Eur Respir J 2003; 22: 802–808
DOI: 10.1183/09031936.03.00013003
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European Respiratory Journal
ISSN 0903-1936

Short-term effects of air pollution on daily asthma emergency room admissions

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ABSTRACT: Many time-series studies have shown positive associations between air pollutants and asthma morbidity. However, few studies have included pollen as a potential confounder when examining this relationship.

This study analysed the short-term association between air pollutants (sulphur dioxide (SO_2), particles measured with a median aerodynamic diameter of <10 μm (PM_{10}), nitrogen dioxide (NO_2) and ozone (O_3)) and asthma emergency room admissions in Madrid, Spain, in 1995–1998, adjusting for four types of pollen with allergenic potential (*Olea europaea*, *Plantago sp.*, Poaceae and Urticaceae). Data were analysed using autoregressive Poisson regression and generalised additive models (GAM).

The strongest associations were observed at 1 day lag for O_3, and 3 days lag for the remaining pollutants. Using Poisson regression, a single-pollutant model showed that a 10-μg·m^{-3} rise in pollutant level led to relative risks of: 1.039 for PM_{10}; 1.029 for SO_2; 1.033 for NO_2; and 1.045 for O_3. Adjustment for the different types of pollen led to no substantial variation in these associations. In the multipollutant models for cold-season pollutants (including PM_{10}, SO_2 and the four types of pollen) and photochemical pollutants (including NO_2, O_3 and the four types of pollen) the associations for PM_{10}, NO_2 and O_3 held, but no relationship with SO_2 was evident. GAM analysis yielded the same results, both in terms of lags and of quantification of the effect for all pollutants.

In conclusion, the usual air pollution levels in Madrid were associated with an increase in asthma emergency room admissions, and this association remained controlling for the presence of ambient pollen.

Eur Respir J 2003; 22: 802–808.

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Keywords: Air pollution, asthma, emergency room admissions, pollen, time-series

Received: February 5 2003
Accepted after revision: July 16 2003

This study was funded by the Advisory Committee to the Madrid Regional Asthma Prevention and Control Programme (Comisión Asesora del Programa Regional de Prevención y Control del Asma de la Comunidad de Madrid). A. Tobías had a postgraduate fellowship from the Universidad Autónoma de Madrid.

There is wide evidence showing that asthma-related morbidity has been increasing in recent years [1, 2]. Among the population of the Madrid region aged 2–44 yrs, 7.3% have had an attack of asthma at some time and 3% suffer from current asthma. Also, an increase has been seen both in prevalence and in healthcare attendance for asthma, in terms of primary care and hospital emergency settings. This increase in morbidity has led to the study of different environmental factors that might be associated with the risk of developing asthma [3].

The most extensively studied environmental factor has been air pollution, since it can increase the risk of developing asthma attacks through several different mechanisms including: 1) a direct irritant effect on sensitive airways; 2) a toxic effect on the respiratory epithelium; 3) generating bronchial hyperreactivity, both allergen-specific and nonspecific; or 4) modifying the immune response, by increasing susceptibility to an immunological trigger [4, 5]. Although experimental studies conducted on animals and humans suggest an effect for sulphur dioxide (SO_2), ozone (O_3) and nitrogen dioxide (NO_2), and more recently, for particulates [4, 5], other studies have yielded contradictory results [6–9]. Furthermore, a number of studies have investigated the acute effects using time-series methodology, but here again the results reported have proved somewhat inconsistent concerning the pollutants implicated [8, 10, 11]. Inconsistencies in the associations between single pollutants and asthma morbidity can be partly due to differences among studies in the levels of pollutants and in prevailing mixtures [6, 10]. Thus, it is of interest to examine the effect of each pollutant adjusted for the others, and the effect of pollutant mixtures. Also, pollen levels can be a potential confounding factor in the relationship between air pollution and asthma. However, few studies have included the measurement of pollen as a confounder to obtain a more valid estimate of the effect of air pollutants [10, 12]. Finally, other studies have addressed interactions between pollens and air pollutants on the one hand, and allergies on the other [10, 13].

The city of Madrid offers an excellent challenge to study the relationship between atmospheric pollutants and asthma-related hospital emergencies. Madrid constitutes the centre of a dense metropolitan area. The main source of pollutant emission is road traffic. In addition, Madrid′s geographical setting has climatological conditions directly linked to emission levels, with frequent anticyclonic situations in summer and winter, which impede the dispersion of pollutants. Moreover, owing to the prevailing botanical and climatic conditions, Madrid has especially high concentrations of different types of pollen [14]. The peak Poaceae pollenisation season from May–June accounts for 20% of all asthma attacks that take place throughout the year in Madrid [3].

The objective of this study was to analyse the short-term association between asthma emergency room admissions and air pollutants in Madrid during 1995–1998, controlling for the potential confounding effect of pollen levels, as well

as to compare results obtained by using different statistical methods.

Materials and methods

Asthma emergency room admissions

Asthma (International Classification of Diseases, code 493 for asthma) daily emergency room admissions to the Emergency Ward of the Gregorio Marañón University Hospital, a facility covering an urban catchment area of 555,153 inhabitants, were studied during 1995–1998.

Air pollution, pollen and weather data

The pollutants and analytical methods used were the following: 1) particulates measured as the daily average of particles with a median aerodynamic diameter of <10 μm (PM10) (attenuation of β radiation); 2) daily average of SO_2 (absorption of ultraviolet fluorescence); 3) daily average of NO_2 (chemiluminiscence); and 4) average of maximum 8 h O_3 values (ultraviolet absorption). Pollution data were obtained from the automated network of the Madrid City Comprehensive Air-Pollution Monitoring, Forecasting and Information System. The numbers of monitoring stations that furnished information for the respective pollutants were 13 for PM10, 15 for SO_2 and NO_2, and two for O_3.

Pollen data were drawn from the Madrid Regional Health Authority Palynology Network, a network comprising 10 monitoring stations. Information was collected on the daily average levels of pollens having highest allergenic potential in Madrid, namely, *Olea europaea*, *Plantago sp.*, Poaceae and Urticaceae (volumetric method with Burkard samplers).

Daily mean temperature and mean relative humidity, as registered at the Barajas meteorological observatory, situated 8 km North East of Madrid, were used. Information was also obtained on reported cases of influenza shown on the registry kept by the Notifiable Disease Surveillance System, and cases of acute respiratory infection attended at the Gregorio Marañón Hospital Emergency Ward.

Statistical analysis

Generalised additive models (GAM) [15] have become the most widely used method for assessing the short-term health effects of air pollution. GAM models provide a flexible alternative to parametric time-series regression models, since, by means of nonparametric smoothing functions, they enable control for the effect of seasonal components of variable frequency and amplitude, and also for the effect of confounding factors whose relationship with asthma-related emergencies is nonlinear, such as temperature, which usually plots a U- or V-shaped relationship. However, recently DOMINICI *et al.* [16] have reported that, in the standard case of studies looking for the short-term health effects of air pollution where regression coefficients are very small and adjustment is made for at least two confounding factors using nonparametric smoothing functions, estimated GAM models using the gam function in the S-Plus statistical package may provide biased estimates.

For this reason, and as a sensitivity analysis, two analytical strategies were pursued. The authors made use of the classic methodology as standardised by the Air Pollution and Health, European Approach (APHEA) project [17] and widely used in other multicentre studies [18]. Parametric modelling of the confounding variables was performed, using autoregressive Poisson models that included the following: 1) terms of linear and quadratic trend, as well as dummy variables for each year, to control for long-term trends; 2) sinusoidal terms (sines and cosines) up to the sixth order to control for seasonality; 3) dummy variables for each day of the week, also for public holidays (work and school) to control for short-term variations; 4) linear and quadratic terms for temperature and humidity; and 5) linear terms for daily cases of influenza and acute respiratory infections. The pollutants were next included on a linear basis, with assessment of individual lags up to the fourth order. Lastly, linear terms were included to assess the confounding effect of pollen. The variables included in the model were chosen either individually, on the basis of their respective levels of significance or jointly, on the basis of those that minimised Akaike′s information criterion (AIC) [19]. Once the best-fitted model had been selected with the support of Pearson residuals, the authors then tested for overdispersion using the overdispersion parameter (ϕ^2), and for residual autocorrelation using graphs of the simple (ACF) and partial autocorrelation functions (PACF) [17]. If necessary, autoregressive terms were included to correct for variance in the effect estimate ascribable to overdispersion and autocorrelation [17].

Alternatively, GAM models were used to evaluate the robustness of the results obtained. The GAM analysis included the following: 1) a cubic smoothing spline with degrees of freedom (df) approximately equal to the number of months of the study period, to control for temporal trend and seasonality [20]; 2) cubic smoothing splines of up to four df to control for the effects of the meteorological variables (temperature and relative humidity), daily cases of influenza and acute respiratory infections, and pollen levels; and 3) dummy variables for each day of the week and public holidays. The choice of the number of df for each nonparametric smoothing function was made on the basis of minimisation of the AIC criterion and of observed residual autocorrelation using the ACF and PACF [20]. Analyses were performed using more restrictive than usual convergence parameters, as suggested by the National Morbidity, Mortality and Air Pollution Study (NMMAPS) [16] and APHEA researchers [21], in order to avoid any bias due to problems of convergence in the iterative calculation of the estimates.

Results

A total of 4,827 asthma attacks were registered during the period 1995–1998, with a daily mean of 3.3 and range of 0–26 emergencies (table 1). A total of 50% of all attacks involved children aged 0–14 yrs, 25% of whom were aged <5 yrs, and 52.3% were female. The temporal distribution for daily asthma emergency room admissions registered a seasonal pattern, with two epidemic peaks occurring in the second fortnight of May 1996 and May 1998 (fig. 1).

PM10 and SO_2 registered a predominantly winter-based pattern, whereas NO_2 was distributed homogeneously and O_3 showed a strong seasonal component that peaked during the summer months (fig. 1). In general, pollution levels remained below the standards proposed by the European Community. PM10, SO_2 and NO_2 were positively correlated, while O_3 was negatively correlated with these pollutants and with SO_2 in particular (table 2). The levels of *O. europaea*, *Plantago sp.*, and Poaceae had a strong seasonal distribution showing peak levels in May and June. Urticaceae showed lower levels than other pollens, as well as a bimodal distribution, which increased in April and June.

Table 1. – Descriptive analysis of daily asthma emergency room admissions, air pollutants, pollen levels and weather variables, in Madrid during 1995–1998

Variables		Percentiles						
		Minimum	P10	P25	P50	P75	P90	Maximum
Asthma	3.3 (2.8)	0	1	1	3	5	7	26
PM10 24 h $\mu g \cdot m^{-3}$	32.1 (12.1)	11.2	20.5	24	29.1	37.1	47.5	108.6
SO_2 24 h $\mu g \cdot m^{-3}$	23.6 (15.4)	5	9.2	12.3	18.7	31.3	43.9	121.2
NO_2 24 h $\mu g \cdot m^{-3}$	67.1 (18.0)	25.8	46.5	55.2	64.3	75.7	91.8	147.5
O_3 8 h $\mu g \cdot m^{-3}$	45.8 (28.2)	1.9	11.4	23.6	42.6	63.7	85.4	152.8
O. europaea grains$\cdot m^{-3}$	6.3 (27.2)	0	0	0	0	0.6	6.3	321.2
Plantago sp. grains$\cdot m^{-3}$	4.3 (10.3)	0	0	0	0.2	2.3	15.3	72.8
Poaceae grains$\cdot m^{-3}$	11.1 (27.7)	0	0	0.5	2.0	6.7	27.8	237.5
Urticaceae grains$\cdot m^{-3}$	2.1 (2.8)	0	0.2	0.3	1.0	2.8	6	25.8
Mean temperature °C	15.0 (7.0)	-0.6	6.2	9.1	14.4	20.7	24.9	31.8
Relative humidity %	61.6 (16.4)	22.3	40.4	48.6	60.8	74.6	85.1	100.0

Data are presented as mean (SD) unless otherwise stated. PM10: particles with a median aerodynamic diameter of <10 μm; SO_2: sulphur dioxide; NO_2: nitrogen dioxide; O_3: ozone; *O. europaea*: *Olea europaea.* Number of days in the study period=1461.

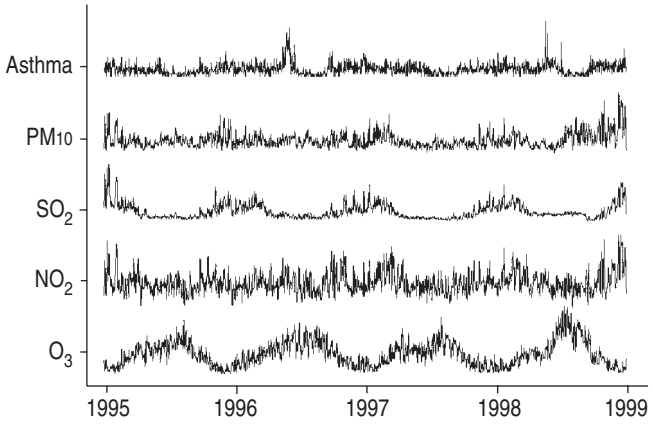

Fig. 1. – Distribution of asthma-related hospital emergencies and air pollution levels in Madrid during 1995–1998.

The core parametric model selected included linear trend, sinusoidal terms of up to the sixth order, dummy variables for years, days of the week and public holidays, linear and quadratic terms for temperature and relative humidity, and a linear term for acute respiratory infections. Although this model showed no residual autocorrelation, it did show overdispersion (ϕ^2=1.42). Hence, the model was only corrected for the overdispersion. For its part, the core GAM model selected included a cubic smoothing spline with 72 df to control for trend and seasonality, dummy variables for days of the week and public holidays, and cubic smoothing splines with four df for temperature and two df for relative humidity and acute respiratory infections. This model showed no residual autocorrelation, and also reduced overdispersion (ϕ^2=1.11).

Table 3 shows the relative risks (RR) of asthma emergency room admissions for a 10 $\mu g \cdot m^{-3}$ rise in pollutant levels in models for a single air pollutant, with assessment of individual lags up to the fourth order, by using Poisson regression.

Table 2. – Matrix of linear correlation coefficients between air pollutants, pollen levels and weather variables

Variables	PM10	SO_2	NO_2	O_3	*O. europaea*	*Plantago sp.*	Poaceae	Urticaceae	Temperature
SO_2	0.581								
NO_2	0.717	0.610							
O_3	-0.188	-0.547	-0.209						
O. europaea	-0.066	-0.157	-0.067	0.165					
Plantago sp.	-0.202	-0.242	-0.070	0.244	0.472				
Poaceae	-0.132	-0.169	-0.055	0.314	0.465	0.775			
Urticaceae	-0.104	-0.093	-0.046	0.258	0.224	0.444	0.447		
Temperature	-0.122	-0.653	-0.251	0.768	0.162	0.207	0.234	0.133	
Humidity	0.119	0.390	0.073	-0.746	-0.122	-0.160	-0.209	-0.238	-0.687

PM10: particles with a median aerodynamic diameter of <10 μm; SO_2: sulphur dioxide; NO_2: nitrogen dioxide; O_3: ozone; *O. europaea*: *Olea europaea.* Variable n=1461.

Table 3. – The increase of 10-$\mu g \cdot m^{-3}$ in air pollution level, by means of Poisson regression models for a single-pollutant

Lags	PM10	SO_2	NO_2	O_3
Current-day lag	1.011 (0.980–1.042)	1.018 (0.984–1.054)	1.013 (0.991–1.035)	1.039 (1.010–1.068)
1-day lag	1.006 (0.976–1.037)	1.005 (0.972–1.039)	1.011 (0.989–1.032)	1.045 (1.018–1.073)
2-day lag	1.008 (0.978–1.038)	1.002 (0.970–1.036)	1.013 (0.992–1.034)	1.043 (1.016–1.070)
3-day lag	1.039 (1.010–1.068)	1.029 (0.997–1.062)	1.033 (1.013–1.054)	1.034 (1.009–1.061)
4-day lag	1.027 (0.999–1.056)	1.025 (0.994–1.058)	1.026 (1.006–1.047)	1.020 (0.994–1.046)

Data are presented as relative risk (95% confidence interval). PM10: particles with a median aerodynamic diameter of <10 μm; SO_2: sulphur dioxide; NO_2: nitrogen dioxide; O_3: ozone.

Table 4. – Effect of pollen levels on the increase of 10-$\mu g \cdot m^{-3}$ in air pollution level, by means of Poisson regression models for a single-pollutant

Single-pollutant model	PM10 (3-day lag)	SO_2 (3-day lag)	NO_2 (3-day lag)	O_3 (1-day lag)
Without adjustment for any type of pollen*	1.039 (1.010–1.068)	1.029 (0.997–1.062)	1.033 (1.013–1.054)	1.045 (1.018–1.073)
Adjusting for a single type of pollen				
O. europaea	1.041 (1.011–1.071)	1.030 (0.998–1.063)	1.033 (1.013–1.054)	1.045 (1.017–1.073)
Plantago sp.	1.046 (1.017–1.076)	1.020 (0.998–1.053)	1.029 (1.009–1.049)	1.043 (1.016–1.070)
Poaceae	1.043 (1.015–1.073)	1.017 (0.986–1.050)	1.025 (1.005–1.046)	1.027 (1.001–1.054)
Urticaceae	1.038 (1.009–1.068)	1.021 (0.989–1.054)	1.028 (1.007–1.048)	1.039 (1.011–1.067)
Adjusting for the four types of pollen	1.045 (1.016–1.074)	1.013 (0.982–1.045)	1.024 (1.004–1.044)	1.032 (1.005–1.059)

Data are presented as relative risk (95% confidence interval). PM10: particles with a median aerodynamic diameter of <10 μm; SO_2: sulphur dioxide; NO_2: nitrogen dioxide; O_3: ozone; *O. europaea*: *Olea europaea*; *: best lag based on single-pollutant models reported in table 3.

All the RR proved positive, and were statistically significant ($p<0.01$) for some effects of PM10, NO_2 and O_3. The highest magnitude was registered for O_3 and PM10, with an increase of asthma emergency admissions of ~4% for a 10 $\mu g \cdot m^{-3}$ rise of air pollutant. The lag that describes the strongest association is day 3, with the exception of O_3 that relates best to the previous day. Furthermore, statistically significant associations were observed in the structure of third- and fourth-order lags for NO_2, and all orders except fourth day lag for O_3. Table 4 sets out the results by means of Poisson regression for the single-pollutant model that yielded the best lag, taking pollen levels into account, individually and jointly. Control for pollen failed to lead to great changes in the magnitude of the effect of the air pollutants.

Multipollutant models were fitted for cold-season pollutants (including PM10 and SO_2, jointly with the four types of pollen) and for photochemical pollutants (including NO_2 and O_3, jointly with the four types of pollen) (fig. 2). Associations remained consistent for PM10 (RR=1.066, 95% confidence interval: 1.027–1.107), NO_2 (1.024, 1.005–1.045) and O_3 (1.031, 1.003–1.060), and remained unaltered by the introduction of the other pollutants and the four pollen types. SO_2 was the most affected (0.966, 0.925–1.009), becoming negative after the introduction of PM10. Since PM10 and NO_2 showed a rather mixed pattern, other combinations of multipollutant models were accounted for. Although associations for PM10 remained statistically significant ($p<0.05$), it decreased ~2% when adjusting for photochemical pollutants (1.044, 1.001–1.090, and 1.044, 1.015–1.073, when adjusting for NO_2 and O_3, respectively). Results for NO_2 did not change when adjusting for SO_2 (1.031, 1.004–1.059), but it was affected after introducing PM10 (1.001, 0.971–1.032), probably due to their high correlation. Finally, slight differences were observed between the estimates obtained with parametric modelling and those obtained with GAM models (PM10: 1.058, 1.025–1.091; SO_2: 0.979, 0.948–1.010; NO_2: 1.022, 1.005–1.040; and O_3: 1.028, 1.006–1.049 (fig. 2)).

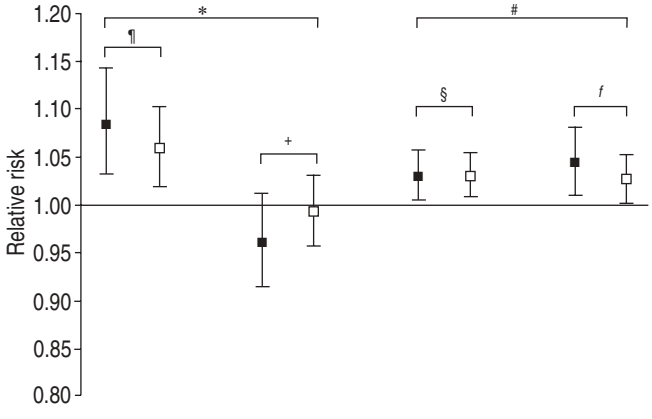

Fig. 2. – Relative risks of asthma emergency room admissions, with 95% confidence intervals, for an increase of 10 $\mu g \cdot m^{-3}$ in air pollution level, by means of Poisson regression and generalised additive models (GAM) for multipollutant models. Adjustment includes all types of pollen (*Olea europaea, Plantago sp.*, Poaceae, and Urticaceae). *: photochemical air pollutants; #: cold season air pollutants; ¶: particles measured with a median aerodynamic diameter of <10 μm (PM10) with pollen and sulphur dioxide (SO_2) (lag 3); +: SO_2 with pollen and PM10 (lag 3); §: nitrogen dioxide (NO_2) with pollen and ozone (O_3) (lag 3); ƒ: O_3 with pollen and NO_2 (lag 3). ■: Poisson regression; □: GAM.

Discussion

The main results yielded by this study suggest that, in the single pollutant models, PM10, NO_2 and O_3 are positively and statistically significantly associated with asthma-related hospital emergencies. These associations hold stable for the cold-season and photochemical pollutant models, where the remaining pollutants of each type are simultaneously introduced. Likewise, no variations are in evidence when pollen is included as a confounding variable. The association of highest size occurs with PM10. The most immediate effects are seen for O_3, associated with previous-day pollutant levels. These results are in line with those reported by a number of studies based on time-series methodology [10, 22–32].

Particulates have been one of the pollutants most frequently studied in the assessment of acute health effects, particularly in the case of respiratory diseases. Although particulate sources tend to vary from place to place, the chief source of emission is diesel-engine combustion, inasmuch as diesel engines emit 100 times more particulates than gasoline engines equipped with catalysers [33]. Laboratory studies confirm that the emission of diesel particulates can have effects on the immune system, by acting as an adjuvant that boosts allergic inflammation [34]. One of the first studies ever to analyse the short-term effects of particulates on asthma-related emergencies was conducted on a <65-yr-old population in Seattle by SCHWARTZ *et al.* [22], who reported a positive association with PM10 at an average lag of 0–4 days; their figure of a 3.7% increase in emergencies for every 10-$\mu g \cdot m^{-3}$ rise in PM10 is very similar to that observed in the current study. In the same period, ROSSI *et al.* [23] also described a positive relationship between total suspended particulates and asthma-related emergencies in the population aged 15–85 yrs. Subsequently, CASTELLSAGUÉ *et al.* [24] reported an association at an average lag of 0–3 days between black smoke and emergency room visits in Barcelona among subjects aged >14 yrs. Again, the magnitude was of the same order as that described both by SCHWARTZ *et al.* [22] and the current study. Recently, studies in Santa Clara [25], London

[26] and Belfast [27] have also observed a significant association between PM10 and asthma-related emergencies. In contrast, other authors, working in different geographical settings and in populations of different age ranges, have failed to observe this association [28–32, 35].

Furthermore, experimental studies have demonstrated that SO_2 can induce bronchospasm in nonasthmatics and asthmatics alike. Although the concentrations required provoking these effects in healthy individuals are very high, among asthmatic subjects changes in pulmonary function are brought about at low dose [36]. In time-series studies, SO_2 has been the pollutant for which an association with asthma-related emergencies has least frequently been detected. In Vancouver, BATES *et al.* [37] observed an association between this pollutant and asthma-related emergency visits among subjects aged >15 yrs. ROSSI *et al.* [23] also observed positive results, as did other recent studies in Birmingham [38], Tel Aviv [39], London [26] and Belfast [27], where a statistically significant relationship was detected with current- or previous-day pollutant levels. Against this, other studies [22, 29, 35, 40, 41] have failed to demonstrate asthma-related effects. In Spain, under pollution conditions very similar to those prevailing in Madrid, CASTELLSAGUÉ *et al.* [24] and SUNYER *et al.* [30] in Barcelona, and TENIAS *et al.* [32] in Valencia, have also failed to observe a statistically significant relationship.

In the case of photochemical pollutants, high concentrations of NO_2 act through oxidative mechanisms to produce epithelial cell damage, reduce resistance to infectious agents, alter alveolar macrophage function and favour the release of mediators of inflammation [42]. In epidemiological time-series studies, this pollutant has been described more frequently in European cities. Once again, CASTELLSAGUÉ *et al.* [24] describe significant associations in Barcelona between previous-day pollutant levels and asthma-related emergencies among persons aged >14 yrs. On the other hand, SUNYER *et al.* [30], also working in Barcelona within the framework of the APHEA study, failed to detect an association in a subsequent series. Recently, TENIAS *et al.* [32] observed a relationship of considerable magnitude in Valencia. Likewise, studies in London [26] and Belfast [27] reported a significant positive association, while other authors have found no such associations [35, 38].

O_3 leads to changes in lung function, which appears to fall off after repeated exposures on consecutive days, and induces bronchial hyperreactivity, both allergen-specific and nonspecific, thereby giving rise to inflammatory changes in the airways [43]. Although in Madrid there were only two O_3 measurement stations available, in contrast to a large number of stations for other air pollutants, these were located in areas of the city that they are not directly influenced by the emission of traffic. Furthermore, it has been well guaranteed that the functions, as well as the quality, of data provided were representative for the entire city [44]. O_3 has been the pollutant to be most frequently associated with asthma-related emergencies. CODY *et al.* [40] in New Jersey were among the first authors to report statistically significant associations. Subsequently, positive associations have also been observed in European cities [30, 32, 35], as well as in North America (Mexico [41], Canada [29] and Nevada [28, 31]), though the magnitude of the relationship varies considerably, as does the lag that corresponds to the best association, even though this could depend on the relative prevalence of other interacting pollutants in those different places. However, most of the reviewed studies where a positive association with O_3 was found reported the strongest association in early lags, lag 1 the most frequently reported [30, 32, 35, 41]. In this sense, the O_3 has a great oxidant capacity, causing inflammation of the airways and bronchial reactivity. It has also been shown that repeated exposures to O_3 cause tolerance. This could explain the relationship with immediate exposures to this pollutant. The mechanisms of action of NO_2 are less well known, although its oxidant capacity is smaller than that of O_3 [9]. In contrast, in other European [24, 26] and North American studies [22, 25, 37] of similar setting, this relationship has not been observed.

In epidemiological time-series studies aimed at assessing the short-term effects of air pollution on health indicators, the suitability of basing results on single or multipollutant models is debatable, since separation of the individual effects may prove extremely difficult, owing to collinearity between the various air pollutants. In the current study, PM10 estimates show a slight increase in response to the introduction of SO_2, the other pollutant predominant in winter. SO_2, in contrast, is vulnerable to the introduction of PM10. The reported levels of SO_2 in Madrid were low, showing a decreasing trend. This could be mainly due to the change of coal to gas heaters. Although SO_2 is a strong bronchoconstrictor, it is mainly absorbed in the upper tract when air is uptaken by the nose. In experimental studies, although effects have been observed at low levels, these have been of slight intensity and of quick improvement [4]. Then, the association found in single-pollutant models with SO_2 can be due to concealing the effect of other pollutants, and disappear when also adjusting for PM10 due to its high correlation. NO_2 and O_3 remained unaltered on inclusion of the other photochemical pollutant. This behaviour pattern was also in evidence in the study by TENIAS *et al.* [32], where SO_2 proved to be the most vulnerable pollutant, while the relationship with the photochemical pollutants remained unchanged when these were simultaneously introduced.

An aspect of special interest is the possibility of pollen confounding or modifying the association between air pollution and asthma [45]. In Madrid, the temporal distribution of asthma emergencies plots epidemic increases during the second fortnight in May and first fortnight in June, coinciding with the abrupt release of Poaceae and *Plantago sp.* pollen [3]. Recently, ANDERSON *et al.* [10] in London, and FAUROUX *et al.* [35] in Paris have also included different types of pollen in the analysis and, like the current study, have observed that the relationships between the different air pollutants and asthma remain independent of, and also not modified by, the effect of such pollen types. Experimental studies have shown that exposure to pollutants, especially particulates and O_3 (but also NO_2 and SO_2), may enhance airway response to environmental allergens in susceptible individuals [46–49]. In time-series studies there is still little information on this point. Due to skewed pollen distributions this variable (pollen) was fitted using different transformations, such as the square root, and alternatively as a dummy variable comparing days without pollen *versus* days with pollen levels [10]. However, results for air pollutants did not change when adjusting pollens transformed with square root, while using dummy variables there were slightly changes, <3% for cold-season pollutants and 1% for photochemical pollutants.

With the use of GAM models, bias can occur both due to too lax convergence criteria and concurvity [16, 21]. However, the results obtained in this study on the basis of parametric modelling do not differ substantially, in terms of magnitude of association and of choice of best lag, when compared to the more flexible modelling using GAM. This consistence coincides with the GAM-based reanalysis, which was performed in the APHEA study [50] to assess heterogeneity in the regional results, and which in the case of West European cities yielded similar estimates to those obtained using the parametric methodology of the initial analysis. In this regard, the authors can only agree with the recommendations made by NMMAPS [16] and APHEA [21] researchers to the effect

that cautious use must be made of GAM models, with care being taken to avoid automatic restriction to the default convergence parameters included in statistical programmes, in order to prevent possible biases in the estimates. The authors have also considered the daily number of acute respiratory infection cases because it is widely demonstrated that this is an important cause of asthma, or even of asthma attacks. Rhinovirus is the main virus that causes asthma exacerbations [51]. However, in most of the time-series studies to assess the short-term effects of air pollution on asthma researchers used influenza because it is easier to obtain from registers. However, the authors found a best goodness of fit, in terms of reduction of core model likelihood, when adjusting for the daily number of acute respiratory infections instead of influenza. When available it should be desirable to use information on acute respiratory infections because it is more directly related with asthma.

This study suffers from the usual limitations of ecological designs, particularly insofar as lack of accuracy in the measurement of exposures is concerned. Despite the small magnitude of the associations, these may be relevant to the public heath point of view. In terms of attributable risk, the association observed with PM10 would imply that if the levels of this pollutant were reduced an average of 5 $\mu g \cdot m^{-3}$, it could prevent between 0.5–3.3% of the asthma emergencies, that is, between six and 39 annual asthma attacks. However, these results must be interpreted with caution, given that variables not controlled for in the model or complex relationships between pollutants may confound the results. For instance, it has recently been observed that when other pollutants that are not usually measured, such as benzene, are incorporated into multipollutant models, the relationship with the classic pollutants decreases to a great extent [27, 52]. Caution must therefore be exercised when it comes to drawing conclusions of a causal nature.

In conclusion, and taking into consideration the limitations of this study, the evidence produced to assess the association between air pollution and asthma-related hospital emergencies in this study, suggests that the usual air pollution levels in Madrid, specifically those of particles measured with a median aerodynamic diameter of <10 μm, ozone and nitrogen dioxide, are associated with an increase in asthma emergency room admissions, and that this effect is independent of ambient pollen concentrations. The authors also advise the use of generalised additive models, which provides the best fit, for the reduction of both autocorrelation and overdispersion.

Acknowledgements. The authors are grateful to M. Saez, F. Ballester, also the anonymous referees and the Editor for the useful comments. They would also like thank the following groups for the data supplied: Regional Health Authority Palynology Network (*Red Palinológica de la Consejería de Sanidad*), Madrid Municipal Air Pollution Control Department (*Departamento de Control de Contaminación Atmosférica del Ayuntamiento de Madrid*), Ministry of the Environment Subdirectorate-General for Environmental Quality (*Subdirección General de Calidad Ambiental del Ministerio de Medio Ambiente*) and Regional Asthma Prevention and Control Programme (*Programa Regional de Prevención y Control del Asma*), and the Gregorio Marañón Hospital Emergency Ward, Madrid.

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