Lung function growth in children with long-term exposure to air pollutants in Mexico City

Online data supplement

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METHODS

Study design

The main objective of the EMPECE (Estudio Metropolitano Para evaluar los Efectos de la Contaminación en Escolares) study, a prospective study undertaken by the Mexican Ministry of Health in April 1996, was to evaluate the effects of long-term exposure to different levels of ozone (O_3), particulate matter with a mass median diameter of less than 10 µm (PM_{10}), and nitrogen dioxide (NO_2) on lung function growth in children living and attending elementary school in Mexico City. The target population consisted of schoolchildren aged 8 years at baseline, living in Mexico City during the study period and not diagnosed as asthmatic.

Ten fixed-site air monitoring stations were selected to provide the most complete environmental and meteorological information and to give a representative sample from all areas of the city. They included one in the north-west area, two in the north-east, three in the central area, two in the south-west and two in the south-east. Thirty-nine elementary schools within 2 km of the monitoring stations were randomly selected from the elementary school census, which covers both private and public schools, nine in the north-west area, ten in the north-east, nine in the central area, six in the south-west and five in the south-east. All third graders in each school were invited to participate in the study. Only children whose parents signed a consent letter were enrolled.

Most elementary school students in Mexico City attend school either in the morning (8 am to 2 pm) or the afternoon (2 pm to 6 pm). Seventy-five percent of our study population attended the morning session.

The study population for phase 1 included 1,819 children. This phase consisted of a spirometric test of each child and a baseline questionnaire completed by parents. 1,351 new participants of the same age (+/- 1 month) as the previously enrolled children were added to the cohort in subsequent phases. Children diagnosed as asthmatic during the phase following their enrolment were excluded. The children were followed every 6 months (spring and fall) over three years, for up to seven phases. Follow-up consisted of spirometric testing and two questionnaires per phase. One questionnaire, answered at home by the mother, included information on socio-economic status, the child's respiratory health history, time spent in different types of activities, outdoor activities, transportation time, environmental tobacco smoke (ETS) exposure, and history of changes of residence. The other, answered in school by the children and their teachers during school hours, inquired about school time spent in indoor and outdoor activities and ETS exposure.

A number of children were lost to the study, mainly because they moved to another area of the city or to another city altogether. Information was obtained from a total of 3,170 children.

Lung function testing

Spirometric lung function was measured in the morning or early afternoon during 6-monthly visits to each school. Before the start of each study phase, technicians received refresher training covering all spirometric techniques as recommended by American Thoracic Society (ATS) standards(E1).. They also reviewed instructions for standardizing any assistance in the completion of the parent questionnaires.

Lung volumes and flows were measured with computerized dry rolling-seal spirometers (Model 922, SensorMedics, Yorba Linda, CA, USA), which perform the spirometric test according to ATS standards (E1). Every day before data collection, the spirometers were calibrated with a three-liter syringe (SensorMedics, Yorba Linda, CA, USA), and quality control checks were performed with a flow-volume syringe (Flow-Volume Calibrator, Jones Medical Instruments Co., Oak Brook, IL, USA). Spirometric reproducibility in this study and a complementary study has been previously reported (E2). To avoid inhaling from spirometers, only the expiratory section of forced expiratory maneuvers was registered. Disposable mouthpieces were used. The main variables recorded by the spirometers are forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), the ratio between the two (FEV_1/FVC), and forced midexpiratory flow ($FEF_{25'-75\%}$).

The spirometric technicians conducted the tests at school during school hours. They also obtained height and weight measurements from each child and entered them in the computerized spirometer. Each child performed up to eight maximal forced expiratory flow volume maneuvers, at least three of which were acceptable by ATS criteria (i.e. maximal effort, no cough or glottic closure during the first second, good start-of-test, no early termination or cutoff) (E1). The highest FVC and FEV_1 were selected for analysis. The results presented in this document are the selected best spirometry measurements. Further details on the spirometry methods used are described in a previous report(E3). Ambient temperature before each study was measured with a digital wall thermometer. The measurements were entered in the data base and used in the analysis.

Air pollution monitoring

The Mexico City air monitoring system is managed by the city government and was developed according to the standards of the Word Health Organization, the USA Environmental Protection Agency and the German Federal Environmental Agency. Automatic fixed-site monitoring stations measure ozone (O_3) concentrations by ultraviolet photometry. They also record hourly concentrations of nitrogen monoxide (NO), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), carbon monoxide (CO) and particulate matter with a mass median diameter of less than 10 μm (PM_{10}). SO_2 is measured by pulsed fluorescence, CO by non-dispersive infrared photometry, NOx by chemoluminescence and PM_{10} by tapered element oscillating microbalance (TEOM) (E4).

The selected schools were located within 2 km of 10 fixed-site monitoring stations. Children's exposure assessment was based on data from the station closest to their school. Five monitoring stations (Plateros, Hangares, Taxqueña, Lagunilla and San Agustín) were not equipped with a TEOM so could not be used to assign PM_{10} exposure. The PM_{10} exposure of children attending the schools concerned was based on data from the nearest station measuring PM_{10} (Pedregal, Merced, Cerro de la Estrella, Merced and Tlalnepantla respectively). The maximum distance between these schools and the PM_{10} monitoring stations was 6 km.

The hourly O_3 and NO_2 concentrations provided by the monitoring stations were expressed in ppm. We calculated 8-hour means between 10 am and 6 pm for O_3 and 24-hour means for PM_{10} and NO_2 for each day for which hourly data were available for more than 75% of the time, converting ppm into ppb. Means for other days were classified as missing data.

Long-term exposure for each day of the study period was estimated as the O_3 8-hour mean, PM_{10} 24-hour mean and NO_2 24-hour mean averaged over the previous 6 months. These averages vary depending on the station assigned to each school. Exposure to CO and SO_2 was not analyzed as only low concentrations were registered. The Mexican standard for CO (above 11 ppb) was exceeded only once during 2000 and not at all during 2001 or 2002. The Mexican standard for SO_2 was exceeded once during 2000, eight times in 2001 and not at all during 2002.

Statistical analysis

Univariate analysis was performed on all data – questionnaire results, spirometry results and air pollutant concentrations – to identify possible inconsistencies and outliers. All inconsistencies and outliers in the questionnaire data base were checked against the paper records. Data analysis included univariate and bivariate analyses to describe the study population. Continuous outcome variables (FVC, FEV_1, $FEF_{25\%-75\%}$) were plotted against study phases to identify trends or potential irregularities.

Data from the best spirometry test, based on the highest FVC and FEV_1, were used for the analysis. The distributions of the outcome variables (FVC, $FEV_{1,}$ and $FEF_{25-75\%}$) were reviewed to ensure they had an approximately normal distribution.

The data bases for long-term air pollutant exposure data and lung function tests were merged by day of spirometry test. Questionnaire data bases were linked to spirometry results by child identification number and study phase. Correlation coefficients were obtained between mean pollutant concentrations (O_3, PM_{10}, and NO_2) averaged over 6 months.

General linear mixed models were used to evaluate dependent data. Repeated data from the same children were used to evaluate the association between air pollutant concentrations and a deficit in lung function growth variables over time. The outcome variables were the lung function parameters FVC, FEV_1, FEV_1/FVC and $FEF_{25-75\%}$.

A three-level model was used to distinguish the sources of variation in the response: a first level to identify the variation between phases within children nested within monitoring stations, a second level to identify the variation between subjects within monitoring stations and a third level to identify the variation between monitoring station variables.

Let the random variable Y_{ijk} denote the FVC, FEV_1 or $FEF_{25-75\%}$ measurement at phase i (recoded to years after the first phase) for children j in monitoring station k. Y_{ijk} was modeled using a sex-specific general linear mixed model:

Level 1: Between phases (*i*) within children (*j*)

$$Y_{ijk} = \beta_{0jk} + \beta_{1jk}(\text{PHASE})_{ijk} + \beta_{2jk}(\text{AGE})_{ijk} + \beta_{3jk}(\text{HEIGHT})_{ijk} + \beta_{4jk}(\text{BMI})_{ijk} + \beta_{5jk}(\text{ENVIRONMENTAL\_SMOKE})_{ijk} + \beta_{6jk}(\text{TIME\_OUTDOORS})_{ijk} + \beta_{7kj}(\text{O3\_6MONTHS})_{ijk} + \beta_{8jk}(\text{PM10\_6MONTHS})_{ijk} + \beta_{9jk}(\text{HEIGHT x AGE})_{ijk} + \beta_{10jk}(\text{O3\_6MONTHS x PHASE})_{ijk} + \beta_{11jk}(\text{PM10\_6MONTHS x PHASE})_{ijk} + \varepsilon_{ijk}$$

Level 2: Between children within monitoring stations (k)

$$\beta_{0jk} = \gamma_{00k} + u_{0jk}$$

$$\beta_{1jk} = \gamma_{10k} + u_{1jk}$$

Level 3: Between monitoring stations

$$\gamma_{00k} = \delta_{000} + \delta_{001}W_k + \zeta_{00k}$$

$$\gamma_{10k} = \delta_{10k} + \zeta_{10k}$$

A negative coefficient in β_{7kj} indicates a deficit in the lung function growth mean associated with O_3 exposure over time. Study phase, taken as the time variable, was recoded to time in years after phase 1 in order to obtain annual effects.

We compared various variance-covariance matrix forms including unstructured, autocorrelation, and compound symmetry. With the last two forms, the convergence criterion was met but the final Hessian was not positive, and several models required more iterations than the unstructured option. We therefore decided to specify the variance-covariance matrix as unstructured.

We also compared random intercept models and random intercept and slope models. Better goodness-of-fit statistics, smaller Akaike's Information Criterion (AIC) scores and a statistically significant interaction term between time and sex were obtained using random intercept and slope models for the three lung function parameters. This indicates that the intercepts and rate of change for the lung function parameters (FVC, FEV_1, FEV_1/FVC and $FEF_{25-75\%}$) differ according to sex. We decided to use random intercept and slope models and fit sex-specific models.

The independent variables included in the model were: study phase 8-hour mean O_3 concentration averaged over 6 months, 24-hour mean PM_{10} concentration averaged over 6 months, 24-hour mean NO_2 concentration averaged over 6 months, interaction terms between 8-hour mean O_3 concentration averaged over 6 months and phase, 24-hour mean PM_{10} concentration averaged over 6 months and phase and 24-hour mean NO_2 concentration averaged over 6 months and phase. Temperature, pets in house, gas combustion appliances, age, height, natural-log transformed height, height by age, body mass index, ETS exposure, type of school (private or public), father's schooling, mother's schooling, and weekday time spent in outdoor activities were included as fixed effects; and intercept and study phase as random effects. Some explanatory variables were kept in the final models because of their biological plausibility and importance, and because they improved the goodness-of-fit statistics (AIC) from the model.

Residual assumptions from final models were examined. We compared residual distributions from random intercept and slope models, using normal probability plots. Residuals from between-person variation, intercept and slope residuals and within-person variation had approximately normal distributions with approximately equal variability at every categorical predictor value. Within-person residuals had approximately equal range and variability at all phases, indicating that the homoscedasticity assumption was met.

We estimated the rate of change in lung function parameters (FVC, FEV_1, $FEF_{25-75\%}$ and FEV1/FV (%)) for an interquartile (IQ) increase in O_3 and NO_2 and PM_{10} . We also calculated the change in FVC and FEV1 percent of predicted per 10ppb increase in O_3 and NO_2 and 10 $\mu g/m^3$ in PM_{10} using our models. Longitudinal analysis was performed on untransformed data using the PROC MIXED procedure of SAS 8.2 (SAS Institute Inc, Cary NC).

References

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E3. Perez-Padilla R, Regalado-Pineda J, Rojas M, Catalan M, Mendoza L, Rojas R, Chapela R, Villalba J, Torres V, Borja-Aburto V, Olaiz G. Spirometric function in children of Mexico City compared to Mexican-American children. Pediatr Pulmonol 2003;35(3):177-183.

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Table E1. Study population by fixed-site monitoring station and sex. Mexico City, 1996-1999

Region		Monitor	Schools	Participants*		
				Girls (%)	Boys (%)	TOTAL
NW	TLA	Tlalnepantla	9	194 (45.4)	233 (54.6)	427
NE	SAG	San Agustín	4	123 (42.9)	164(57.1)	287
NE	XAL	Xalostoc	6	189 (47.6)	208 (52.4)	397
CE	LAG	Lagunilla	3	185 (54.1)	157 (45.9)	342
CE	MER	Merced	3	103 (62.8)	61 (37.2)	164
CE	HAN	Hangares	3	223 (47.5)	246 (52.5)	469
SW	PED	Pedregal	3	72 (39.1)	112 (60.9)	184
SW	PLA	Plateros	3	141 (50.7)	137 (49.3)	278
SE	CES	Cerro de la Estrella	2	218 (51.4)	206 (48.6)	424
SE	TAX	Taxqueña	3	99 (50.0)	99 (50.0)	198
TOTAL			39	1547 (48.8)	1623 (51.2)	3170

* Children with three or more spirometries.

NW=North-west; NE=North-east; CE=Central; SW=South-west; SE=South-east.

Table E2. Mean air pollutant concentrations averaged over 6 months during the study. Mexico City, 1996-1999

	Study phase						
	1 Spring 1996	2 Fall 1996	3 Spring 1997	4 Fall 1997	5 Spring 1998	6 Fall 1998	7 Spring 1999
Air pollutant							
Ozone* (ppb)	78.9	64.4	70.1	64.2	74.8	65.0	73.4
NO_2 (ppb)	42.1	31.5	40.1	32.5	36.5	26.0	29.7
PM_{10} ($\mu g/m^3$)	86.6	63.2	92.7	72.9	94.0	56.5	65.9

*8-hour mean.

Table E3. Pearson correlation coefficients of air pollutants averaged over 6 months and p-value. Mexico City, 1996-1999.

	8-hour mean ozone concentration	24-hour mean PM_{10} concentration	24-hour mean NO_2 concentration
8-hour mean ozone concentration	1.000	-0.231*	0.166*
24-hour mean PM_{10} concentration		1.000	0.250*
24-hour mean NO_2 concentration			1.000

*<0.001

Table E4. One-, two- and multi-pollutant model* for the annual effect on FVC and FEV_1 growth in schoolchildren by sex, expressed as a percentage of predicted values. Mexico City, 1996-1999.

Models*	FVC (%) Coefficient (95% CI)	FEV_1 (%) Coefficient (95% CI)
Girls		
One-pollutant model		
O_3 †	-1.07 (-1.28, -0.86) ***	-0.68 (-0.89, -0.48) ***
PM_{10}‡	-0.36 (-0.45, -0.27) ***	-0.24 (-0.33, -0.14) ***
NO_2 †	-1.26 (-1.51, -1.01) ***	-0.70 (-0.96, -0.44) ***
Two-pollutant models		
O_3†	-0.81 (-1.02, -0.60) ***	-0.55 (-0.76, -0.34) ***
PM_{10}‡	-0.28 (-0.37, -0.19) ***	-0.19 (-0.28, -0.10) ***
O_3†	-0.74 (-0.96, -0.52) ***	-0.51 (-0.73, -0.28) ***
NO_2 †	-1.20 (-1.46, -0.94) ***	-0.81 (-1.07, -0.54) ***
Multi-pollutant model		
O_3†	-0.62 (-0.85, -0.39) ***	-0.40 (-0.63, -0.16) **
PM_{10}‡	-0.14 (-0.24, -0.04) *	-0.10 (-0.21, 0.003)
NO_2†	-1.05 (-1.32, -0.77) ***	-0.71 (-1.00, -0.42) ***
Boys		
One-pollutant model		
O_3†	-0.76	-0.46

	(-0.94, -0.58) ***	(-0.65, -0.27) ***
PM_{10}‡	-0.27	-0.22
	(-0.35, -0.18) ***	(-0.31, -0.14) ***
NO_2†	-1.18	-0.56
	(-1.42, -0.94) ***	(-0.81, -0.32) ***
Two-pollutant models		
O_3†	-0.62	-0.34
	(-0.81, -0.44) ***	(-0.54, -0.15) **
PM_{10}‡	-0.21	-0.17
	(-0.29, -0.13) ***	(-0.26, -0.09) ***
O_3†	-0.50	-0.28
	(-0.70, -0.29) ***	(-0.49, -0.07) *
NO_2 †	-1.16	-0.75
	(-1.41, -0.91) ***	(-1.01, -0.50) ***
Multi-pollutant model		
O_3†	-0.36	-0.18
	(-0.58, -0.14) **	(-0.40, 0.04)
PM_{10}‡	-0.10	-0.12
	(-0.20, -0.01) *	(-0.22, -0.02) *
NO_2†	-1.09	-0.64
	(-1.36, -0.82) ***	(-0.92, -0.37) ***

* We used mixed models adjusted for age, BMI, height, height by age, outdoor activity time, ETS exposure, previous-day mean air pollutant concentration, and time since first test (study phase).

† Annual change in lung function growth as percentage of predicted values per 10 ppb increase in 6-month mean pollutant concentration.

‡ Annual change in lung function growth as percentage of predicted values per 10 $\mu g/m^3$ increase in 6-month mean pollutant concentration.

* $p < 0.05$

** $p < 0.005$

*** $p < 0.0001$