ORIGINAL ARTICLE

Personal Exposure to Particulate Matter Is Associated With Worse Health Perception in Adult Asthma

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Abstract

Background: Epidemiological studies have shown positive associations between particulate matter (PM) air pollution and short-term mortality and morbidity for asthma. The hypothesis that lung inflammation is responsible for these effects has been tested in panel and controlled exposure studies in asthmatic adults, with inconsistent results.
Objectives: We investigated whether personal exposure to PM_{10} and $PM_{2.5}$ were related to changes in the clinical course of asthma and to lung inflammatory responses in adult asthmatics.
Methods: A cohort of 32 asthmatic patients was followed for 2 years. Asthma control test (ACT) and St George's Respiratory Questionnaire (SGRQ) scores, forced expired volume in the first second (FEV_1), exhaled nitric oxide (Fe_{NO}), and pH of exhaled breath condensate (EBC) were determined on 6 occasions during different seasons. Personal exposure to PM was measured for 24 hours prior to clinical assessments.
Results: A 10 $\mu g/m^3$ increase in PM_{10} personal exposure was associated with an increase in SGRQ scores (regression coefficient ß=0.22; 95% confidence interval [CI], –0.005 to 4.451; *P*=.055) and with a decrease in ACT scores (ß=-0.022; 95% CI, –0.045 to 0.001; *P*=.060), whereas no associations were found between PM_{10} and FEV_1, Fe_{NO}, or EBC pH. A positive association was detected between Fe_{NO} and outdoor O_3 (*P*=.042) and SO_2 (*P*=.042) concentrations in the subgroup of nonsmoking asthmatics.
Conclusions: We concluded that increments in personal exposure to PM_{10} are associated with a decrease in asthma control and health-related quality of life. However, this study does not provide evidence that 24-hour exposures to PM are associated with short-term changes in lung function or inflammatory responses of the lung.

Key words: Pollution. Inflammation. Lung. Questionnaire. Exhaled nitric oxide. Breath condensate.

Resumen

Antecedentes: En estudios epidemiológicos se han observado relaciones positivas entre la contaminación atmosférica por material particulado (MP) y la mortalidad y la morbilidad a corto plazo en el asma. La hipótesis de que la inflamación pulmonar provoca estos efectos se ha analizado en estudios de grupo y con exposición controlada en adultos asmáticos y no se han obtenido resultados uniformes.
Objetivos: Se investigó si la exposición personal a MP_{10} y $MP_{2,5}$ estaba relacionada con cambios en la evolución clínica del asma y con las respuestas pulmonares inflamatorias en adultos asmáticos.
Métodos: Se realizó el seguimiento de una cohorte de 32 pacientes asmáticos durante 2 años. Se determinaron las puntuaciones de la Prueba de Control del Asma (ACT) y del cuestionario respiratorio de St. George (SGRQ), el volumen espiratorio máximo en el primer segundo (VEM1), el óxido nítrico exhalado (NOe) y el pH del condensado de aire exhalado (CAE) en 6 ocasiones durante diferentes estaciones. La exposición personal a MP se determinó durante las 24 horas previas a las evaluaciones clínicas.
Resultados: Un aumento de 10 $\mu g/m^3$ en la exposición personal a MP_{10} se asoció a un aumento en las puntuaciones del SGRQ (coeficiente de regresión: ß=0,22; intervalo de confianza [IC] del 95%: –0,005 a 4,451; *p*=0,055) y con una disminución de las puntuaciones de la ACT (ß = –0,022; IC del 95%: –0,045 a 0,001; *p*=0,060), si bien no se halló ninguna relación entre el MP_{10} y el VEM_1, el NOe o el pH del CAE. Se detectó una relación positiva entre el NOe y las concentraciones de O_3 (*p*=0,042) y SO_2 (*p*=0,042) en exteriores en un subgrupo de no fumadores.
Conclusiones: Se concluyó que los aumentos en la exposición personal a MP_{10} están relacionados con una disminución del control del asma y de la calidad de vida relacionada con la salud. No obstante, este estudio no demuestra que las exposiciones de 24 horas a MP estén relacionadas con cambios a corto plazo en la función pulmonar o en las respuestas pulmonares inflamatorias.

Palabras clave: Contaminación. Inflamación. Pulmón. Cuestionario. Oxido nítrico exhalado. Condensado de aire.

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Introduction

Several epidemiological studies have shown positive associations between exposure to particulate matter (PM) and short-term mortality and morbidity for pulmonary diseases, including asthma [1]. Since asthma exacerbations are associated with increased lung inflammation, an inflammatory mechanism of PM toxicity has been proposed [1]. However, regardless of the cause, the mechanisms of asthma exacerbation are unknown [2], and panel and controlled exposure studies have not been able to consistently demonstrate a relationship between PM exposure, lung inflammation, and changes in lung function in either healthy or asthmatic volunteers [3]. Unlike studies in asthmatic children, most panel studies in asthmatic adults have relied on fixed-site measurements of PM, which may not reflect individual exposures. Thus, the accuracy of an exposure-response relationship may be reduced by a misclassification of exposure. Only one study has examined the association between personal exposure to PM and health effects in adult asthmatics, but it was limited to 7 patients [4]. The aim of the present study was to investigate whether 24-hour personal exposure to PM_{10} and $PM_{2.5}$ were related to changes in the clinical course of adult asthma and to an inflammatory response of the lung. The study focused on patients with moderate to severe asthma as these are considered to have a greater risk of exacerbation. The cohort was selected from the electronic archives of the Italian public insurance system and based on the drug prescriptions register of the general population resident in Padua, Italy. The clinical course of asthma was investigated using standardized questionnaires and spirometry. To assess lung inflammation we chose exhaled nitric oxide (Fe_{NO}) and exhaled breath condensate (EBC) pH as noninvasive biomarkers that correlate with the clinical course of asthma. Fe_{NO} correlates with eosinophilic inflammation of the airways, is elevated in patients with untreated asthma, and decreases during corticosteroid treatment [5]. EBC pH is currently considered a robust variable to determine the degree of airway acidification in various inflammatory lung diseases [6].

Methods

Patients and Study Design

The Italian public health insurance system has an electronic database containing drug prescription data dating back to 1997 for all residents in Padua. This database holds both patient identification data and information concerning drug prescriptions, which are coded according to the Anatomical Therapeutic Chemical (ATC) classification system. In order to identify the cohort of asthmatic patients, we examined prescriptions for inhaled $ß_2$-agonists, either alone or in combination with corticosteroids (ACT R03A), during the period 1999 to 2003. We identified 118 025 asthma drug prescriptions and 23 207 patients with at least 1 prescription per year. For the cohort, patients aged 15 to 44 years with at least 1 prescription a year for 3 consecutive years and from the quartile with the highest number of drug prescriptions (average >6 per year for the 3 years) were selected (n=158). After linkage to the population archive to confirm that the individuals were alive and still residing in Padua, the cohort was reduced to 138 patients. Fe_{NO} was considered the primary variable to calculate sample size. We assumed that an increase of 15 parts per billion (ppb) in Fe_{NO} concentration from baseline would be clinically significant. Such an increase represents approximately one third of the increase in Fe_{NO} seen during exacerbation in asthmatic patients [5]. Taking into account variability in measurements in the literature and our laboratory, a sample size of approximately 30 patients was calculated to be sufficient to reject the null hypothesis with a power of 90% and an alpha level of 5%. This calculation assumed a simplified model that compares 2 measures from each individual in 2 different situations of air-pollutant concentrations (winter/summer). Assuming a loss of 20% to follow-up, it was decided to recruit at least 40 patients. The candidates were randomly sampled using an implicit stratification method. Nineteen were not eligible because they worked in other towns (n=11), did not have asthma (n=4), or were unable to follow the study procedures (n=4). The first 42 patients who agreed to participate and were eligible for the study were selected. The diagnosis of asthma was confirmed in each case by history and lung function tests according to the Global Initiative for Asthma guidelines [2] prior to the start of the study. Atopy was assessed by skin-prick testing to a panel of aeroallergens (house dust mite, molds, cat and dog dander, and tree and grass pollens) [7].

The cohort of 42 patients was followed for 2 consecutive years. During this period, each participant underwent 6 examinations at different times of the year: summer (visits 1 and 4), autumn (visits 2 and 5), and winter (visits 3 and 6). These periods were chosen because of the high interseasonal variability of air pollutant concentrations shown by historical time-series analyses of air pollution in Padova. On each occasion individual exposure to both PM_{10} and $PM_{2.5}$ was measured during the 24 hours preceding the clinical evaluation. Data on outdoor pollution and meteorological variables from fixed sites were also recorded during the same period. Clinical evaluation included examination of the record of clinical course of asthma, the administration of a questionnaire on health-related quality of life (HRQoL), and, in sequence, measurement of Fe_{NO}, collection of EBC, and lung function tests. Drug treatment was not modified by the investigators. On inclusion, the subjects received a detailed explanation of the study and written consent was obtained. The study design was approved by the local ethics committee.

Exposure Assessment

Personal exposures to PM_{10} and $PM_{2.5}$ were assessed using single-stage impactors (Personal Environmental Monitor-PEM; SKC Inc., Eighty Four, Pennsylvania, USA), connected with flow-controlled battery-operated pumps (Air-Check Sampler; SKC Inc.) at a flow rate of 2 L/min. The impactors for PM_{10} and $PM_{2.5}$ were held for 24 hours in the breathing zone, attached to the shoulder straps of a backpack containing the pumps. When the patients were sleeping or showering, the instruments were left operating in the same room. Particles were collected on 37-mm Teflon filters (SKC Inc.). The

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filters were conditioned in a dry box (Aquaria, Milan, Italy) at 20±1°C and 50±5% relative humidity for 48 hours and then weighed before and after sampling using a microbalance (Sartorius MC-5; Sartorius AG, Goettingen, Germany) with an accuracy of 1 μg.

Outdoor concentrations of PM_{10}, NO_2, SO_2, O_3, and CO were measured continuously at 2 fixed sites within the city of Padua by the local environmental protection agency (Agenzia Regionale per la Prevenzione e Protezione Ambientale del Veneto, ARPAV). PM_{10} was collected on glass fiber filters using sampling heads (as defined in CEN EN 12341) connected to pumps (Explorer plus, Zambelli, Milan, Italy) at a flow rate of 38.3 L/min. Previous experiments have demonstrated that PM_{10} concentrations measured with personal and stationary samplers are comparable [8]. NO_2, SO_2, O_3, and CO were measured according to national regulations with Thermo Environmental Instruments (K50312, K50313, K50314, K50315; Philips, Eindhoven The Netherlands). Temperature, humidity, and pressure values were also provided by the ARPAV Meteorological Center.

Health measurements

Questionnaires

Level of asthma control was evaluated with the Asthma Control Test (ACT). The ACT sum score ranges from 5 to 25, with higher values indicating better asthma control [9]. HRQoL was assessed using the St George's Respiratory Questionnaire (SGRQ) [10]. The total possible score ranges from 0 to 100, with lower scores indicating a better quality of life.

Spirometry

Forced vital capacity (FVC) and forced expiratory volume in the first second (FEV_1) were measured by a dry spirometer (PFT Horizon, mod. 922; Sensor Medics, Milan, Italy), as previously described [7]. The best values for FVC and FEV_1 from 3 tests for each patient were recorded. The predicted normal values established by the European Coal and Steel Community were used [11].

Exhaled Nitric Oxide Measurement

Fe_{NO} was measured online using a chemiluminescence analyzer with a real-time display (NIOX, Nitric Oxide Monitoring System, version 2.0; Aerocrine AB, Solna, Sweden). The calibration and measurement procedures were performed according to the recommendations of the American Thoracic Society/European Respiratory Society [5]. Individuals performed at least 3 exhalations of 12 seconds with a constant flow of 50 mL/s. The fractional Fe_{NO} concentration was expressed in ppb. Ambient NO at the time of each test was recorded.

Measurement of pH in Exhaled Breath Condensate

EBC was collected during tidal breathing for 15 minutes in a condenser kept at a temperature of –55°C, as previously described [12]. The patients were instructed to breathe normally through their mouth and to temporarily discontinue collection if they needed to cough or swallow saliva. No food was taken 1 hour before collection. Samples were stored in 200-mL aliquots and Argon gas was bubbled in the sample for 3 minutes to remove the air. Then, pH was measured using a calibrated pH meter (model pH300; Hanna instruments, Padova, Italy) with a flat membrane electrode (5207; Crison Instruments S.A., Alella, Spain) with an accuracy of ±0.01 pH.

Amylase was measured in all samples using an enzymatic colorimetric test (IFCC, Roche Diagnostic Modular, Milan, Italy; lower detection limit of 3 U/L) to assess salivary contamination. Samples containing amylase were discarded.

Statistical Analysis

Ten individuals who attended fewer than 3 visits were excluded from the analysis. The χ^2 test was used to compare the characteristics of the 10 patients excluded with those of the remaining 32.

The daily average of the values measured at the 2 sites were used for the analysis. Missing outdoor measurements were imputed with a previously described method [13]. Personal PM exposures, outdoor air pollutants, and outcome variables between visits were compared by analysis of variance. To compare personal and outdoor PM_{10} exposures, a paired *t* test was performed for each visit.

The association between air pollutants and health outcomes was examined using marginal logistic regressions for binary outcomes and marginal linear models for continuous variables, based on the generalized estimating equations (GEE) proposed by Liang and Zeger [14]. This method generates robust estimators regardless of the specification of the covariance matrix, and as autocorrelation is included in the covariance, coefficients can be interpreted as usual. The correlation structure selected was exchangeable. All the models were adjusted for an average of 24-hour temperature, relative humidity, and atmospheric pressure along with use of asthma drugs and smoking habit (yes/no).

Results from the analyses of outcome parameters are reported as changes per 10 $\mu g/m^3$ increase in pollutant concentrations (except for CO, where the unit increase is 1 mg/m^3). The analyses were performed using the statistical package Stata with the XTGEE procedure (Stata software version 8; Stata Corp., College Station, Texas, USA). Values of $P<.05$ were considered significant.

Results

The analyses included 166 observations from 32 patients, whose characteristics are shown in Table 1 and compared with those of the 10 patients excluded from the analysis. No differences were observed between the 2 groups with regard to sex, age, smoking status, corticosteroid therapy, or asthma severity.

The distribution of the outcome variables during the study is presented in Table 2. No significant differences were observed for any of the parameters at any time. A decrease in mean Fe_{NO} levels was observed in the examinations successive to the first visit. This decrease was probably attributable to the increase in the number of patients taking inhaled corticosteroids at visits 2 to 6. In fact, as expected [5], the mean±SEM Fe_{NO}

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Table 1. Characteristics of Patients at Study Enrolment

Variable	Analyzed	Not Analyzed
Sex, No. (%)		
Male	16 (50.0)	5 (50.0)
Female	16 (50.0)	5 (50.0)
Age, mean (SD), y	39.6 (7.5)	38.3 (8.0)
Smoking status, No. (%)		
Nonsmoker	13 (40.6)	3 (30.0)
Ex-smoker	9 (28.1)	2 (20.0)
Current smoker	10 (31.3)	5 (50.0)
Asthma severity[a], No. (%)		
Intermittent	3 (9.4)	0 (0.0)
Mild persistent	3 (9.4)	2 (20.0)
Moderate persistent	8 (25.0)	6 (60.0)
Severe persistent	18 (56.2)	2 (20.0)
Atopy, No. (%)	29 (90.6)	9 (90.0)
Current corticosteroid use, No. (%)		
None	10 (31.2)	3 (30.0)
Low dose[a]	7 (21.9)	4 (40.0)
Medium dose[a]	9 (28.1)	1 (10.0)
High dose[a]	6 (18.8)	2 (20.0)

[a]Workshop report: Global Initiative for Asthma, 2006.

level was lower in patients on corticosteroids (37.5±2.8 ppb; sample n=127) than in those not on this treatment (50.2±8.5 ppb; sample n=38).

Significant differences were detected between seasonal outdoor air pollutant levels and meteorological parameters (Table 3). In contrast, lower variability was observed for personal exposure to PM_{10} and $PM_{2.5}$, which remained consistently above the current standards (Figure). Personal exposure to PM_{10} was significantly higher than the corresponding PM_{10} concentrations measured at the fixed sites in autumn and summer (paired *t* test, $P<.001$), but not in winter (paired *t* test, $P>.17$).

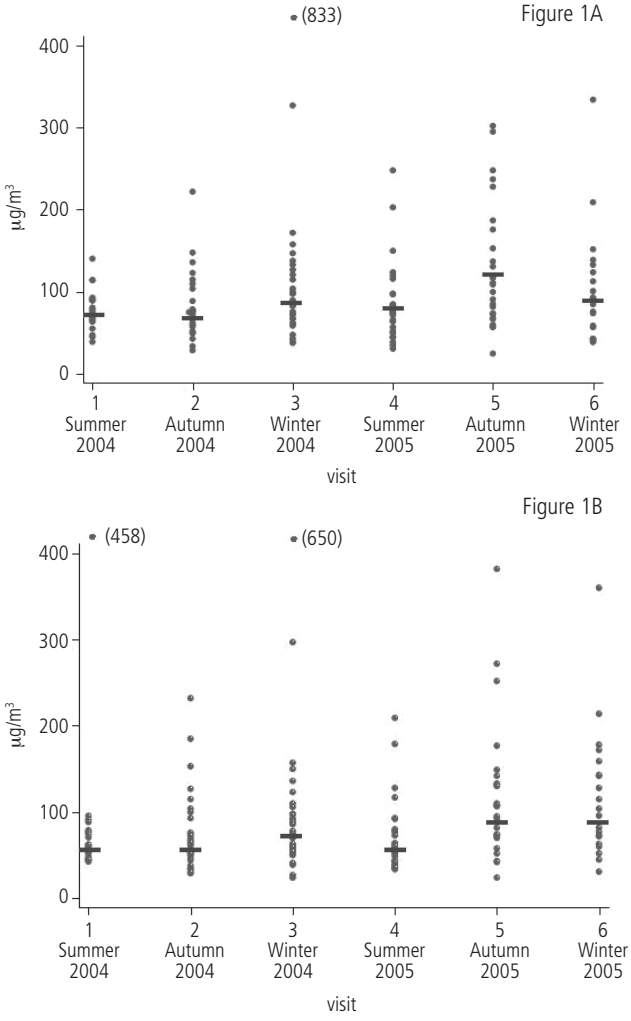

Figure. Distribution of personal exposures to particulate matter (PM) measured for 24 hours prior to health measurements. A, PM_{10}, analysis of variance between visits, $P=.08$. B, $PM_{2.5}$, analysis of variance between visits, $P=.07$. Bars represent medians.

Table 2. Asthma Control Test (ACT) Sum Score, Saint George's Respiratory Questionnaire (SGRQ) Total Score, Forced Expiratory Volume in the First Second (FEV_1), pH Values of Exhaled Breath Condensate (EBC pH), Concentrations of Exhaled Nitric Oxide (Fe_{NO}) at Each Visit[a]

Visit Variable	1 Summer 2004	2 Autumn 2004	3 Winter 2005	4 Summer 2005	5 Autumn 2005	6 Winter 2006
ACT sum score	17.8±0 .8	18.7±0.8	18.7±0.9	18.5±0 .9	18.3±1.0	17.8±1.0
SGRQ score	28.1±2.8	25.1±3.1	28.4±3.2	23.1±3.0	21.2±3.3	25.4±3.8
FEV_1, % predicted[b]	72.7±4.1	74.4±3.5	79.9±4.0	82.5±4.4	84.3±4.8	82.9±4.7
EBC pH	7.7±0.1	7.7±0.1	7.8±0.0	7.6±0.1	7.8±0.1	7.8±0.0
Fe_{NO}, ppb	62.1±8.5	37.8±5.4	34.7±6.4	37.1±5.7	34.8±7.9	39.9±8.8

Abbreviation: ppb, parts per billion.
[a]Data are expressed as mean±SEM.
[b]Prebronchodilator in patients not receiving long-acting bronchodilators and postbronchodilator in patients receiving long-acting bronchodilators.

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Table 3. Concentrations of Outdoor Air Pollutants and Selected Meteorological Parameters Measured for 24 Hours Prior to Health Measurements at Fixed Sites[a]

Visit Variable	1 Summer 2004 n=24	2 Autumn 2004 n=32	3 Winter 2004 n=32	4 Summer 2005 n=28	5 Autumn 2005 n=26	6 Winter 2006 n=24
PM_{10}, $\mu g/m^{3b}$	43.8 (12.9) 43.2 (35.3-51.8)	47.2 (14.0) 44.2 (36.5-56.5)	84.6 (29.3) 83.3 (66.5-97.5)	37.1(10.9) 39 (29.5-48)	66.5 (15.0) 64 (54.5-80.5)	82.9 (39.2) 87 (46.5-105)
NO_2, $\mu g/m^{3b}$	51.8 (5.9) 53.9 (47.8-56.2)	56.9 (7.3) 57.0 (49.7-60.1)	64.6 (11.6) 64.8 (58.1-72.6)	39.2 (5.6) 40.4 (35.0-43.3)	51.6 (8.9) 50.9 (46.5-59.4)	69.6 (12.8) 70.0 (60.6-79.9)
SO_2, $\mu g/m^{3b}$	3.3 (1.5) 3.2 (2.3-4.4)	2.5 (1.0) 2.3 (1.4-3.4)	7.9 (3.0) 7.1 (5.4-10.8)	2.7 (1.2) 2.7 (1.5-3.4)	2.7 (1.6) 2.6 (1.1-4.6)	5.3 (2.2) 4.6 (4.3-5.7)
O_3, $\mu g/m^{3b}$	124 (17.1) 125 (116-134)	42.3 (29.4) 28 (23-48)	69.4 (15.2) 74 (58-77)	135 (26.5) 138.5 (121-162)	64.7 (19.8) 71 (44-82)	63.4 (17.7) 68 (54.5-76.5)
CO, mg/m^{3c}	0.8 (0.1) 0.8 (0.8-0.9)	1.8 (0.7) 1.4 (1.3-2.4)	3.0 (1.0) 2.7 (2.2-3.8)	1.0 (0.1) 1.0 (0.9-1.1)	1.6 (0.3) 1.-5 (1.5-1.8)	1.7 (0.4) 1.8 (1.3-1.9)
Temperature, ºC[c]	23.1 (1.6) 22.9 (22.0-24.4)	14.3 (3.0) 13.1 (11.9-16.1)	2.1 (1.7) 1.6 (0.6-3.5)	24.8 (2.6) 25.4 (22.7-26.9)	12.9 (2.1) 13.1 (11.4-14.6)	2.5 (3.1) 1.6 (-0.3-56.4)
Relative humidity, %[b]	72.1 (7.5) 74.3 (66.4-77.9)	87.5 (11.7) 91.9 (81.4-96.2)	59.1 (12.1) 57.4 (49.0-68.7)	60.3 (8.4) 59.5 (53.6-69.0)	77.9 (8.0) 76.1 (70.2-86.4)	77.6 (12.6) 75.9 (72.1-89.2)
Barometric pressure, hPa[b]	1015 (1.6) 1016 (1014-1016)	1016 (2.6) 1016 (1014-1018)	1016 (8.6) 1017 (1010-1023)	1009 (2.7) 1010 (1006-1012)	1016 (1.0) 1016 (1015-1016)	1015 (6.0) 1015 (1008-1020)

Abbreviation: PM, particulate matter.
[a] Data are expressed as means (SD) (upper line) and medians (interquartile range)(lower line).
[b] 24h concentrations; analysis of variance between visits, $P<.001$.
[c] Maximum daily peak; analysis of variance between visits, $P<.001$.

Table 4. Relation Between Respiratory Outcome Variables and Personal Particulate Matter (PM) Exposure in all Patients (n=32) and in Nonsmokers (n=22) at the 6 Visits

		All Patients (166 observations)		Nonsmokers (115 observations)	
		ß[a]±SEM	*P* Value	ß[a]±SEM	*P* Value
ACT					
	Personal PM_{10}	–0.022±0.012	.060	–0.026±0.013	.053
	Personal $PM_{2.5}$	–0.015±0.016	.331	–0.011±0.018	.542
SGRQ					
	Personal PM_{10}	0.223±1.116	.055	0.279±0.140	.047
	Personal $PM_{2.5}$	0.194±0.142	.174	0.207±0.183	.259
FEV_1					
	Personal PM_{10}	0.175±0.137	.199	0.092±0.158	.561
	Personal $PM_{2.5}$	0.043±0.168	.798	–0.101±0.198	.611
EBC pH					
	Personal PM_{10}	0.005±0.003	.136	0.004±0.002	.088
	Personal $PM_{2.5}$	0.005±0.004	.181	0.005±0.003	.098
Fe_{NO}					
	Personal PM_{10}	–0.496±0.334	.138	–0.700±0.435	.107
	Personal $PM_{2.5}$	–0.271±0.374	.469	–0.666±0.450	.179

Abbreviations: ACT, asthma control test; EBC, exhaled breath condensate; FeNO, exhaled nitric oxide; FEV_1, forced expiratory volume in the first second; SGRQ, St George's Respiratory Questionnaire.
[a] Regression coefficient from generalized estimating equation models for panel data controlling for repeated individual observations, temperature, relative humidity, atmospheric pressure, corticosteroid dose, and smoking habit (when appropriate). Changes per 10 $\mu g/m^3$ increase in PM concentrations.

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Table 5. Relation Between Respiratory Outcome Variables and Outdoor Pollutant Concentrations in all Patients (n=32) and in Nonsmokers (n=22) at the 6 Visits

		All Patients (166 observations)		Nonsmokers (115 observations)	
		ß[a]±SEM	*P* Value	ß[a]±SEM	*P* Value
ACT					
	Fixed site PM_{10}	–0.048±0.030	.118	–0.074±0.038	.051
	O_3	–0.024±0.028	.391	–0.020±0.034	.556
	SO_2	0.291#+0.363	.423	0.037±0.440	.933
	NO_2	–0.127±0.074	.087	–0.081±0.087	.349
	CO	–0.227±0.096	.018	–0.316±0.114	.006
SGRQ					
	Fixed site PM_{10}	0.124±0.286	.665	0.458±0.372	.218
	O_3	0.373±0.260	.151	0.520±0.323.	107
	SO_2	5.174±3.382	.126	6.971±4.213	.098
	NO_2	1.321±0.690	.056	1.928±0.821	.019
	CO	1.749±0.900	.052	2.779±1.130	.014
FEV_1					
	Fixed site PM_{10}	0.588±0.385	.127	0.4290.488	.379
	O_3	0.107±0.371	.773	–0.189±0.453	.676
	SO_2	–0.815±4.783	.865	–4.194±5.648	.458
	NO_2	0.284±1.037	.785	0.347±1.172	.767
	CO	–1.908±1.235	.123	–1.155±1.538	.453
EBC pH					
	Fixed site PM_{10}	0.009±0.011	.423	0.008±0.008	.343
	O_3	–0.001±0.010	.888	–0.004±0.008	.589
	SO_2	0.175±0.129	.175	0.068±0.100	495
	NO_2	0.003±0.027	.921	–0.025±0.020	.206
	CO	0.004±0.035	.896	0.028±0.026	.288
Fe_{NO}					
	Fixed site PM_{10}	–0.480±0.962	.618	–0.191±1.400	.892
	O_3	1.559±0.872	.074	2.407±1.184	.042
	SO_2	21.045±11.192	.060	31.172±15.309	.042
	NO_2	0.822±2.357	.727	0.780±3.140	.804
	CO	–5.045±3.002	.093	–7.002±4.180	.094

Abbreviations: ACT, asthma control test; EBC, exhaled breath condensate; Fe_{NO}, exhaled nitric oxide; FEV_1, forced expiratory volume in the first second; SGRQ, St George's Respiratory Questionnaire.
[a]Regression coefficient from generalized estimating equation models for panel data controlling for repeated individual observations, temperature, relative humidity, atmospheric pressure, corticosteroid dose, and smoking habit (when appropriate). Changes per 10 $\mu g/m^3$ increase in pollutant concentrations (except for CO where the unit increase is 1 mg/m^3).

Table 6. Relation Between Questionnaire Scores (ACT and SGRQ) and Outdoor Fixed Site PM_{10} (Lag 0-28) Concentrations in the Observations of all Patients and Nonsmokers at the 6 Visits

	Fixed site PM_{10} Lag 0-28	ß[a]	SEM	*P* Value
ACT				
All patients (n=32)		-0.133	0.084	0.113
Nonsmokers (n=22)		-0.128	0.102	0.206
SGRQ				
All patients (n=32)		2.093	0.764	0.006
Nonsmokers (n=22)		3.350	0.926	0.000

Abbreviations: ACT, asthma control test; PM, particulate matter; SGRQ, St George's Respiratory Questionnaire.
[a]Regression coefficient from generalized estimating equation models for panel data controlling for repeated individual observations, temperature, relative humidity, atmospheric pressure, corticosteroid use, and smoking habit. Changes per 10 $\mu g/m^3$ increase in PM concentrations.

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Personal exposures to PM_{10} and $PM_{2.5}$ and other pollutants were not found to have any effect on FEV_1, Fe_{NO}, or EBC pH, except for a weak positive association detected between Fe_{NO} and O_3 (*P*=.074) and SO_2 (*P*=.060) (Table 4). We found a weak negative association for the ACT score (p=.060) and a weak positive association for the SGRQ score (p=0.055) with increasing personal exposure to PM_{10} but not to $PM_{2.5}$. An increase of 10 $\mu g/m^3$ in PM_{10} was associated with an average decrease of 0.022 in the ACT score (worsened asthma control) (corresponding to a variation of 0.6%) and an average increase of 0.223 (worsened HRQoL), (variation of 0.9%) in the SGRQ score. An increase in outdoor concentrations of CO also showed associations with worsened asthma control (*P*=.018) and HRQoL (*P*=.052). Some effects of outdoor NO_2 exposure were detected on SGRQ scores (*P*=.056) (Table 5). Although smoking was controlled for in the analysis of the whole panel, we applied the same regression model to the subgroup of nonsmokers and confirmed the associations between personal exposure to PM_{10} and both ACT and SGRQ scores (*P*=.053 and *P*=.047, respectively); these scores were also associated with outdoor CO and NO concentrations in this analysis. In addition, significant associations were detected between Fe_{NO} and both O_3 (*P*=.042) and SO_2 (*P*=.042) (Table 5).

Since ACT and SGRQ scores reflect asthma control and HRQoL perceptions during the preceding weeks, the average PM_{10} concentrations measured at the fixed sites in the 4 weeks (lag 0-28 days) before the administration of the questionnaires were associated with these scores in the regression model. Whereas no associations were detected for ACT scores, the regression coefficients between SGRQ scores and lag 0-28 PM_{10} were highly significant (Table 6).

Discussion

The results indicate that the effects of PM_{10} personal exposure in asthmatics were detected by the worsening of asthma control and HRQoL rather than by objective measures of respiratory impairment or biomarkers of airway inflammation. We used a new method to select a cohort from the general population rather than from a clinical series which might be affected by selection bias. Few studies have selected random patients from the general population [15]; the majority of studies have analyzed patients selected by general practitioners or chest physicians, or on the basis of visits to chest departments or outpatient clinics, meaning that they are not representative of the average asthmatic population [16-20]. The use of a prescription database yielded a population-based cohort with a high percentage (81%) of patients with moderate to severe asthma, which is higher than the estimated proportion in the general population in Italy (31%) [21].

We also chose to measure individual exposure to PM_{10} and $PM_{2.5}$ and our results showed that PM_{10} exposure levels varied between fixed sites and personal sampling and also between seasons. Whereas interseasonal variability of urban air PM is widely recognized, caution should be exercised when PM exposure is assessed at fixed sites because it might underscore individual exposures, which are dependent on indoor pollution as well. This could be particularly relevant in adults, who generally spend more time indoors than children. PM derived from cigarette smoke may partially explain why personal exposure to PM_{10} was higher than that measured outdoors. Indeed, the subgroup of smokers had higher mean (SEM) levels of PM_{10} and $PM_{2.5}$ exposure than the nonsmokers (128±10 vs 89±8 $\mu g/m^3$, *P*<.01; 120±10 vs 81±8 $\mu g/m^3$, *P*<.01 respectively). In a companion paper, we demonstrated that smoking was the main factor affecting personal exposure to PM_{10}, contributing to 41% of variability. Outdoor PM_{10} concentrations (25%), temperature (12%), and season (15%) also contributed to personal PM_{10} exposure. In contrast, other indoor sources of pollution contributed little, even though the individuals analyzed spent a mean (SD) of 20 (2) hours indoors a day [22].

The association between ACT and SGRQ scores and personal exposure to PM_{10} may be surprising because the questionnaires reflect perceptions in the preceding 4 weeks, whereas exposure data refer to the previous 24 hours. Furthermore, similar associations were not found with $PM_{2.5}$. The relationship between poorer health perception and increasing PM_{10} exposure may be due to either recent or repeated exposures to PM, or both. However, the stronger association between SGRQ scores and 4-week average ambient PM_{10} than between these scores and shorter lags, and the observations that PM metrics are more robustly associated with health measurements when multi-day moving averages are used, are consistent with a cumulative respiratory effect of the particulate [23-25]. The effects of outdoor CO and NO_2 on health perception might mirror those of other pollutants. A recent study of the associations between personal, indoor, and outdoor pollutant concentrations showed that outdoor quasi-ultrafine particles were correlated with outdoor concentrations of CO and nitric oxides; the association is reasonable since all of these species are emitted by the same combustion sources, and also because their atmospheric transport and removal are affected by similar meteorological processes [26].

Several panel studies on asthmatics have assessed the effects of short-term ambient PM exposure on lung function. Unlike our patients, the patients in those studies showed inverse associations between peak expiratory flow and PM concentrations [27,28]. However, few studies have evaluated lung function by supervised spirometry in asthmatic adults, as for instance in a panel study of individuals off medications, where no effects of PM_{10} and $PM_{2.5}$ measured at fixed sites were detected [20]. Similarly, Jansen et al [4] did not find associations between standard spirometry measures and outdoor or personal exposure to air particulate. However, short-term exposure to diesel traffic has been found to induce transient reductions in spirometric indices in adults with mild to moderate asthma [29]. In asthmatic children, Koenig et al [30] showed that FVC and FEV_1 decreased in association with increases in particulate air pollution, and Trenga et al [31] drew attention to the fact that this association was particularly evident in children not on anti-inflammatory medications. It therefore seems that children are more susceptible to air pollution than adults; this is also suggested by the higher number of emergency visits for asthma exacerbations in children than in adults [32].

Inflammation in the lungs due to PM is thought to be the cause of short-term asthma exacerbations [1], but the inconsistency of results may suggest an alternative

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pathophysiology [3]. Our results indicate that PM exposures do not correlate with alterations of inflammatory indices, though some weak associations were observed between Fe_{NO} and urban O_3 and SO_2 air concentrations. Whereas the latter associations may reflect mild irritation due to these pollutants, our results for PM are in agreement with those of a recent study [20]. In addition, Fe_{NO} has not been found to change significantly after short-term exposure to diesel traffic in asthmatic adults [29]. An association between air pollution and Fe_{NO} has been detected but only in senior adults with chronic obstructive pulmonary disease [33]. The characteristics of the population of adults in our study, most of whom (68.7%) were on corticosteroid treatment, might explain some of the differences between our results and those reported by other studies [15,28]. In fact, despite adjustment for medication, the effect of PM pollution might have been underestimated or compensated by inhaled corticosteroid use.

No relationship was found between EBC pH and either PM_{10} or $PM_{2.5}$, coinciding with previous findings [29].

There are some weaknesses in our study which should be taken into account when interpreting the results. The 24-hour lag design limited the possibility of detecting shorter-term effects of PM and those of repeated exposures. In addition, variability in personal PM exposure was lower than expected. This design may thus have prevented the detection of an exposure-response relationship. Limited statistical power should also be considered, particularly when evaluating the lack of association. However, the number of observations in our study is within the range used in similar investigations which have found significant associations [4,19,29]. It should be noted that studies of this type including a larger number of individuals can be extremely difficult because of the assessment of personal exposures. Smoking could be a confounder in this study since it influences personal exposure to PM. However, we deliberately did not exclude asthmatic smokers since the aim was to analyze a cohort representative of the population of asthmatics in our area. Exclusion of smokers would have implied omitting information on 30% of affected individuals. Since smokers have higher exposure to PM, their inclusion in the study would have widened the range of exposures and maximized the probability of identifying a dose-response relationship.

In conclusion, our data indicate that increments in personal exposure to PM_{10} have negative effects in adult asthmatic patients, shown by the decrease in asthma control and HRQoL. However, the study does not provide evidence that levels of 24-hour exposure to PM correlate with short-term changes in lung function or with an inflammatory response of the lung.

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