals for $PM_{2.5}$ and preterm birth. Warren et al.[40] used a flexible model to identify critical periods in weeks 4–22. Rappazzo et al.[41] found associations in early- and late-pregnancy. Acute $PM_{2.5}$ exposure in late-pregnancy was also associated with preterm birth.[42,43] The literature for NO_2 and birth outcomes is more limited, providing little basis for evaluating the mid-pregnancy critical period we observed for NO_2.

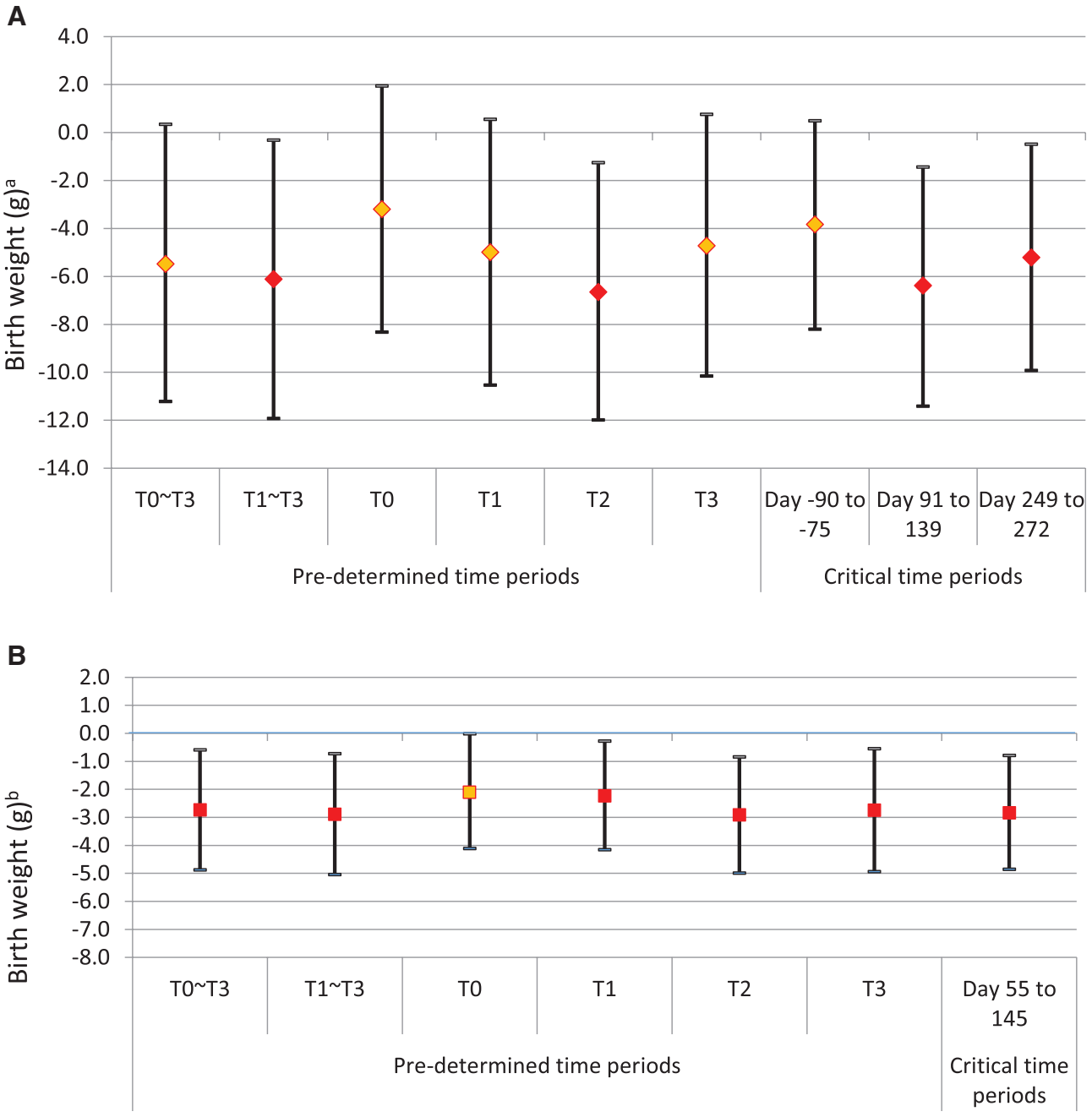

FIGURE 3. A, Associations between $PM_{2.5}$ and birth weight with 95% credible intervals (per 1 μg/m^3 $PM_{2.5}$): six fixed time intervals (left) and three critical time intervals identified by random selection method (right). Pre-pregnancy (T_0); trimester 1 (T_1); trimester 2 (T_2); trimester 3 (T_3); pregnancy (T_1–T_3); and Pregnancy + Pre-pregnancy (T_0–T_3). [a]The Y-axis indicates the reduced birth weight in gram per 1 unit change in $PM_{2.5}$. B, Associations between NO_2 and birth weight with 95% credible intervals (per 1 ppb NO_2): six fixed time intervals (left) and one critical time interval identified by random selection method (right). Pre-pregnancy (T_0); Trimester 1 (T_1); Trimester 2 (T_2); Trimester 3 (T_3); Pregnancy (T_1–T_3); and Pregnancy + Pre-pregnancy (T_0–T_3). [b]The Y-axis indicates the reduced birth weight in gram per 1 unit change in NO_2.

Mechanisms for Time-dependent Associations

Several mechanisms have been posited to explain air pollution-induced impacts on fetal growth and preterm birth, including oxidative stress, inflammation, blood viscosity/coagulation, hemodynamic responses/endothelial function, and endocrine disruption.[1,4,20,21,44–46] Through these mechanisms, $PM_{2.5}$ and NO_2 can induce morphological changes that disrupt the flow of oxygen and nutrients across the placenta, resulting in reduced fetal growth; or triggering preterm birth.[1,4,21,42–46] Mechanistic studies of air pollution-induced

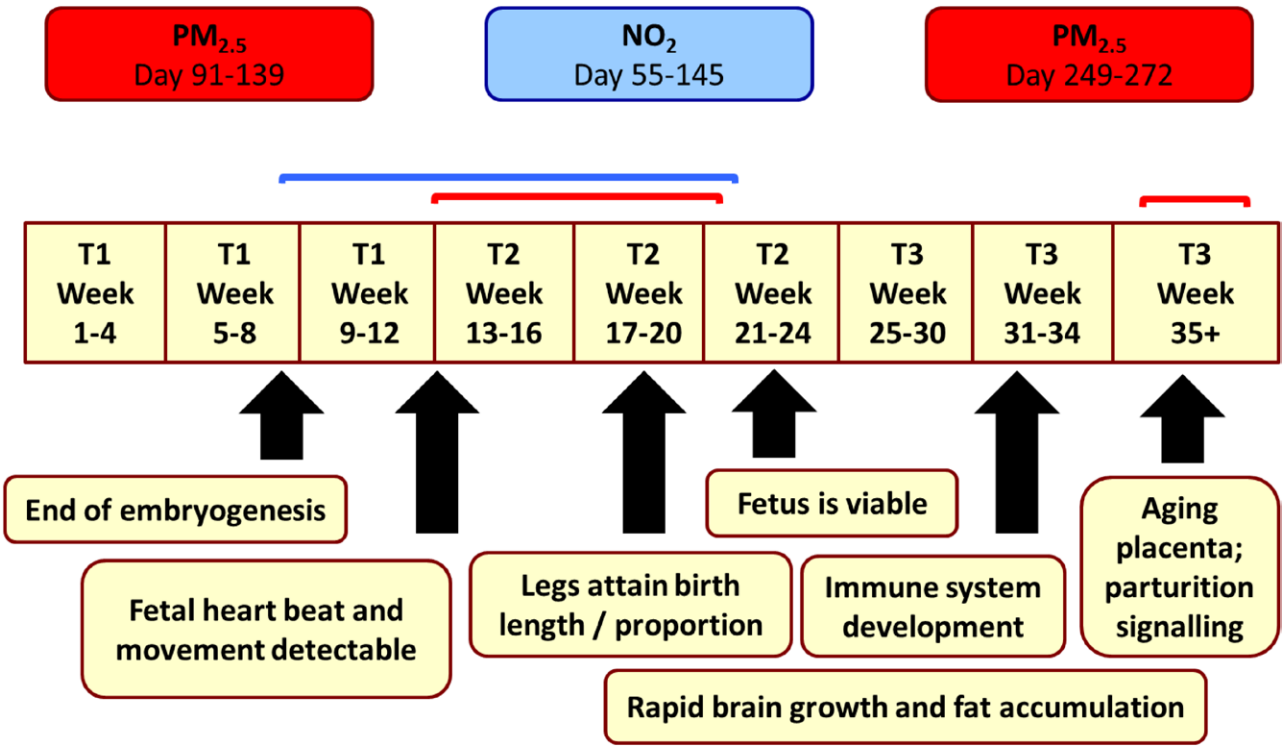

FIGURE 4. A timeline of critical periods for reduced birth weight associated with $PM_{2.5}$ and NO_2 during pregnancy.

fetal impacts are limited with respect to timing of exposure. The critical exposure period we observed in late-pregnancy may be associated with decreased birth weight through induction of early delivery due to inflammation and oxidative stress, while the critical periods in early- to mid-pregnancy may be associated with placental disruption.

Pollutant-specific Associations

Critical exposure periods differed between $PM_{2.5}$ and NO_2 in this study. We identified two relatively narrow critical exposure periods for $PM_{2.5}$ and one wider critical period for NO_2. Associations between $PM_{2.5}$ and birth weight were also slightly greater in magnitude compared with NO_2.

The disparate critical periods identified for $PM_{2.5}$ and NO_2 may reflect differences in the chemical properties of the pollutants—for example, their relative oxidative potential and absorption—or different mechanisms of action. We also observed greater temporal variation in $PM_{2.5}$, but greater spatial heterogeneity in NO_2, which could impact their critical exposure periods. Differences in exposure assessment methodologies could also impact identification of critical windows. Previous studies have primarily relied on ground level monitoring data,[47] which provides limited information regarding spatial variability, and may be poorly suited to characterizing variation in NO_2 exposure. In contrast, we relied on a combination of temporally and spatially resolved air pollution data to estimate daily exposure.

Although methodologic differences limit direct comparison, pollutant-specific results in the current study are generally consistent with results of trimester-based analyses. Previous studies of $PM_{2.5}$ suggest stronger effects in early- and late-pregnancy, while exposure to NO_2 at multiple stages during pregnancy have been linked to adverse birth outcomes.[1,20,48] Further, Klepac et al.[7] reported that effect estimates for air pollution and preterm birth were more consistent for exposures in T_3 for $PM_{2.5}$, and T_2 for NO_2.

Sensitivity Analyses

Our findings were robust to alternative thresholds for density selection, imputed exposure data, and the inclusion/exclusion of large forward sortation areas. While our method identified critical exposure windows that did not directly align with predetermined exposure periods, the magnitudes of association estimated by flexible versus fixed exposure periods were comparable for both pollutants. This was expected, because our method is able to examine finer time periods.

We compared critical periods identified using our Bayesian random selection approach with distributed lag nonlinear models. Distributed lag nonlinear models returned comparable time periods for $PM_{2.5}$ but not NO_2 (see eAppendix; http://links.lww.com/EDE/B865 for further discussion). For both pollutants, the flexible selection method identified narrower critical periods, while distributed lag nonlinear models suggested wider time periods smoothly changing over daily lags. Smoother changes in exposure timing may be more realistic than fluctuating

changes across pregnancy, but distributed lag nonlinear models are not as flexible as our method. Distributed lag nonlinear models need to specify a smoother, as well as the number and location of internal knots, *a priori*, which is problematic when no prior information is available. In contrast, our method provides a truly agnostic, flexible approach for identifying critical exposure windows, which is why our method returned narrower time windows than distributed lag nonlinear models.

Limitations

We classified exposure based on residential locations obtained at birth. The lack of detailed residential history during pregnancy could result in potential exposure misclassification; however, the moving rate was low (7.7%) in this study. Also, previous studies which compared exposure classification based on a single location versus detailed residential history reported that absence of residential history had a minimal impact on estimated associations between air pollution and birth outcomes,[47–49] even for short (weekly) exposure windows.[50] We also linked air pollution estimates to participants using forward sortation areas, that vary in size, which may have introduced exposure misclassification despite our exclusion of participants residing in the largest forward sortation areas.

Our models accounted for detailed sociodemographic and behavioral factors associated with adverse birth outcomes. However, there may be model misspecification, missing or mis-specified confounders, or unmeasured confounding due to historical or cumulative exposures, which could have resulted in unmeasured bias in our estimated associations.

The study population had, on average, higher income and education levels, but lower smoking rates compared with the general population, which may limit the generalizability of our results.

Future Work

We restricted analyses to live, full-term, singleton births, which may have underestimated time-dependent impacts of air pollution on fetal development by excluding the most vulnerable pregnancies. Future analyses are needed to identify critical windows for preterm birth and jointly examine associations between air pollution, preterm birth, and fetal growth, as well as miscarriage and subfertility.

Multipollutant models would help to elucidate potential mechanisms and critical time periods for pollution-mediated decreases in birth weight. Improved accuracy and coverage of daily pollutant concentrations would support identification of critical exposure periods. Replicating these results in a larger, population-based cohort would also be useful. Finally, this approach could be adapted to identify critical periods for childhood diseases such as asthma, autism, and attention-deficit hyperactivity disorder.

CONCLUSIONS

Our results highlight the importance of using flexible selection methods to identify critical exposure windows during gestation, and provide further evidence that exposure to $PM_{2.5}$ and NO_2 during pregnancy is associated with decreased birth weight. Our method identified critical time periods during for $PM_{2.5}$ and mid-pregnancy for NO_2, when maternal exposure to air pollution was associated with decreased birth weight. In contrast with conventional methods, our approach was not limited to predetermined exposure periods such as weeks, months, or trimesters, but rather was able to capture any critical time periods (≥2 days) within the prenatal period. Once replicated, these results could raise awareness of critical time windows for exposure to air pollution and support protective guidelines and interventions for pregnant women.

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Data are accessible through the MIREC Biobank, with restrictions. https://www.mirec-canada.ca/en/biobank/.