Original Research Article

ENVIRONMENTAL EPIDEMIOLOGY

OPEN

Associations between early-life exposure to $PM_{2.5}$ and reductions in childhood lung function in two North American longitudinal pregnancy cohort studies

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Background: Data integration of epidemiologic studies across different geographic regions can provide enhanced exposure contrast and statistical power to examine adverse respiratory effects of early-life exposure to particulate matter <2.5 microns in diameter ($PM_{2.5}$). Methodological tools improve our ability to combine data while more fully accounting for study heterogeneity.
Methods: Analyses included children enrolled in two longitudinal birth cohorts in Boston, Massachusetts, and Mexico City. Propensity score matching using the 1:3 nearest neighbor with caliper method was used. Residential $PM_{2.5}$ exposure was estimated from 2 months before birth to age 6 years using a validated satellite-based spatiotemporal model. Lung function was tested at ages 6–11 years and age, height, race, and sex adjusted z scores were estimated for FEV_1, FVC, $FEF_{25–75\%}$, and FEV_1/FVC. Using distributed lag nonlinear models, we examined associations between monthly averaged $PM_{2.5}$ levels and lung function outcomes adjusted for covariates, in unmatched and matched pooled samples.
Results: In the matched pooled sample, $PM_{2.5}$ exposure between postnatal months 35–44 and 35–52 was associated with lower FEV_1 and FVC z scores, respectively. A 5 μg/m^3 increase in $PM_{2.5}$ was associated with a reduction in FEV_1 z score of 0.13 (95% CI = –0.26, –0.01) and a reduction in FVC z score of 0.13 (95% CI = –0.25, –0.01). Additionally $PM_{2.5}$ during postnatal months 23–39 was associated with a reduction in $FEF_{25–75\%}$ z score of 0.31 (95% CI = –0.57, –0.05).
Conclusions: Methodological tools enhanced our ability to combine multisite data while accounting for study heterogeneity. Ambient $PM_{2.5}$ exposure in early childhood was associated with lung function reductions in middle childhood.

Chronic respiratory diseases affect over half a billion people worldwide, and rank among the top contributors to the global burden of disease.[1] The perinatal environment is a contributor to disease risk[2,3] including lung disease.[4–7] In life course models of lung disease, risk increases because of the sequential effects of the early environment on development and growth setting different lung growth trajectories.[2,8] This is followed by an age-dependent decline in plasticity, and more modest responses to environmental challenges.[9] Longitudinal studies are needed to identify the early-life exposures that affect lung function[10–12] and lung growth trajectories to prevent chronic respiratory disease and rapid functional decline in adults.[13–15]

Exposure to ambient air pollution during early life, a period of rapid lung development, has been linked to lung function deficits in childhood.[16,17] However, whether exposure to air pollution during this vulnerable period is related to lung function in mid-childhood independent of postnatal air pollution exposure has not been completely elucidated. Relatively few studies have investigated susceptibility windows throughout childhood, and available studies show mixed results.[18–22] Variable findings may in part result from a relatively restricted range of air pollution exposure levels in the area of study as well as lack of accounting for timing of exposure, that is, sensitive windows for exposure effects.

What this study adds

We investigated exposure to early-life fine particulate matter in relation to childhood lung function among participants enrolled in the ACCESS cohort in Boston and the PROGRESS cohort in Mexico City. We used propensity score matching to account for study heterogeneity and distributed lag nonlinear models to examine time-varying associations between monthly fine particulate matter and lung function assessed in middle childhood. We found increasing exposure to air pollution during particular time periods in childhood, postnatal months 23–52 was associated with reductions in lung function outcomes.

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

The PROGRESS study was supported by the National Institute of Environmental Health Sciences grants R00ES027496, R01ES014930, R01ES013744, R24ES028522, P30ES023515, R01ES021357, R01ES034521, and R01ES032242. The ACCESS study was supported by National Institutes of Health grants R01ES010932, U01HL072494, R01MD006086, R01HL080674, UG3OD023337. Biostatistics methods development was funded by U54TR004213. We also thank the ABC (American British Cowdray Medical Center) in Mexico for providing some of the needed research facilities.

A deidentified, limited dataset is available upon reasonable request to the corresponding author.

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Data integration of epidemiologic studies across different geographic areas can provide greater exposure contrast and enhance statistical power to examine associations between ambient air pollution and respiratory outcomes. New methodological tools have improved our ability to combine data across sites while more fully accounting for study heterogeneity in factors that influence exposure and response, such as socioeconomic status and the racial/ethnic makeup or culture-related factors of the cohorts of interest.

We leveraged existing data from two longitudinal population-based birth cohorts, in the United States and in Mexico City, to first examine their combinability and then to test associations between postnatal particulate matter <2.5 microns in diameter ($PM_{2.5}$) exposure and lung function in childhood in the integrated sample. We also implemented advanced statistical models to examine windows of susceptibility to air pollution over early childhood in relation to lung function outcomes.

Methods

Study cohorts

We included two prenatally enrolled cohorts based in the United States and Mexico with similarly derived air pollution and temperature measures as well as implementation of the same standardized approach to spirometry. Here, we provide details on enrollment procedures.

Asthma Coalition on Community Environment and Social Stress (ACCESS) Project

The ACCESS Project recruited mother child-dyads to study the effects of both chemical and nonchemical exposures on urban childhood asthma risk. Pregnant women with singleton pregnancies, who spoke either English or Spanish, were at least 18 years old and were receiving care at two Boston hospitals and affiliated health centers were enrolled between August 2002 and July 2007 (N = 500). Of these, 455 women gave birth to a live singleton infant. A subset (230 of 375) of children were actively followed and participated in a pulmonary function visit. A detailed flow diagram of participants included in analysis is shown in Figure S1, http://links.lww.com/EE/A209. Written informed consent in the mother's primary language was obtained from all mothers. Assent was also obtained from participating children who were ≥7 years of age at time of spirometry. Procedures were approved by the human studies committees at the Brigham and Women's Hospital and Boston Medical Center.

Programming Research in Obesity, Growth, Environment and Social Stressors (PROGRESS) study

PROGRESS is a prospective birth cohort originally designed to study the modifying effects of stress on metals toxicity and on the neurotoxicity of metal mixtures. Between July 2007 and February 2011, 1,054 pregnant women receiving prenatal care through the Mexican Social Security System (Instituto Mexicano del Seguro Social –IMSS) were recruited (Burris et al., 2013).[23] Women were eligible to participate if they met the following criteria: <20 weeks gestation, ≥18 years old, planned to stay in Mexico City for the next 3 years, had access to a telephone, had no medical history of heart or kidney disease, did not consume alcohol daily, and did not use any steroid or antiepilepsy medications. Nine hundred forty-eight women gave birth to a live singleton child. Lung function was subsequently assessed when children were with 8–11 years of age with 277 children completing testing between October 2018 and March 2020. Prebronchodilator, 245 (88%) tests met the criteria for acceptability and reproducibility. A detailed flow diagram of participants included in analysis is shown in Figure S1, http://links.lww.com/EE/A209. Procedures were approved by institutional review boards at the Harvard School of Public Health, the Mexican National Institute of Public Health, and the Icahn School of Medicine at Mount Sinai. Mothers provided written informed consent and children provided assent once they reached 7 years of age.

Ambient air pollution

Daily residential postnatal exposure to $PM_{2.5}$ was estimated using a validated hybrid satellite-based spatiotemporal prediction model for both cohorts. In ACCESS, Moderate Resolution Imaging Spectroradiometer (MODIS) derived aerosol optical depth (AOD) measurements were combined with meteorological and traditional land use regression (LUR) variables. using a geospatial smoothing technique to yield daily $PM_{2.5}$ estimates as previously described.[24,25] The model was calibrated against $PM_{2.5}$ measurements derived from 78 ground monitoring stations covering New England at a 1 × 1–km resolution. For days without AOD measurements, exposures were estimated using within-season spatial smoothing and the time-varying mean from local ground monitors. Model performance was excellent with an out of sample ten-fold cross validation R^2 for daily values of 0.88.

For PROGRESS, daily residential postnatal exposure to $PM_{2.5}$ was also estimated at a 1 × 1 km spatial resolution using day-specific calibrations of AOD data calibrated against $PM_{2.5}$ measurements from 12 ground monitoring stations covering Mexico City.[26] LUR and meteorological variables were also incorporated into the model. Mixed effect models with spatial and temporal predictors and day-specific random effects were used to account for temporal variations in the $PM_{2.5}$–AOD relationship. The model was fit with a seasonal smooth function of latitude and longitude and time-varying average incorporating local monitoring for days without AOD data. Model performance was excellent with an out of sample ten-fold cross validation R^2 of 0.724. For both cohorts, daily $PM_{2.5}$ measures were averaged into monthly measurements.

Pulmonary Function Testing

In both ACCESS and PROGRESS, a trained research assistant or nurse measured child height, weight, and lung function. Height was measured to the nearest 0.1 cm on a stadiometer and weight was measured to the nearest 0.1 kg on an electronic scale. Spirometry was performed in participant homes with a portable MedGraphics laptop supported spirometer and testing procedures met American Thoracic Society (ATS) guidelines for acceptability and reproducibility,[27,28] which were modified for children in the ACCESS cohort who were less than 8 years of age as per the guidelines (e.g., minimum forced expiratory time of 1 second in those <8 years old).[29,30] Flow was measured with a heated screen pneumotachograph (flow range 0 ± 20 l/s,

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Environmental Epidemiology (2022) 7:e234

Received: 7 September 2022; Accepted 12 November 2022

Published online 14 December 2022

DOI: 10.1097/EE9.0000000000000234

accuracy 0.2–12 l/s ± 2%) and volume was measured by digital integration. A standard 3L syringe was used for calibration preceding each session with accounting of ambient temperature, air pressure and humidity. Participants were excluded if they reported acute respiratory symptoms in the last 2 weeks. Short-acting beta-agonists, anticholinergic, and theophylline preparations were withheld 4 hours before testing; long-acting beta-agonists were withheld for 12 hours and long-acting theophylline preparations for 24 hours. Parameters recorded from a minimum of 3 (and no more than 8) maneuvers included: FEV_1 (liters), FVC (liters), FEV_1/FVC, and $FEF_{25–75\%}$ (L). Raw FEV_1, FVC, and $FEF_{25–75\%}$ values were adjusted for age, sex, height, and additionally for race/ethnicity in ACCESS only using multivariable regression, and then converted to z scores with a mean of 0 and a standard deviation of 1 to describe each child's position relative to that of other individuals in the distribution.[31] FEV_1/FVC ratio was then calculated by dividing FEV_1 z scores by FVC z scores. All tests were over read for acceptability and reproducibility by a respiratory technician or pediatric pulmonologist.

Covariates

We considered covariates previously linked to air pollution exposure and lung function and confirmed covariates based on formulation of a Directed Acyclic Graph (DAG; Supplemental Figure 2, http://links.lww.com/EE/A209). Models were adjusted for the minimal sufficient adjustment sets for estimating the total effect of air pollution on childhood lung function. Maternal age, race/ethnicity (ACCESS only), and maternal education as an indicator of individual-level socioeconomic status (SES) were ascertained by questionnaire. In ACCESS maternal prepregnancy height and weight were determined via self-report at enrollment; body mass index (BMI) was calculated by dividing weight by height squared (kg/m^2); self-reported height and weight was validated with direct measurements in a subset as previously reported.[32] In PROGRESS, prepregnancy BMI was estimated using a previously validated model.[33] In ACCESS gestational age was calculated based on maternal report of last menstrual period (LMP) and updated based on ultrasound data from medical record review at delivery if discrepant by more than 3 weeks.[34] In PROGRESS, gestational age was based on LMP and updated by measurements from a standardized physical examination at birth to determine gestational age if discrepant by more than 3 weeks.[35] Birth weight data were extracted from labor and delivery records for all studies. We derived Fenton birth weight for gestational age z scores which facilitates harmonization across different cohorts, including those from different countries.[36] Due to low rates of maternal smoking during pregnancy in PROGRESS, we report prenatal environmental tobacco smoke exposure (ETS) for both cohorts. ETS exposure after birth was defined as report of the mother currently smoking and any other smoker in the home at any postnatal visit. In ACCESS, daily postnatal temperature was derived using a model that calibrated Moderate Resolution Imaging Spectroradiometer satellite surface temperature measurements to air temperature monitors by using LUR as previously described.[37] In PROGRESS, daily postnatal temperature was similarly assessed with a spatiotemporally resolved hybrid satellite-based land use regression model.[38]

Statistical analysis

As previously demonstrated, including a term for "site" in regression models as a covariate may not fully account for the unmeasured effects of cohorts being combined in pooled analyses.[39] Herein, propensity scores were first estimated from logistic models with site as the outcome and baseline cohort variables as the predictors. These variables included: education (≤high school or >high school), maternal prepregnancy BMI (continuous), birthweight z score (continuous), mother's age at birth (continuous), child sex, ETS exposure in pregnancy (yes vs. no). Propensity scores were calculated by taking the inverse of the probabilities obtained from the binomial logistic models, which constituted the conditional probability of an individual belonging to their actual study given covariates.

We then examined four matching methods to determine the best covariate balance to ensure the distribution of covariates was similar across both cohorts. The matching methods examined were (1) nearest neighbor, which selects the closest eligible PROGRESS participant to be paired with each ACCESS participant based on distance, defined as the propensity score difference, (2) nearest neighbor (same as above) additionally discarding matches outside of the region of common support (defined as the area where the densities of the estimated propensity scores for both ACCESS and PROGRESS participants overlap, indicating they share common support on the selected covariates), (3) 1:3 nearest neighbor using a 0.20 caliper,[40] which limits the distance between paired units and, and (4) optimal matching, which is similar to nearest neighbor but chooses matches that collectively optimize an overall criterion (the smallest average absolute distance across all the matched pairs). Standardized mean differences, variance ratios, and visual diagnostics (Love plots) were used to choose the best matching method.[41] Matching was implemented using the MatchIt package in version 2.4.2 in R Version 3.5.1 (R Development Core Team).

Finally, distributed lag nonlinear models (DLNMs) were implemented to estimate the time-varying association between estimated monthly postnatal $PM_{2.5}$ levels and lung function outcomes. The models included an exposure period starting 2 months before birth (assuming a 9-month pregnancy), in order and ending at 6 years. The 2 months before birth were included to allow a more precise estimation of the association within our period of interest (postnatal) as DLNMs have wider confidence intervals at both ends. DLNMs were adjusted for postnatal ETS exposure, maternal age and education and for temperature by including a separate cross-basis for monthly mean temperatures covering the same lags. The DLNMs were based on a generalized additive model with linear terms for the association of exposure and outcome and a penalized spline basis for the lag structure with penalties for overall smoothness. A sensitive window was identified when the pointwise 95% confidence bands did not contain zero. In sensitivity analysis, we additionally adjusted for birthweight z score. The DLNMs were run (1) separately for each cohort, (2) after combining data from the cohorts without matching and adjusting for site, and (3) combining data from the cohorts taking into account the propensity score analysis and matching. In secondary analyses, we also evaluated the association between postnatal $PM_{2.5}$ levels and lung function z scores with the inclusion of birthweight z score as a covariate to determine if air pollutant exposure impacts lung growth and development through pathways other than somatic growth. DLNMs were implemented using the dlnm package version 2.4.2[42] in R Version 3.5.1 (R Development Core Team), and other analyses were performed in SPSS version 24 (Chicago, IL).

Results

Descriptive statistics

As seen in Table 1, many demographic characteristics varied across the ACCESS and PROGRESS cohorts. Notably, PROGRESS, which was recruited in Mexico, included 100% Hispanic participants whereas 91% of ACCESS participants were non-white and Hispanic. PROGRESS participants had a greater proportion of mothers with less than a high school education compared with ACCESS women. On average, PROGRESS participants had higher levels of $PM_{2.5}$ exposure compared with those followed in ACCESS across all

Table 1.

Descriptive characteristics for pooled sample and individual cohorts.

		Pooled sample	Access	Progress
Continuous variables		**421**	**196**	**225**
Averaged first postnatal year $PM_{2.5}$ (μg/m³; median, IQR)[a]		18.6 [11.1, 22.7]	11.0 [9.95, 11.9]	22.4 [19.6, 24.5]
Averaged second postnatal year $PM_{2.5}$ (μg/m³; median, IQR) [a]		19.4 [10.9, 22.8]	10.6 [9.69, 11.5]	22.6 [21.1, 24.6]
Averaged third postnatal year $PM_{2.5}$ (μg/m³; median, IQR) [a]		20.0 [10.1, 22.8]	10.0 [8.94, 10.8]	22.5 [21.3, 23.7]
Averaged forth postnatal year $PM_{2.5}$ (μg/m³; median, IQR) [a]		19.0 [9.74, 22.0]	9.66 [8.65, 11.0]	21.8 [20.8, 23.5]
Average fifth postnatal year $PM_{2.5}$ (μg/m³; median, IQR) [a]		18.5 [9.28, 21.4]	9.17 [8.32, 9.88]	21.2 [19.5, 22.3]
Average sixth postnatal year $PM_{2.5}$ (μg/m³; median, IQR) [a]		18.7 [8.76, 20.9]	8.71 [7.97, 9.19]	20.7 [19.3, 22.4]
Averaged first postnatal year temperature (°C; median, IQR) [a]		13.2 [10.9, 15.2]	10.8 [10.4, 11.2]	15.1 [14.0, 16.0]
Averaged second postnatal year temperature (°C; median, IQR) [a]		13.3 [11.1, 15.2]	11.0 [10.5, 11.3]	15.2 [14.2, 16.1]
Averaged third postnatal year temperature (°C; median, IQR) [a]		13.3 [11.0, 15.2]	10.9 [10.4, 11.3]	15.2 [14.1, 16.0]
Averaged forth postnatal year temperature (°C; median, IQR) [a]		13.2 [11.0, 15.2]	11.0 [10.5, 11.5]	15.1 [14.1, 15.9]
Average fifth postnatal year temperature (°C; median, IQR) [a]		13.1 [11.1, 15.1]	11.1 [10.4, 11.8]	15.0 [13.9, 15.8]
Average sixth postnatal year temperature (°C; median, IQR) [a]		13.1 [11.8, 15.2]	11.8 [11.2, 12.4]	15.1 [13.9, 16.1]
z scores of FEV_1 (median, IQR) [b]		–0.04 [–0.59, 0.65]	0.00 [–0.56, 0.56]	–0.04 [–0.68, 0.73]
z scores of FVC (median, IQR) [b]		–0.02 [–0.74, 0.65]	–0.01 [–0.64, 0.63]	–0.02 [–0.82, 0.68]
z scores of $FEF_{25–75\%}$ (median, IQR) [b]		–0.02 [–0.71, 0.68]	–0.01 [–0.72, 0.622]	–0.02 [–0.65, 0.68]
z scores of FEV_1/FVC ratio (median, IQR) [b]		0.81 [0.28, 1.37]	0.81 [0.25, 1.37]	0.79 [0.30, 1.41]
Age at spirometry test (years; mean, SD) [a]		8.45 (1.66)	6.96 (0.830)	9.76 (0.947)
Height at spirometry test (cm; mean, SD) [a]		130 (10.8)	122 (7.41)	136 (8.36)
Birth weight for gestational age z scores (median, IQR) [a]		–0.26 [–0.89, 0.38]	–0.10 [–0.80, 0.75]	–0.38 [–0.95, 0.20]
Maternal prepregnancy BMI* (median, IQR) [a]		26.5 [24.1, 30.3]	27.1 [24.4, 31.9]	26.1 [23.7, 29.4]
Maternal age at enrollment (years; median, IQR)		27.3 [23.6, 31.8]	26.3 [23.1, 32.2]	27.7 [24.2, 31.5]
Categorical variables, n (%)				
Sex	Male	223 (53)	102 (52.)	121 (53.8)
	Female	198 (47)	94 (48)	104 (46.2)
Race/Ethnicity[a]	White, Non- Hispanic	18 (4.3)	18 (9.2)	0 (0)
	Non-White and/or Hispanic	403 (95.7)	178 (90.8)	225 (100)
Education	< High School	172 (40.9)	72 (36.7)	100 (44.4)
	≥High School	249 (59.1)	124 (63.3)	125 (55.6)
ETS exposure in pregnancy[a]	Yes	126 (29.9)	43 (21.9)	83 (36.9)
	Missing	31 (7.4)	31 (15.8)	0 (0)
ETS exposure postnatally [a]	Yes	179 (42.5)	52 (26.5)	127 (56.4)

[a] $P < 0.05$, differences tested using t-tests for continuous variables and Chi-Square for dichotomous variables.

[b]Adjusted for age, sex, height and race/ethnicity (latter in ACCESS only).

postnatal years. PROGRESS also had greater reported proportion of children exposed to ETS in both pregnancy and postnatally.

DLNM analysis of individual cohorts

We first show results for the association between monthly $PM_{2.5}$ and lung function outcomes considering each cohort separately. Figure S3, http://links.lww.com/EE/A209 shows results for the both the ACCESS and PROGRESS cohorts. For ACCESS, we did not identify any windows of susceptibility for FEV_1, FVC, or FEV_1/FVC z scores. A 5 μg/m³ increase in $PM_{2.5}$ at 17–27 months postnatal was associated with a cumulative reduction in $FEF_{25–75\%}$ z score of –0.58 (95% CI = –1.10, –0.05). In PROGRESS, a sensitive window was identified at prenatal months 8–9 and postnatal months 1–9 in which $PM_{2.5}$ was associated with an increase in FEV_1. We did not detect any windows for any other lung function parameter.

DLNM analysis of combined cohorts with adjustment for site as a covariate

Next, we analyzed the association between monthly $PM_{2.5}$ and lung function outcomes in our combined sample with the adjustment for site as a covariate, shown in Figure 1. We did not identify any windows of susceptibility for FEV_1, FVC, or FEV_1/FVC z scores. A 5 μg/m³ increase in $PM_{2.5}$ at 25–30 months postnatal was associated with a cumulative reduction in $FEF_{25–75\%}$ z score of –0.20 (95% CI = –0.39, –0.01).

Combinability analyses

Propensity scores were then estimated from logistic models using maternal education, prepregnancy BMI, birthweight z score, mother's age at birth, child sex, and ETS exposure in pregnancy as the predictors. The optimal matching was obtained using the 1:3 nearest matching method with 0.20 caliper. With this method, 128 ACCESS participants were matched to 214 PROGRESS participants for a total of 342 participants in the matched sample. We generated a Love plot to graphically display covariate balance before and after matching. Absolute standardized mean differences (ASMD) close to zero indicate good balance and a threshold of 0.1 has been previously recommended in the literature.[41] As shown in the Love plot in Figure 2, the balance of our covariates is greatly improved after matching and all ASMDs fall within the desired threshold. Figure 3 also shows a greater balance in the distribution of propensity scores after matching. Empirical Cumulative Density Function statistics all approached 0 (ranging from 0.01 to 0.04) and variance ratios ranged from 1.07 to 1.37 also indicating good balance. In the supplemental material, we also provide Love plots (Figure S4, http://links.lww.com/EE/A209) and balance in propensity scores (Figure S5, http://links.lww.com/EE/A209) derived through other matching approaches used to further demonstrate the superiority of the 1:3 nearest matching method with 0.20 caliper.

DNLMs using matched sample

Finally, DLNMs were run using the matched sample. As shown in Figure 4, we identified a window of susceptibility for $PM_{2.5}$

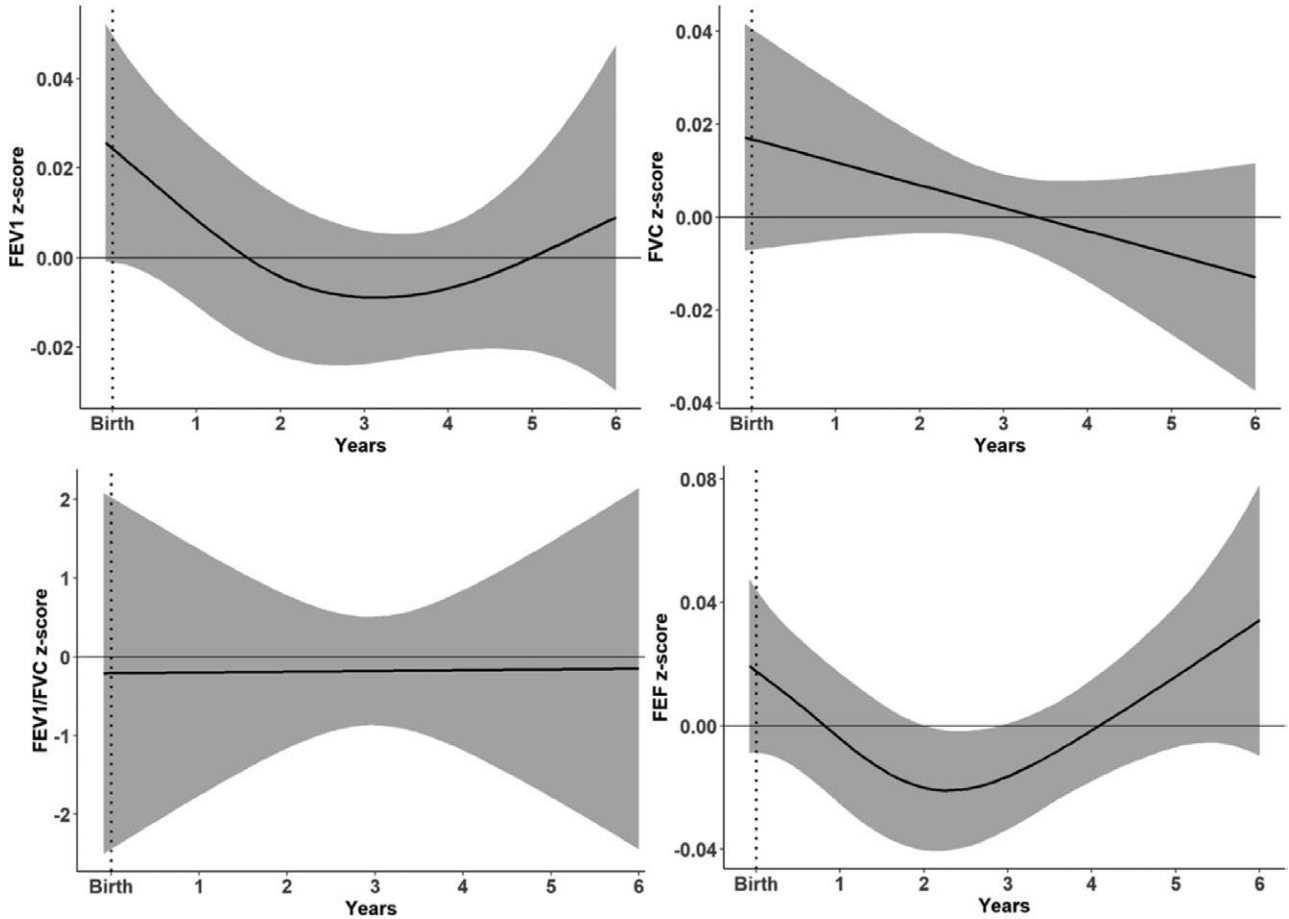

Figure 1. Associations between monthly average postnatal $PM_{2.5}$ and FEV_1, FVC, FEV_1/FVC and $FEF_{25-75\%}$, z scores in unmatched sample. Models adjusted for, maternal age and education at birth, postnatal ETS exposure, monthly temperature, and site.

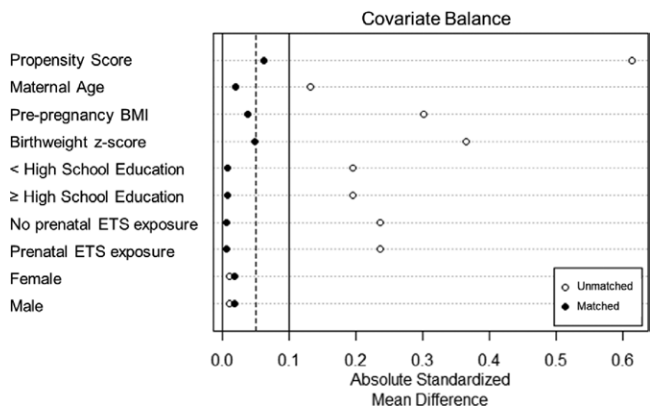

Figure 2. Love plot comparing absolute standardized mean differences in propensity scores and covariates between unmatched and matched samples.

exposure in early childhood in relationship to lower FEV_1, FVC and $FEF_{25-75\%}$ z scores. Specifically, we found that $PM_{2.5}$ exposure between postnatal months 35–44 was associated with a lower FEV_1 z score. A 5 μg/m^3 increase in $PM_{2.5}$ throughout this critical window was associated with a cumulative reduction in FEV_1 z scores of 0.13 (95% CI = –0.26, –0.01). Similarly, a 5 μg/m^3 increase in $PM_{2.5}$ at 35–52 months postnatal was associated with a cumulative reduction in FVC z score of –0.13 (95% CI = –0.25, –0.01) and an increase during postnatal months 23–39 was associated with a reduction in $FEF_{25-75\%}$ z score –0.31 (95% CI = –0.57, –0.05). We did not find any windows of susceptibility for $PM_{2.5}$ in relation to FEV_1/FVC z scores. Additional adjustment for birthweight z score did not significantly impact our findings (Figure S6, http://links.lww.com/EE/A209).

Discussion

These analyses leveraged data from two North American pregnancy cohorts with varying levels of air pollution to assess the associations between perinatal and early childhood exposure to $PM_{2.5}$ and middle childhood lung function outcomes. With a more careful accounting of site-specific effects to account for underlying cohort differences, we were able to identify significant associations between prenatal $PM_{2.5}$ exposure and lung function outcomes that were not detected using more traditional methods. We combined monthly ambient $PM_{2.5}$ exposure estimates with advanced statistical modeling to determine susceptible windows of exposure to $PM_{2.5}$. We found that exposure to $PM_{2.5}$ during 35–44 months postnatally was associated with lower FEV_1 z scores later in childhood. We found a similar window for $PM_{2.5}$ exposure during postnatal months 35–52 and a reduction in FVC z score. Additionally exposure during postnatal months 23–39 was associated with decrements in $FEF_{25-75\%}$.

Although our results are in line with previous longitudinal studies that found negative associations of early-life air pollution exposure with lung function in childhood and adolescence, the majority did not detect specific windows. He and colleagues reported that both NO and NO_2 exposure during the prenatal period, infancy (0–2 years), and childhood (2 to <8 years) were associated with lower lung function parameters in adolescents living in Hong Kong.[19] In a large UK birth cohort, PM_{10} at all time periods examined (prenatal, 0–6 months, 7–12 months, and

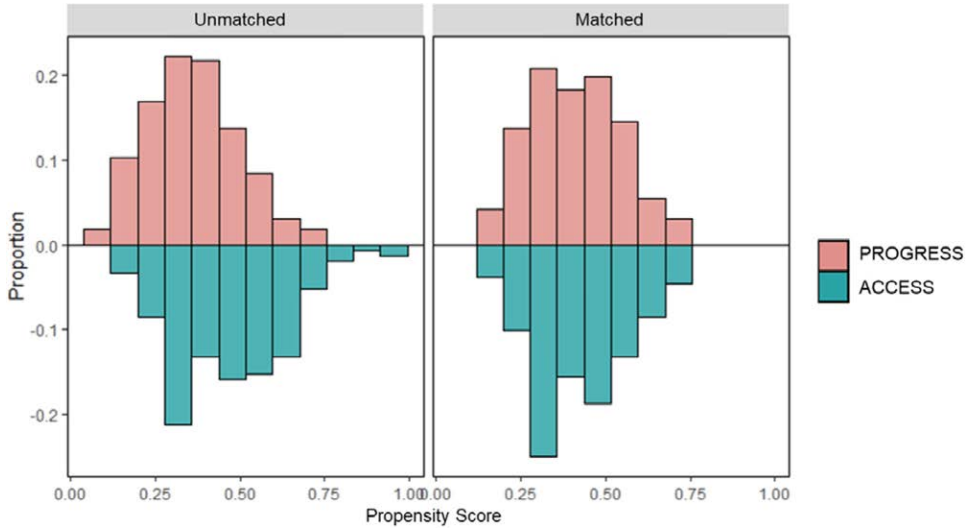

Figure 3. Distributional balance of propensity scores in unmatched and matched samples.

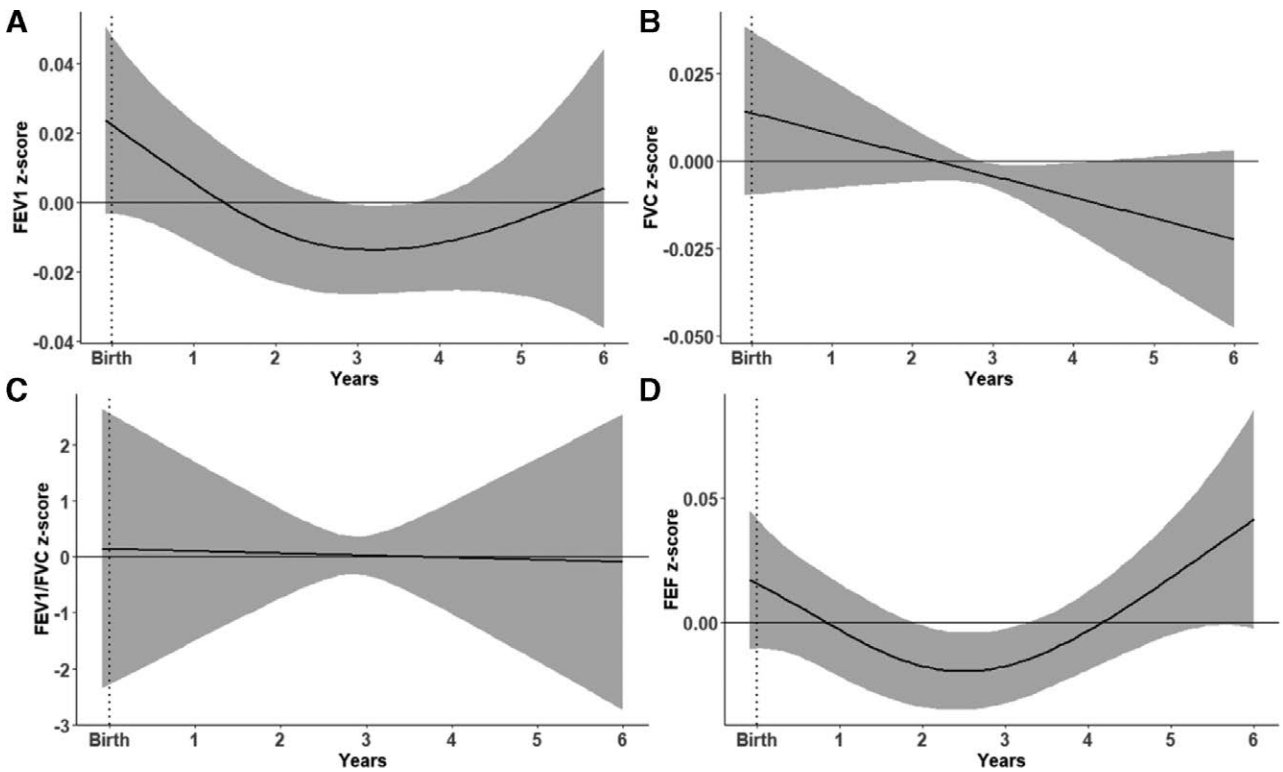

Figure 4. Associations between monthly average postnatal $PM_{2.5}$ and (A) FEV_1 z scores, (A) FVC z scores, (C) FEV_1/FVC z scores, and (D) $FEF_{25–75\%}$ z scores in propensity score matched combined sample. Models adjusted for maternal age and education at birth, postnatal ETS exposure, and monthly temperature.

0–7 years) was associated with lower percent predicted FEV_1 and FVC, with the authors positing that no susceptibility periods were identified due to the high correlation in PM measures across time periods.[22] In a study of Taiwanese children aged 6–15 years, the authors reported that the effects of PM_{10} effects across the lifetime (birth age at lung function measure) on FEV_1, FVC, and $FEF_{25–75\%}$ were stronger than those for exposure during the first year of life or for the interval spanning 2–6 years of life.[18] The PIAMA birth cohort reported that $PM_{2.5}$, $PM_{2.5}$ absorbance, PM_{coarse}, NO_2, and PM_{10} exposure during preschool (birth age 4) was associated with reduced FEV_1 growth from ages 8–16.[20] The BAMSE cohort reported that PM_{10} exposure only during the first year of life and not at any time after was associated with reduced FEV_1 at age 8[43] and at age 16.[44] The majority of these studies used less temporally resolved exposure data (yearly vs. monthly averages) which prevented them from utilizing DLNM models, different exposure assignments (e.g., land use regression vs. dispersion models vs. monitor assignment) and associations were examined in areas with relatively lower levels of air pollution which may account for discrepancies in the ability to detect sensitive windows. Moreover, the DLNM approach accounts for correlated measures of air pollution over time enhancing the power to detect sensitive periods of exposure.[45] Our results suggest that air pollution exposure impacts both airway development (FEV_1) and lung size (FVC). Other studies have reported associations between airborne pollutants and lower $FEF_{25–75\%}$, indicating that peripheral small airway function might also be susceptible to the detrimental effects of these pollutants, although the interpretation of this measure is still debated.[17]

Our detected window of susceptibility overlaps with a developmental period characterized by rapid cellular differentiation and morphogenesis including the formation of 23 airway generations and approximately 300 million alveoli. Rapidly proliferating cells are most susceptible to the detrimental effects of inhaled pollutants during these developmental periods.[46,47] Furthermore, the risk of respiratory damage is greater for young children compared with adults given a faster respiratory rate, greater ventilation rate, and a smaller alveolar surface area. Owing to its small size, $PM_{2.5}$ can travel deep into the lungs and oxidative stress and airway inflammation, both local and systemic, are hypothesized as potential mechanisms for its adverse effects.[48] Alterations in immune development, the neuroendocrine system and epigenetic changes have also been proposed as links between exposure to air pollution and respiratory health effects.[46] Air pollution exposure may also contribute to airway remodeling with subsequent effects on lung function.[17,49]

Our study has several strengths. Both the ACCESS and PROGRESS studies are established prospective birth cohorts with well-characterized demographic and covariate data. For both cohorts, satellite models allowed us to reconstruct longitudinal ambient exposure estimates from birth to early childhood based on residential locations and prospectively collected data. These modeled ambient exposure metrics are less at risk for confounding and biases by individual behaviors than personal exposure measurements.[50] We were also able to adjust for important confounders like temperature and potential pathway variables. Other strengths include our focus in lower income populations more likely to be impacted by both higher air pollution levels and reduced lung function. However, this focus may also limit generalizability to populations with differing demographics.

We also acknowledge some limitations. Our reliance on ambient exposure estimates may not completely reflect personal exposure because they do not capture indoor sources. Although $PM_{2.5}$ is attributed as the largest component of the global burden of disease owing to air pollution, ambient pollution is a complex mixture and our analysis cannot account for the potential contribution of other airborne toxicants. We also cannot rule out that the chemical composition of $PM_{2.5}$ varies between sites and that there might be residual confounding owing to unmeasured factors or incomplete adjustment for measured factors related to $PM_{2.5}$ that may also influence childhood lung function. Nevertheless, our findings were limited to specific periods in time, therefore unmeasured confounders would have to co-vary with $PM_{2.5}$ and time-invariant characteristics would not explain these associations.[51] Our use of propensity score matching would make our results generalizable only to the characteristics of the included participants and not the cohort as a whole. Additionally, both of the studies had small sample sizes which might have contributed to the lack of associations found when examining them individually.

In conclusion, the implementation of methodological tools to enhance our ability to combine multisite data while accounting for study heterogeneity demonstrated significant adverse effects of early-life ambient $PM_{2.5}$ exposure on lung function in middle childhood. Findings in these analyses suggest an impact on the airways and further work investigating $PM_{2.5}$ exposure with longitudinal lung function trajectories later in adolescence will be an important next step.

Acknowledgments

We are grateful to the ACCESS and PROGRESS participants and staff at the National Institute of Public Health/Ministry of Health of Mexico and the National Institute of Perinatology.

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