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Exposure to ultrafine particles and the incidence of asthma in children

A population-based cohort study in Montreal, Canada

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Background: Asthma is the most prevalent chronic respiratory disease in children. The role of ultrafine particles (UFPs) in the development of the disease remains unclear. We used a population-based birth cohort to evaluate the association between prenatal and childhood exposure to low levels of ambient UFPs and childhood-onset asthma.

Methods: The cohort included all children born and residing in Montreal, Canada, between 2000 and 2015. Children were followed for asthma onset from birth until <13 years of age. Spatially resolved annual mean concentrations of ambient UFPs were estimated from a land use regression model. We assigned prenatal exposure according to the residential postal code at birth. We also considered current exposure during childhood accounting for time-varying residence location. We estimated hazard ratios (HRs) using Cox proportional hazards models adjusted for age, sex, neighborhood material and social deprivation, calendar year, and coexposure to ambient nitrogen dioxide (NO_2) and fine particles ($PM_{2.5}$).

Results: The cohort included 352,966 children, with 30,825 children developing asthma during follow-up. Mean prenatal and childhood UFP exposure were 24,706 particles/cm^3 (interquartile range [IQR] = 3,785 particles/cm^3) and 24,525 particles/cm^3 (IQR = 3,427 particles/cm^3), respectively. Both prenatal and childhood UFP exposure were not associated with childhood asthma onset in single pollutant models (HR per IQR increase of 0.99 [95% CI = 0.98, 1.00]). Estimates of association remained similar when adjusting for coexposure to ambient NO_2 and $PM_{2.5}$.

Conclusion: In this population-based birth cohort, childhood asthma onset was not associated with prenatal or childhood exposure to low concentrations of UFPs.

Keywords: Childhood asthma; Outdoor Air Pollution; Particulate matter; Ultrafine Particles

Introduction

Asthma is among the most prevalent chronic respiratory disease in children, and in the last decade, its prevalence has been increasing in many countries.[1,2] Asthma is also responsible for an increased burden on health systems and may adversely impact children's development through school absences and psychological effects.[1,3] The associations between fine particles ($PM_{2.5}$) and adverse health outcomes (i.e., symptoms exacerbation, emergency room visit, and hospitalization) in asthmatic children is well established.[4,5] However, the link between air pollution and asthma onset is still uncertain.[3]

Several epidemiological studies have suggested that prenatal or childhood exposure to traffic-related pollutants may play a role in the initial development of asthma.[3,6–8] Although nitrogen dioxide (NO_2) has been the pollutant most studied, it is still unclear whether it is the causal agent in the association linking traffic-related air pollution and asthma onset.[3] Ultrafine particles (UFPs)—a pollutant also mainly emitted by vehicle exhaust in urban areas—have recently been given more attention for their potential contribution to asthma onset and other respiratory diseases.[9–14] The smaller size of UFPs (aerodynamic diameter of <0.1 μm) allows a higher pulmonary deposition efficiency and increases their ability to induce both localized and systemic effects such as airway inflammation and enhanced allergic responses.[6,15] UFPs can translocate to the placenta, where it could possibly adversely affect pregnancy outcomes, or lead to respiratory diseases in later life.[16]

What this study adds

Epidemiological evidence on the role of ambient ultrafine particles (UFPs) in the development of childhood asthma remains scarce. We made use of a population-based birth cohort to assess whether childhood asthma onset was associated with long-term exposure to low concentrations of UFPs estimated from a land use regression model built from mobile monitoring surveys. We found no evidence of an association between prenatal or childhood UFP exposure and childhood asthma onset. There was however a positive association with both prenatal and childhood exposure to ambient $PM_{2.5}$.

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AdSF and JV are cofirst authors.

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Access to data from the Quebec Integrated Chronic Disease Surveillance System (QICDSS) is restricted and limited to authorized personnel of the Chronic Disease and Injury Surveillance Unit at Institut national de santé publique du Québec (INSPQ). Therefore, distribution of the data to other parties is prohibited. The code used in the analyses can be made available through a request to the corresponding author.

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Recommendations from the most comprehensive review about the association between exposure to traffic-related air pollution and risk of development of childhood asthma include expanding the focus on NO_2 to other traffic-related pollutants including UFPs.[7] Yet, only two studies have evaluated the associations between exposure to UFPs and the development of childhood asthma.[11,17] In this study, we used a population-based birth cohort to assess if prenatal and childhood exposure to ambient UFPs were associated with asthma onset among children in Montreal, Canada.

Methods

Description of the cohort

We used a retrospective open birth cohort constructed from the Quebec Integrated Chronic Disease Surveillance System (QICDSS).[18] The QICDSS includes demographic information, such as sex and date of birth, as well as the time-varying address of residence according to the Canadian six-character residential postal code. It also includes all health services used since birth (i.e., cabinet and ER visits, hospital admissions) and death. The project was carried out in the context of the Quebec ministerial health surveillance plan and the use of the QICDSS has been approved by the government for agencies managing databases, the Research Ethics Board of public health and the Commission d'accès à l'information (CAI).

The cohort includes all children born in the province of Quebec between 2000 and 2015. Our study population was restricted to newborns who were resident of the island of Montreal. These were followed from birth until they developed asthma, died, moved out of Montreal, reached 13 years of age or reached the end of the study period (i.e., 31 December 2015) without developing the disease.

Asthma onset

Incident cases of asthma were identified from the surveillance system QICDSS using the diagnostic codes 493 and J45-J46 from the International Classification of Diseases (ICD), nine and tenth revisions, respectively.[19,20] Asthma onset was defined according to a validated algorithm as having at least two physician claims (i.e., physician visits in clinics or emergency room visits) with a diagnosis of asthma within a 2-year period or one hospital discharge with a primary or secondary diagnosis of asthma. The sensitivity and specificity of this definition are 89% and 72%, respectively. This definition is also consistent with the one used for surveillance purpose in Canada.[21]

Exposure assessment to UFPs and other air pollutants

We considered two main exposures: (i) prenatal exposure based on the location of the residence at birth, and (ii) time-varying childhood exposure based on the locations of the residences throughout the follow-up. Both exposures were assigned using six-digit postal codes, which cover one side of one street block in the core of the city of Montreal. These exposures were assessed using spatially resolved annual mean concentrations of ambient UFPs from a land use regression (LUR) model developed specifically for Montreal at a resolution of 100×100 m^2.[22]

Briefly, the LUR model for UFPs was based on concentrations measured using a portable condensation particulate counter (TSI CPC Model 3007) during a winter (5 weekdays in March 2011) and a summer (23 weekdays in June/July 2012) mobile monitoring campaigns over multiple circuits. Each circuit was about 25 km in circumference and aimed at covering different types of urban environments (e.g., downtown vs. suburban). UFP data for each road segment was associated with land-use, built environment characteristics and meteorological parameters. The LUR model was developed using the machine learning method kernel-based regularized least squares (KRLS), which outperformed a standard multivariable linear LUR model at explaining the variance in ambient UFP concentrations (79% vs. 62%).[22]

In addition to UFPs, we further considered co-exposure to ambient NO_2 and $PM_{2.5}$. We used the annual mean concentrations of ambient NO_2 from a LUR model for Montreal (100×100 m^2 resolution).[23] The model was developed from monitoring campaigns conducted across three seasons in 2014 at 79 stationary sites selected to represent high spatial variability in traffic intensity and in population density. The model considered land use and built environment characteristics, as well as meteorological parameters achieving a R^2 of 86%. For ambient $PM_{2.5}$, we used concentrations from a geographically weighted regression model using satellite-derived data (1×1 km optimal estimation aerosol optical depth related to a chemical transport model and geographically weighted using ground monitoring stations' data).[24] Data for North America for 2003 to 2012 were used in our study. Consistently to UFPs, we assigned annual mean estimates of ambient NO_2 and $PM_{2.5}$ to subjects of the cohort using their residential postal code at birth and throughout their follow-up.

Covariates

Data on family history of asthma was not available for the cohort used. To account for socioeconomic status (SES), we used an area-based indicator of material and social deprivation developed by Pampalon et al.[25] This indicator was constructed with the education level, income, and employment status of each dissemination area of Montreal for the years 2001, 2006, 2011, and 2016. The index is reported in quintiles (the first quintile represents the least deprived). We attributed the value of the dissemination area of the centroid of the residential postal code at birth and throughout the follow-up. A dissemination area includes on average 400–800 individuals. The 2001 quintile data was used for the years 2000–2003, the 2006 data for 2004–2008, the 2011 data for 2009–2013, and the 2016 data for 2014–2015.

Statistical analysis

We performed Cox proportional hazards models to assess associations between prenatal and childhood exposure to ambient UFPs and the onset of asthma. The Cox models used age from birth (in days) as the timescale, thus implying that hazard ratios (HRs) were implicitly adjusted for current age. All models were adjusted for sex, calendar year, and socioeconomic status using quintiles of material deprivation.[25] Specifically, sex and calendar year were treated as strata rather than covariates to satisfy the proportional hazards assumption. Individuals with missing material deprivation quintiles were not excluded but treated as a separate category in the analysis.

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We assessed potential nonlinearity of the relation between air pollutants and the hazard of asthma onset using restricted cubic splines (three knots located at 10th, 50th, and 90th percentile).[26] We determined linearity by visual inspection of the response-function and comparison of Akaike information criterion (AIC)[27] between the linear and nonlinear models (eFigures 1 and 2, http://links.lww.com/EE/A213). As we found no strong evidence of nonlinearity, we report HRs for an interquartile range (IQR) increase in UFP exposure.

In addition to single pollutant models, we also performed multipollutant models accounting for co-exposures to ambient NO_2 and $PM_{2.5}$ to evaluate if UFPs are independently associated with asthma onset.

Results

Descriptive statistics

The cohort included 352,966 children, who contributed a total of 1,732,644 person-years of follow-up (Table 1). The diagnosis of asthma was more frequent in males; of the 30,825 asthma onset cases identified between 2000 and 2015, 61% were boys. The mean age at asthma onset was between 2 and 3 years old with most cases occurring before the age of 6 years old (eFigure 3, http://links.lww.com/EE/A213).

Table 2 shows descriptive statistics of ambient UFP exposures, as well as for copollutant exposures. The annual mean concentration of UFPs during the follow-up was 24,525 particles/cm^3 (IQR: 3,427 particles/cm^3), whereas the annual mean concentrations of ambient NO_2 and $PM_{2.5}$ were 19.16 ppb (IQR: 11.06 ppb) and 9.05 μg/m^3 (IQR: 0.77 μg/m^3), respectively. Annual mean concentrations at birth were 24,706 particles/cm^3 (IQR: 3,785 particles/cm^3) for UFPs, 19.76 ppb (IQR: 11.48 ppb) for NO_2, and 9.48 μg/m^3 (IQR: 1.53 μg/m^3) for $PM_{2.5}$. There were weak positive correlations between concentrations of UFPs and NO_2 (Pearson r = 0.24), between concentrations of UFPs and $PM_{2.5}$ (Pearson r < 0.05), and moderate correlations between concentrations of NO_2 and $PM_{2.5}$ (Pearson r < 0.38) for both birth exposure and through-out the follow-up.

Table 1.

Description of the cohort of children born in Quebec City (Quebec, Canada), 2000–2015.

Cohort characteristics	n (% male)
No of newborns enrolled	352,966 (51.25)
No of children with asthma onset	30,825 (60.79)
Children censored	
End of study	193,882
Reached 13 years old	34,202
Other	94,057
	Person-year of follow-up (%)
Person-years by age group	
<1 years	171,368 (9.9)
1–2 years	297,580 (17.2)
2–4 years	452,111 (26.1)
4–6 years	310,906 (17.9)
6–10 years	367,897 (21.2)
10+ years	132,782 (7.7)
Quintiles of material deprivation index	
1 (least deprived)	309,168 (17.8)
2	306,869 (17.7)
3	316,431 (18.3)
4	340,695 (19.7)
5 (most deprived)	407,041 (23.5)
Missing	52,440 (3.02)
Quintiles of social deprivation index	
1 (least deprived)	394,760 (22.8)
2	367,060 (21.2)
3	330,525 (19.1)
4	302,743 (17.5)
5 (most deprived)	285,117 (16.5)
Missing	52,440 (3.02)

Associations between UFPs and other copollutants and asthma onset

Table 3 presents the HRs per IQR increase in ambient UFPs and in co-pollutants for childhood and prenatal exposures. Results are shown for crude single pollutant models, fully adjusted single pollutant models, and for the fully adjusted multipollutant (UFPs + NO_2 + $PM_{2.5}$) models. Results for all models—i.e., single-, two- and three-pollutants models—are available in eTables 1–4, http://links.lww.com/EE/A213.

Prenatal and childhood UFP exposures were not associated with asthma onset in children. In fully adjusted single pollutant models, the HRs per IQR were 0.99 (95% CI = 0.98, 1.00) for childhood exposure (IQR: 3,423 particles/cm^3) and 0.99 (95% CI: 0.98, 0.99) for prenatal exposure (IQR: 3,785 particles/cm^3). Childhood and prenatal exposure to ambient NO_2 were both positively associated asthma onset in single pollutant models, however this association was attenuated in the fully adjusted multipollutant models for childhood exposure (HR per IQR = 1.01; 95% CI = 1.00, 1.03) and prenatal exposure (HR per IQR = 1.01; 95% CI = 0.99, 1.02).

Exposure to $PM_{2.5}$ was positively associated with asthma onset in both single and multipollutant models. In the multipollutant models, the HR per IQR was 1.02 (95% CI = 1.01, 1.03) for childhood exposure (IQR = 0.77 μg/m^3) and 1.06 (95% CI = 1.04, 1.08) for prenatal exposure (IQR = 1.53 μg/m^3). $PM_{2.5}$ estimates were highly sensitive to adjustment for calendar year—for example, removal of calendar year in the fully adjusted multipollutant models increased the HRs per IQR to 1.19 (95% CI = 1.18, 1.20) for childhood exposure and to 1.37 (95% CI = 1.35, 1.39) for prenatal exposure (see eTables 1–4, http://links.lww.com/EE/A213). Contrary to UFPs and NO_2, for which concentrations from a single year were used to assign participants' exposure, data for 2003 to 2012 were used to assign participants' $PM_{2.5}$ exposure. This increased temporal variability in $PM_{2.5}$ exposure may explain this high sensitivity.

Discussion

In this population-based birth cohort study, we assessed whether childhood asthma onset was associated with long-term exposure to low concentrations of UFPs in Montreal (Canada) during the years 2000–2015. Our findings suggest that exposure to ambient UFPs during pregnancy and during childhood is not associated with an increased risk of asthma onset in children.

The evidence about the contribution of UFPs to the development of asthma in childhood remains to be elucidated. To our knowledge, only two other studies have investigated the association between ambient UFP exposure and the onset of asthma in children.[11,17] The study by Lavigne et al.[11] conducted in Toronto, Canada, reported a small positive association between childhood cumulative exposure to UFPs and asthma onset; the adjusted HR was 1.03 (95% CI = 1.00, 1.06) per IQR increment (10,770 particles/cm^3). However, there was no evidence of association after adjustment for co-pollutants ($PM_{2.5}$ and NO_2), implying that the observed association for UFP may be attributable to other pollutants. Lavigne et al.[11] also reported an association with UFP exposure during the whole pregnancy that was fully explained away after adjustments for co-pollutants. However, trimester specific effects suggested an association for exposure during the second trimester of pregnancy that persisted after adjustment for $PM_{2.5}$ and NO_2.[11] In the other study conducted in the United States, Wright et al.[17] reported a positive association between prenatal UFP exposure and asthma onset in children, independent of NO_2 and temperature; the

Table 2.

Distribution of prenatal and childhood exposure to ambient UFPs, NO_2, and $PM_{2.5}$ in Montreal, 2000–2015.

	Childhood exposure[a]			Prenatal exposure		
Pollutant level	**UFPs (particles/cm³)**	**NO_2 (ppb)**	**$PM_{2.5}$ (μg/m³)**	**UFPs (particles/cm³)**	**NO_2 (ppb)**	**$PM_{2.5}$ (μg/m³)**
Mean	24,525	19.16	9.05	24,706	19.76	9.48
Standard deviation	4,835	8.36	1.03	5,482	8.60	1.35
Minimum	1,097	0	2.26	7,146	0.00	2.47
25% (Q1)	22,190	14.21	8.62	22,101	14.65	8.77
50% (median)	23,677	19.99	8.95	23,732	20.62	9.10
75% (Q3)	25,617	25.26	9.39	25,887	26.13	10.30
Maximum	89,376	45.14	13.76	91,056	46.50	13.77
IQR	3,427	11.06	0.77	3,785	11.48	1.53

[a]Childhood exposures are weighted for follow-up duration.

Table 3.

Adjusted hazard ratios and 95% CI per interquartile range for the association between childhood and prenatal exposure to UFPs and to copollutants and the incidence of childhood asthma onset in Montreal, Canada.

	Hazard Ratios (95% CI) per interquartile range[a]		
	UFPs	**NO_2**	**$PM_{2.5}$**
Childhood exposure			
Crude model	0.99 (0.98, 1.00)	1.03 (1.01, 1.04)	1.17 (1.16, 1.18)
Fully adjusted single pollutant model	0.99 (0.98, 1.00)	1.02 (1.01, 1.04)	1.03 (1.01, 1.04)
Fully adjusted multipollutant model	0.99 (0.98, 1.00)	1.01 (1.00, 1.03)	1.02 (1.01, 1.03)
Prenatal exposure			
Crude model	0.99 (0.98, 1.00)	1.02 (1.01, 1.04)	1.34 (1.33, 1.36)
Fully adjusted single pollutant model	0.99 (0.98, 1.00)	1.02 (1.01, 1.04)	1.06 (1.05, 1.08)
Fully adjusted multipollutant model	0.99 (0.98, 0.99)	1.01 (0.99, 1.02)	1.06 (1.04, 1.08)

Crude: single pollutant model with age as the timescale. Fully adjusted single pollutant: model with age as the timescale, stratified by sex and calendar year, and adjusted for social deprivation and material deprivation. Fully adjusted multipollutant (UFPs + NO_2 + $PM_{2.5}$): model with age as the timescale, stratified by sex and calendar year, and adjusted for social deprivation and material deprivation.
[a]IQR for childhood exposure are 3,427 particles/cm³ for UFPs, 11.06 ppb for NO_2, and 0.77 μg/m³ for $PM_{2.5}$. IQR for prenatal exposure are 3,785 particles/cm³ for UFPs, 11.48 ppb for NO_2, and 1.53 μg/m³ for $PM_{2.5}$.

cumulative odds ratios (ORs) were 3.37 (95% CI = 1.55, 7.06) for males and 2.56 (95% CI = 1.15, 5.11) for females per doubling of UFP concentrations across pregnancy. Cumulative OR across pregnancy was 4.28 (95% CI = 1.41, 15.70). Contrary to Lavigne et al.[11] which showed the strongest association during the second trimester, Wright et al.[17] found strongest associations during the third trimester. In the present study, we could not address trimester specific effects as monthly or weekly UFP data were not available.

Although our results do not suggest an association between UFP and asthma onset, there remains support for biological plausibility of this association. UFPs have high potential to induce oxidative stress and have been shown to act as adjuvants in early stages of allergen sensitization, inflammation, and airway hyperresponsiveness in children and in in vivo models.[3,28,29] Moreover, prenatal exposure to $PM_{2.5}$ has previously been associated with an increase risk of childhood asthma,[30,31] while increased asthma susceptibility and lung dysfunction in offspring has been associated with prenatal exposure to UFPs in multiple rodents models.[28] UFPs has been shown to translocate to the placenta in both animals and humans models.[16] Various underlying biological mechanisms have been proposed to explain adverse effects on offspring respiratory health from a prenatal exposure. These include decreased placental efficiency, mitochondrial damages following generation of reactive oxygen species (ROS), altered antioxidant response through disruption of erythroid 2-related factor (Nrf2) signaling and CYP1A1 up-regulation in the placenta.[28]

Development of childhood asthma is usually higher in boys than girls, a trend that is reversed during puberty and adulthood.[32,33] This was the case in our cohort of children up to 13 years of age, where boys accounted for 61% of all asthma cases. Differences in airways growth, an increased immunological response in boys, and hormonal differences may explain the higher incidence of childhood asthma in boys.[34]

Findings from our multipollutant models showed that ambient NO_2 was associated with asthma onset in children when $PM_{2.5}$ was not adjusted for. The magnitude of the associations for NO_2 are consistent with those of a previous study conducted in Montreal for the period of 1996–2011 (HR = 1.04; 95% CI = 1.02, 1.05 per 5.45 ppb[8]), as well as with the findings from a meta-analysis of 41 studies (meta-estimate of 1.05 95% CI = 1.02, 1.07 for every 4 μg/m³; I^2 = 65%).[7] After adjusting for $PM_{2.5}$, NO_2 associations were attenuated but remained weakly positive; $PM_{2.5}$ was positively associated with asthma onset in both fully adjusted single and multipollutant models.

Particulate and gaseous air pollutants in our study area are typical for a major North American city.[11,17,35] They are however lower than levels reported for European and Asian cities.[36,37] Thus, it is unclear if results from our study can be generalized to cities from those regions.

Although traffic is the main source of both UFPs and NO_2 in urban areas, concentrations were weakly correlated (Pearson r = 0.24). UFPs and NO_2 estimated by land use regression models were also weakly correlated in Toronto (Pearson r = 0.01),[11,13] whereas moderate correlations were reported in other studies (Pearson r = 0.65).[38,39] The lack of a strong correlation may hint that while sharing a common major source, the relative importance of this source can differ between UFPs and NO_2 in urban settings (e.g., restaurants and machinery can also be important sources of UFPs). Dispersion of UFPs may also differ from that of NO_2, which may result in greater differences between the two pollutants away from the source.

Assessing UFP exposure of individuals is also more challenging than for $PM_{2.5}$ and NO_2, and errors in exposure levels are expected. UFP concentrations show larger intraurban spatial

and temporal variability (up to factors of 2–3) than other regulated pollutants[40] and are strongly influenced by road traffic (their main source), characteristics of the built environment and meteorological conditions.[29,35] Because UFPs are not measured by routine ambient air monitoring networks, special dense monitoring campaigns are necessary to developed spatially resolved exposure surfaces for the purpose of epidemiological analysis. This mainly explain the scarce epidemiological studies on long-term effects of UFPs.[7,41] The LUR surface used herein to assign exposure was developed from short monitoring periods, especially during winter time (23 weekdays in June/July and 5 weekdays in March)[22]; these monitoring durations are similar to those used to developed the LUR surface used by Lavigne et al.[11] Considering the inverse relation between temperature and UFP concentrations,[29,42,43] winter exposure may have been underestimated. In comparison, Wright et al.[17] used a LUR model developed with hourly estimates of UFP concentrations from mobile and stationary monitoring campaigns over much longer periods (1.5–2.5 years for continuous stationary monitoring and 46–48 days for mobile monitoring across all seasons).

Road measurements may also not adequately capture residential exposure, as UFP levels rapidly decrease with the distance from the road source.[29,44] Moreover, our exposure estimates did not include temporality, thus assuming that the observed spatial variation in UFPs was constant over the years. We assigned exposure at the residence of the children using their six-digit postal codes, the most precise information available because of confidentiality. Because UFPs is a spatially heterogenous pollutant, there may be variations in concentrations within a postal code area. Moreover, we could not account for mobility (time-activity) patterns during pregnancy and childhood, which has the potential to introduce pollutant-specific exposure misclassification errors that could bias the associations.[45] Overall, these exposure errors are likely to be nondifferential, possibly contributing to the null association observed between UFPs and childhood asthma onset.

A key strength of this study was the use of the QICDSS medico-administrative database, which is population-based and captured all newborns in Montreal during 2000–2015. A limitation inherent to the use of medico-administrative data is the lack of individual-level data about potential confounders such as breastfeeding, family history of asthma, and exposure to second-hand smoke. Our analyses adjusted for indicators of neighborhood socioeconomic status, which is strongly correlated with individual socioeconomic status,[46] but residual confounding remains likely. As for unmeasured second-hand smoke, a previous study showed virtually no influence on the estimated associations between traffic-related air pollutants like NO_2 and asthma onset in children of Montreal.[8] Asthma diagnosis in young children remains challenging and although we used a validated algorithm that serves for surveillance purposes in Quebec and Canada,[21] missed and misdiagnosis of asthma is possible.

Conclusions

In this population-based birth cohort study, the incidence of childhood asthma was not associated with prenatal or long-term childhood exposure to low concentrations of UFPs. Further studies are needed to address whether UFPs contribute to childhood asthma onset. Assessing UFP exposure is particularly challenging. Refining the exposure assessment with monitoring data that better capture the spatial and temporal variability of UFP concentrations is essential to improve risk estimates and shed light on critical exposure time windows.

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