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### **Air pollution and asthma severity in adults.**

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on behalf of the Epidemiological Study on the Genetics and Environment of Asthma (EGEA)

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#### **ABSTRACT**

**Objectives** - There is evidence that exposure to air pollution affects asthma, but the effect of air pollution on asthma severity has not been addressed. The aim was to assess the relation between asthma severity during the past 12 months and home outdoor concentrations of air pollution.

**Methods** - Asthma severity over the last 12 months was assessed in two complementary ways among 328 adult asthmatics from the French Epidemiological study on the Genetics and Environment of Asthma (EGEA) examined between 1991 and 1995. The 4-class severity score integrated clinical events and type of treatment. The 5-level asthma score is based only on the occurrence of symptoms. Nitrogen dioxide (NO<sub>2</sub>), sulphur dioxide (SO<sub>2</sub>) and ozone (O<sub>3</sub>) concentrations were assigned to each residence using two different methods. The first was based on the closest monitor data from 1991-1995. The second consisted in spatial models that used geostatistical interpolations and then assigned air pollutants to the geo-coded residences (1998).

**Results** - Higher asthma severity score was significantly related to the 8-hour average of ozone during April-September (O<sub>3</sub>-8hr) and the number of days (O<sub>3</sub>-days) with 8-hour ozone averages above 110 µg.m<sup>-3</sup> (for a 36-day increase, equivalent to the inter quartile range, in O<sub>3</sub>-days, odds ratio (95% confidence interval) 2.22 (1.61-3.07) for one class difference in score). Adjustment for age, sex, smoking habits, occupational exposure, and educational

level did not alter results. Asthma severity was unrelated to NO<sub>2</sub>. Both exposure assessment methods and severity scores resulted in very similar findings. SO<sub>2</sub> correlated with severity but reached statistical significance only for the model based assignment of exposure.

Conclusions - The observed associations between asthma severity and air pollution, in particular O<sub>3</sub>, support the hypothesis that air pollution at levels far below current standards increases asthma severity.

## **INTRODUCTION**

Evidence of adverse effects of current air pollution on human health substantially increased in recent years.[1,2] Despite improvements in air quality in many regions of the world, primary and secondary pollutants from traffic and other sources of fossil fuel combustion such as particulate matter, diesel soot, or ozone remain of particular concern. Photochemical air pollution represented by ozone, oxides of nitrogen produced by vehicles and respirable fine and ultrafine particulates are of interest due to their toxic properties, and asthmatics are a particularly sensitive subgroup.[1] Associations between daily changes in air pollution and various acute respiratory outcomes including sub-clinical functional changes, symptoms, doctors or emergency room visits, hospitalisations and death[3] have been reported among asthmatics.[4,5] Evidence of acute effects is based on several panel studies conducted in children, and to a lesser extent in adults. Greater susceptibility to acute effects of ambient air pollution in asthmatics with more severe asthma was observed in children[6] but were not consistent in adults.[5,7] A challenge and potential source for inconsistent results is the complex interrelationship of asthma symptoms, its triggers, and subjects coping strategies through adaptation of treatment. As the typically moderate daily changes in air quality may lead to fluctuations in the expression of the disease, it is of interest to evaluate markers of asthma severity on a clinically relevant scale along the continuum between non-symptomatic not regularly treated asthma and symptomatic asthma despite regular treatment.

The concept of the definition of asthma severity has evolved over the past years. Despite development of guidelines for clinical practice, it remains difficult to define asthma severity in epidemiology. While different definitions of asthma severity are in use,[8,9] the concept is certainly clinically relevant. Determinants of asthma severity are not much investigated[10] and, to our knowledge, no study investigated the effect of air pollution on asthma severity.

The aim of the present study was to investigate the relationships between individually assigned exposure to ambient air pollution and asthma severity assessed in two complementary ways. First, we use a clinically relevant score that integrates both symptoms and treatment. Second, we use a simpler score based on symptoms alone. We hypothesize that severity among adult asthmatics from the Epidemiological study on the Genetics and Environment of Asthma, bronchial hyperresponsiveness and atopy (EGEA) correlates with the average air quality at the residential location.

## **MATERIAL AND METHODS**

### ***Study population and asthma severity***

The EGEA study combines a case-control study and a family study.[8,11,12] The protocol has been described elsewhere.[13] Asthmatics, living in pre-defined geographical areas were recruited from chest clinics in five French cities (Paris, Lyon, Marseille, Montpellier, and Grenoble) between 1991 and 1995. Within each city, subject's residences spread across large geographic areas, ranging from 300 km<sup>2</sup> (for the area of Lyon) to 9300 km<sup>2</sup> (for the area of Marseille). Cases were classified as living far from the university hospital based on a distance of at least 10-15 km. Asthmatic probands were those who answered positively to the four following standardized questions: Have you ever had attacks of breathlessness at rest with wheezing? Have you ever had asthma attacks? Was this

diagnosis confirmed by a physician? Have you had an asthma attack in the last 12 months? Among relatives from the families of asthmatic probands, asthma was defined by a positive answer to at least one of the first two questions. The present analysis concerned 328 adult asthmatic subjects from 255 families (188 asthmatic cases and 140 asthmatic relatives). Information was recorded for respiratory symptoms, environment, smoking habits and treatment by a detailed face to face interview administered international standardized questionnaire.[14]

We used two operational definitions of 'asthma severity'. The first approach consists in a 4-class asthma severity score defined for the last 12 months that is based on the concept of 2002-2004-GINA (Global Initiative for Asthma) international guidelines.[15] First, asthma severity was assessed using a clinical severity score derived from frequency of asthma attacks, symptoms between attacks, and hospitalisation for asthma.[11,12,16,17] Secondly, the 4-class asthma severity score was developed,[8] which combined the above clinical score, with information about the occurrence of any attack in the last 12 months, and treatment reported in the past 12 months (no treatment, treatment without inhaled corticosteroids and treatment with inhaled corticosteroids)..

The second definition of severity corresponded to the 5-level asthma score introduced by the European Community Respiratory Health Study.[9] The score, allowing assessing the activity of asthma, was derived as the sum of affirmative responses to any of the following five asthma-like symptoms: breathless when wheezing, woken up with a feeling of chest tightness, woken by attack of shortness of breath (SOB), attack of SOB at rest, and attack of SOB after exercise. All questions referred to the occurrence of symptoms during the last 12 months.

The independence of asthma severity with the distance from the university hospital was checked, as it could have biased the association of air pollution with asthma severity.

### ***Air pollution***

Two approaches were used to assign air pollution exposure to each individual: The first assessment of air pollution relied on the 1991-1995 data from the French Agency for Environment and Energy (ADEME) monitoring network. In case of NO<sub>2</sub> and SO<sub>2</sub>, annual arithmetic means were used. In case of O<sub>3</sub> we derived both the 8-hour average (O<sub>3</sub>-8hr) across the six summer months (April to September) and the number of days with 8-hour averages above 110 µg.m<sup>-3</sup> (O<sub>3</sub>-days). No data were available for particulate matter (PM) for the period under study. The individual assignment of exposure is described in the appendix. In brief, annual mean concentrations (Ozone, NO<sub>2</sub>, SO<sub>2</sub>) from the closest monitor were assigned to each residence. For subjects living in proximity to busy roads we used NO<sub>2</sub> and SO<sub>2</sub> data from the closest traffic monitor station. In all other cases, only data from background monitors were used.

In the second approach we derived concentration estimates from a geo-statistical model carried out by Geovariances for the French Institute of Environment (IFEN) and ADEME for the year 1998.[18]. A validation of the procedure has been performed. Modelled data were compared with classical interpolation algorithms such as inverse distance or univariate kriging. High correlation coefficients ( $r > 0.73$ ) between interpolated and measured values, together with low mean quadratic errors, confirm the validity of the multivariate geostatistical models (Nicolas Jeannée, personal communication). The geostatistical interpolation techniques (kriging-like techniques [19]) are commonly applied since several years to estimate air pollution at unsampled locations;[20,21] the estimation process, based on measured concentrations, takes into account the spatial structure of each pollutant. The better the spatial continuity of the pollutant, the better the confidence one can have in the estimate. The interpolation is realized for annual mean concentrations coming from background monitoring stations on a 4km x 4km grid covering France. Land cover was

integrated to the interpolation process as well as specific cofactors correlated to the pollutants: altitude and North-South concentration gradient for ozone, emission registries of nitrogen oxides, road network and population density for NO<sub>2</sub>, and industrial emissions of SO<sub>x</sub> for SO<sub>2</sub>. Residential addresses of all participants were geo-coded to assign estimated annual means for NO<sub>2</sub>, SO<sub>2</sub> as well as summer ozone(O<sub>3</sub>-summer) assessed from the monthly means from April to September.

### **Data Analysis**

Pearson correlation coefficients were derived across individually assigned air pollution concentrations. Univariate relationships between variables were explored with  $\chi^2$  tests and analyses of variance. Ordinal logistic regressions and when appropriate multinomial regressions (see appendix) were performed. Odds ratios were given for one class difference in the scores and for an increase of one inter quartile range (IQR) in air pollution concentrations. Final models took into account age, sex, smoking habits, educational level and occupational exposures. Smoking habits, previously associated to asthma severity[11] were grouped into never, ex- and current smokers. Education was classified in primary, secondary and university level. Occupational exposure was assessed with a job exposure matrix for eighteen asthmogens completed by expert review.[8,22] Environmental tobacco smoke (current smoking of parents or spouse at home) and indoor air pollution, assessed by considering current use of gas heating or gas cooking and water damage in the last 12 months were considered but not retained in the final model. In order to test the sensitivity of results, analyses were repeated in subgroups defined by sex, age, smoking habits, occupational exposure, and education level as well as by city. Odds ratios were expressed for an increase of 10 days of O<sub>3</sub>-days.

In France, ozone seasons are by and large restricted to the summer period, thus summer time O<sub>3</sub> reflects exposure much better than annual concentrations. While severity was assessed for the last 12 months, one may argue that patients would primarily report the more recent experience. Therefore, if ozone affects asthma severity in an acute or sub-acute manner, associations between severity and ozone may be stronger among subjects answering the questionnaire during the mid summer to fall season. We thus stratified the analyses by season of participation (April to September versus October to March). Familial dependence between observations was taken into account using generalized estimated equations (GENMOD procedure) and a random population with one subject per family were performed, but results did not change (data not shown). More details are presented in the appendix. The statistical software package SAS was used (SAS Institute, Cary, NC, USA).

## RESULTS

Clinical characteristics of the population are reported in table 1 and environmental exposures in table 2. With the first approach (i.e. 'closest monitor') we were able to assign annual mean concentrations to most but not all subjects: 88.4% for NO<sub>2</sub>, 77.7% for SO<sub>2</sub>, 64.0% for O<sub>3</sub>-8hr and 88.1% for O<sub>3</sub>-days. The distribution of assigned pollutant concentrations is presented in figure 1. Figure S1 in the appendix presents data by city. The second exposure assignment approach allowed assigning concentrations to 93.9% of subjects.

**Table 1** Clinical characteristics of the asthmatic adults

Clinical characteristic	Value
<b>Age (n=328)</b>	
Mean ± SD, yrs	37.3 ± 13.3
<b>Sex (n=328)</b>	
Men, %	50.9
<b>4-class asthma severity score * (n=328)</b>	
Class 1, %	32.6
Class 2, %	22.6
Class 3, %	15.2
Class 4, %	29.6
<b>5-level asthma score * (n=314)</b>	
Level 0, %	15.0
Level 1, %	10.2
Level 2, %	11.8
Level 3, %	16.2
Level 4, %	18.1
Level 5, %	28.7
<b>Treatment (n=328)</b>	
Inhaled corticosteroids, %	54.3
<b>FEV<sub>1</sub> % predicted (n=325)</b>	
Mean ± SD	93.3 ± 20.8
FEV <sub>1</sub> < 80% predicted, %	22.8
<b>Bronchial hyperresponsiveness (n=166)</b>	
PD <sub>20</sub> ≤ 4 mg, %	74.1

PD<sub>20</sub>: provocative dose of methacholine causing a 20% fall in FEV<sub>1</sub>.

\*For definitions, see methods.

**Table 2** Environmental characteristics of the asthmatic adults

<b>Environmental characteristic</b>	<b>Value</b>
<b>Smoking habits (n=324)</b>	
Never smokers, %	49.7
Ex-smokers, %	30.2
Current smokers, %	20.1
<b>Passive smoking (n=290)</b>	
Current smoking parents or spouse, %	31.4
<b>Educational level (n=259)</b>	
Primary, %	32.4
Secondary, %	27.0
University, %	40.6
<b>Occupational exposure (n=260)</b>	
Exposed to asthmogens, %	19.6
<b>Indoor exposure</b>	
Current gas heating, (n=323), %	34.4
Current gas cooking, (n=324), %	80.9
Water damage in the last 12 months (n=283), %	8.5
<b>Outdoor air pollution (1<sup>st</sup> method: annual concentrations based on 1991-1995 nearby background and traffic monitoring stations data )</b>	
NO <sub>2</sub> (n=290)	
mean ± SD, µg.m <sup>-3</sup>	40.2 ± 14.7
25 <sup>th</sup> -75 <sup>th</sup> percentiles (IQR), µg.m <sup>-3</sup>	31-45 (14)
SO <sub>2</sub> (n=255)	
mean ± SD, µg.m <sup>-3</sup>	21.3 ± 8.6
25 <sup>th</sup> -75 <sup>th</sup> percentiles (IQR), µg.m <sup>-3</sup>	15-27 (12)
O <sub>3</sub> -8hr (n=210)	
mean ± SD, µg.m <sup>-3</sup>	60.5 ± 19.4
25 <sup>th</sup> -75 <sup>th</sup> percentiles (IQR), µg.m <sup>-3</sup>	42-73 (31)
O <sub>3</sub> -days (n=289)	
mean ± SD, days	37.8 ± 24.4
25 <sup>th</sup> -75 <sup>th</sup> percentiles (IQR), days	20-56 (36)
<b>Outdoor air pollution (2<sup>nd</sup> method: model-based annual concentrations assessed for the 1998 year)</b>	
NO <sub>2</sub> (n=308)	
mean ± SD, µg.m <sup>-3</sup>	35.9 ± 9.3
25 <sup>th</sup> -75 <sup>th</sup> percentiles (IQR), µg.m <sup>-3</sup>	28.8-38.7 (9.9)
SO <sub>2</sub> (n=308)	
mean ± SD, µg.m <sup>-3</sup>	9.9 ± 5.6
25 <sup>th</sup> -75 <sup>th</sup> percentiles (IQR), µg.m <sup>-3</sup>	5.3-13.5 (8.2)
O <sub>3</sub> -summer (n=308)	
mean ± SD, µg.m <sup>-3</sup>	63.0 ± 10.4
25 <sup>th</sup> -75 <sup>th</sup> percentiles (IQR), µg.m <sup>-3</sup>	56.9-67.8 (10.9)

IQR: interquartile range; SD: standard deviation

Correlations between assigned pollutant concentrations across the two indicators of ozone based on the first method were strong ( $r = 0.79$ ,  $p \leq 0.0001$ ). The correlation between  $\text{NO}_2$  and  $\text{SO}_2$  was lower ( $r = 0.48$ ,  $p \leq 0.0001$ ).  $\text{O}_3$ -days and  $\text{NO}_2$  as well as  $\text{O}_3$ -days and  $\text{SO}_2$  were not correlated ( $r = -0.05$  and  $-0.04$  respectively). Regarding the two different methods of air pollution assignment, the Pearson coefficients showed significant correlations for  $\text{NO}_2$  concentrations ( $p=0.48$ ), for  $\text{SO}_2$  concentrations ( $p=0.33$ ) and for ozone ( $p=0.66$  between  $\text{O}_3$ -days and  $\text{O}_3$ -summer and  $p=0.76$  between  $\text{O}_3$ -8hr and  $\text{O}_3$ -summer).

All pollutants assigned from the closest monitors (first approach) were positively associated with the integrated 4-class asthma severity score, but the associations reached statistical significance only for the two indicators of ozone. Results remained significant for both  $\text{O}_3$ -8hr and  $\text{O}_3$ -days also in models adjusting for age, sex, smoking habits, occupational exposure, and educational level (table 3). Taking into account the duration of residence did not change the results. Associations between ozone and the 4-class asthma severity score remained significant among the 94.8% of the subjects living since at least 1 year at the current address (OR =2.64 (1.74 – 4.00) for  $\text{O}_3$ -days and 1.65 (1.27 – 2.14) for  $\text{O}_3$ -summer). Results were unchanged when adjusting on the number of years in the current residence.

Effect estimates of ozone were similar in three-pollutant models including  $\text{O}_3$ ,  $\text{SO}_2$ , and  $\text{NO}_2$  (odds ratio (OR) for  $\text{O}_3$ -days (95% confidence intervals (CI)) 2.74 (1.68-4.48). Relations with ambient  $\text{NO}_2$  were not affected by gas cooking and no association was observed between asthma severity score and cooking or heating with gas. Exposure values assigned from the IFEN model correlated with the 4-class asthma severity score in a similar way, and the positive association observed with annual  $\text{SO}_2$  became statistically significant.

**Table 3** Associations between air pollution and the 4-class asthma severity score per each increase of one IQR in air pollutant concentrations

Air pollutant	First method		Second method	
	n	OR (95% CI)	n	OR (95% CI)
<b>NO<sub>2</sub></b>				
crude model	290	1.03 (0.84-1.25)	308	0.95 (0.77-1.18)
adjusted model*	228	1.01 (0.79-1.28)	247	0.92 (0.72-1.18)
<b>SO<sub>2</sub></b>				
crude model	255	1.25 (0.91-1.70)	308	1.81 (1.33-2.46)
adjusted model*	200	1.22 (0.84-1.78)	247	1.70 (1.19-2.44)
<b>O<sub>3</sub></b>				
	<i>O<sub>3</sub>-8hr</i>			
crude model	210	2.56 (1.68-3.91)		
adjusted model*	162	2.56 (1.58-4.14)		
	<i>O<sub>3</sub>-days</i>		<i>O<sub>3</sub>-summer</i>	
crude model	289	2.22 (1.61-3.07)	308	1.57 (1.26-1.96)
adjusted model*	223	2.53 (1.69-3.79)	247	1.57 (1.22-2.03)
<b>Adjusted three-pollutant models</b>				
<i>O<sub>3</sub> (O<sub>3</sub>-days / O<sub>3</sub>-summer)</i>	184	2.74 (1.68-4.48)	247	1.85 (1.29-2.64)
<i>SO<sub>2</sub></i>	184	1.33 (0.85-2.11)	247	2.27 (1.39-3.70)
<i>NO<sub>2</sub></i>	184	0.94 (0.68-1.29)	247	0.99 (0.64-1.52)

OR: odds ratio; 95% CI: 95% confidence interval.

OR given for one class difference in score and for an increase of 1 inter quartile range (IQR) in average concentration (or 36 days for  $\text{O}_3$ -days).

\*model adjusted for age, sex, smoking habits, occupational exposure and educational level.



Results for the simpler 5-level asthma score were very similar for all pollutants and both exposure assessment approaches (table S1 in the appendix). In the three-pollutant model with pollutants from the closest monitor, the 5-level asthma score was significantly associated only with O<sub>3</sub> days (OR=2.02 (1.26-3.23) per one IQR of O<sub>3</sub>-days). With the IFEN model values, O<sub>3</sub>-summer correlated significantly with severity (2.20 (1.54-3.15)).

Table 4 presents relationships between the 4-class asthma severity and ozone (O<sub>3</sub>-days) among subgroups. Associations remained robust among strata defined by sex, age, smoking habits, occupational exposure, and education level. None of the interaction terms was significant. Stratification on periods of examination showed significant associations of ozone exposure to asthma severity score among subjects participating both from October to March as well as from April to September (OR =1.24 (1.08-1.43) and 1.48 (1.19-1.85) respectively). Consistent results regarding stratification by the previous factors were observed for the 5-level asthma score (data not shown). For the 5-level asthma score, stratification was further studied according to treatment. There was no interaction with treatment (Odds ratios were 1.04 (0.73- 1.49) and 1.11 (0.99-1.25) for an increase of 10 days of O<sub>3</sub>-days, for untreated and treated respectively; interaction p value =0.35).

**Table 4** Relationship between the asthma severity score and ozone within subgroups per each increase of 10 days of O<sub>3</sub>-days

<b>Variable</b>	<b>n</b>	<b>OR (95 % CI)</b>
<b>All subjects</b>	223	1.29 (1.16 – 1.45)
<b>Sex</b>		
Men	116	1.21 (1.04 – 1.40)
Women	107	1.46 (1.22 – 1.76)
<b>Age</b>		
< 45 yrs	139	1.34 (1.15 – 1.57)
≥ 45 yrs	84	1.23 (1.03 – 1.47)
<b>Smoking habits</b>		
Never smokers	101	1.35 (1.12 – 1.62)
Ex-smokers	80	1.30 (1.09 – 1.55)
Current smokers	42	1.12 (0.84 – 1.49)
<b>Occupational exposure</b>		
No	180	1.31 (1.16 – 1.48)
Yes	43	1.29 (0.94 – 1.77)
<b>Education level</b>		
Primary	78	1.33 (1.07 – 1.66)
Secondary	57	1.39 (1.09 – 1.77)
University	88	1.23 (1.04 – 1.46)
<b>Center</b>		
Paris	42	0.98 (0.53 – 1.80)
Lyon	45	3.43 (1.82 – 6.47)
Marseille	38	1.26 (0.79 – 2.01)
Montpellier	16	1.22 (0.76 – 1.96)
Grenoble	82	0.98 (0.70 – 1.35)
<b>6-month periods</b>		
October-March	121	1.24 (1.08 – 1.43)
April-September	102	1.48 (1.19 – 1.85)

OR: odds ratio adjusted for age, sex, smoking habits, occupational exposure and educational level; 95% CI: 95% confidence interval.

OR given for one class difference in score and for an increase of 10 days of O<sub>3</sub>-days

Effects of O<sub>3</sub> across centers were statistically not heterogeneous (p for interaction: 0.07). The size of the geographic areas where subjects lived was unequal with subjects from Marseille residing across a region some thirty times the size of the Grenoble area due to the hospital based sampling. Accordingly, the range of O<sub>3</sub> concentrations across subjects also varied across areas. E.g., among participants in Paris the IQR of the O<sub>3</sub>-days was only 5-26 but rather wide in Montpellier (IQR: 3-90) (fig S1 in the appendix). Excluding the center with the highest value of ozone (Marseille) or the center with significant effect (Lyon) did not affect the effect estimates for O<sub>3</sub>-days (OR=1.28 (1.10-1.48) and 1.23 (1.10-1.38) respectively). Defining 'city' as a random effect did not alter the results (OR=1.24 (1.08-1.42)).

## DISCUSSION

In the well characterized sample of more than 300 adult asthmatics from the EGEEA study, higher residential concentrations of ozone were associated with more severe asthma. The findings were very similar for the integrated score of clinical symptoms and treatment over the past 12 months and the novel 5-level asthma symptom score. Moreover, results were not sensitive to the chosen exposure assessment approach nor to adjustment for age, sex, smoking habits, occupational exposure to asthrogens and educational level. Results were also similar for asthmatics with or without treatment, and for smokers or non-smokers. To the best of our knowledge, this is the first study using asthma severity scores to investigate effects of air pollution. As one score is anchored on symptoms and treatment, it better integrates the course of this disease where deteriorations of the state are usually coupled with adaptations in treatments among well managed patients. The consistent associations observed in this study consolidate the findings. While several panel studies and time series studies suggest the course of asthma to be correlated with ambient oxidant concentrations in adults, the severity score is a promising integrated outcome.

The interpretation of the temporal nature of the observed association between O<sub>3</sub> and asthma severity is challenging and must be put in context of the study design. Depending on the assessment of outcomes and exposures, cross-sectional analyses may investigate not only long-term effects but also sub-acute or acute effects. Our questionnaires asked about the occurrence of symptoms and treatment in the last 12 months, thus results may be interpreted as a summary of all acute effects experienced during the past year. In this case, results are comparable to similar findings in panel studies showing asthma symptoms among adults to increase with atmospheric pollutants, both in North America and in Europe[23] although some heterogeneity was observed in European cities. Deleterious effects of O<sub>3</sub> in moderate/severe adult asthmatics studied over one year have been reported from the Paris area.[5] The asthma severity score used in the present analysis includes frequency of attacks as well as symptoms between attacks and adaptive treatment. A complementary interpretation of the observed cross-sectional associations could be that asthma severity is increased as a consequence of chronic processes due to repeated long-term exposure. The fact that subjects who participated during winter showed similar associations with summer time ozone concentrations as those participating during the summer period may be an indication of sub-acute or longer term effects of ozone on asthma severity, as the ozone seasons in France are by and large restricted to the summer period. However, a conclusive distinction of acute, sub-acute or long-term effects of ambient O<sub>3</sub> exposure cannot be made with this cross-sectional approach nor in panel studies but would require large cohort studies. It would be particularly relevant to have repeated measurements at various seasons in large cohorts to disentangle subacute and chronic effects.

The association between acute, sub-acute, and carry-over chronic pathologies due to O<sub>3</sub> exposure is also not fully elucidated in experimental studies. Nevertheless, plausible biological mechanisms could explain the association of ozone with asthma severity. The powerful oxidant capacity of inhaled ozone is well known and could play a role for both acute and chronic effects by maintaining airway inflammation. Ozone has also been shown to

favour a Th2 pattern[24] and increase eosinophils[25] but neither IgE nor eosinophils in our population were related to asthma severity.[26] Endogenous and exogenous determinants of susceptibility to the adverse effects of ozone are most likely important, and a source of random noise if not controlled in the analyses. Interactions of ozone with genes involved in the regulation of oxidative stress, such as glutathione S-transferases have already been observed in children[27] and may play an important role in adults as well. Beyond acute effects, the pulmonary inflammatory response to inhaled ozone and other oxidants, such as cigarette smoke, is a mechanism which could explain sustained effects of these environmental factors. Acute and chronic effects of air pollution may be interrelated, especially among asthmatics, as the repeated acute inflammatory effects may contribute to the chronic processes of airway remodelling and to severity of asthma.[28] The importance of the various inflammatory patterns in severe and persistent asthma has recently been underlined[10] and further studies are needed to understand which pathways may be implicated, by combining environmental exposure, inflammatory markers and relevant genetic polymorphisms. Further studies should be conducted to improve exposure assessment in order to disentangle acute and chronic effects of air pollution. Information on the activity of the asthmatic disease over short periods, such as the last 15 days or 3 months should be collected as well. Indeed, the last recommendations of GINA which focus on asthma control, will favour such data collection.[29]

### **Strengths and limitations**

A strong asset of the EGEA study is the detailed phenotypic characterisation of the sample recruited through chest clinics, allowing studying a wide range of asthma activity and severity. It can never be totally excluded that some subjects, especially among severe asthmatics do have a mixed form of chronic obstructive pulmonary disease (COPD) and asthma. However, in the context of the EGEA study, in which asthmatics were specifically recruited in specialized chest clinics, it is rather unlikely that COPD patients were misdiagnosed as asthma. Population based studies usually lack sufficient numbers of severe asthmatics. Evidence is increasing regarding the heterogeneity of asthma and severe asthma.[10] Asthma severity combining clinical items and treatment was assessed in close accordance to the 2002-2004 GINA guidelines principles,[15] but using the type of treatment rather than the daily doses of treatment. Our asthma severity score has previously been shown to be associated with other risk factors in the EGEA study as occupational exposure[8] and body mass index in women[12] and linked to the 2p23 genetic region.[30]

It is interesting that we see no difference between results based on the integrated severity score and the simpler symptoms score, reflecting more the activity of the disease. The continuous asthma score based on symptoms has recently been recommended following observations from the European Community Respiratory Health survey as a relevant phenotype to assess associations with environmental determinants.[31] While this score is simpler to assess as it requires no treatment information one may argue to encounter difficulties to assess the effect of air pollution on severity due to the interaction between exposure, symptom occurrence, and changes in treatment. In our sample of asthmatics, effects of O<sub>3</sub> were similar for those with or without treatment. More research is needed to understand the strength and limitations of the two scores and their use in etiologic research.

The association of asthma severity with air pollution could have been biased by recruitment characteristics. All hospitals were homogeneous regarding their recruitment. They were all secondary hospitals with a relatively high proportion of severe asthmatics. If greater distance from the main city was related to greater severity, it could have biased the association of asthma severity with ozone. Indeed, the severity was independent of the distance from the hospital and therefore such bias is unlikely.

The estimation of long-term exposure is a challenge. Estimates of concentrations differed between the two approaches due to the inherently differed methods and data used. Both approaches have their strengths and limitations and it is impossible to evaluate which

approach provides estimates closer to the true ambient concentrations. Having two approaches available is a strength of our study and the similarity in the O<sub>3</sub> and NO<sub>2</sub> results across methods support our findings. As mentioned in methods, the IFEN model was available for 1998. Thus for participants in the early 1990's, the assigned exposure may be less accurate than for participants during the later years. In line with this assumption, OR's were slightly smaller among early (1991-1993) participants compared to late (1994-1995) participants, but remained significant in both groups (data not shown). Most importantly though, ozone effects remained unchanged even in three-pollutant models including adjustment for NO<sub>2</sub> as a marker of traffic related emissions.

The null findings for NO<sub>2</sub> must be put in context of the exposure assignment methods. NO<sub>2</sub> concentrations are affected by local traffic sources, and concentrations may substantially differ within the first 100 meters of busy roads. The two approaches used in the present study were not designed to capture these local contrasts. Our 'simpler approach', i.e. the use of the closest monitor, did take into account the closest traffic monitor of NO<sub>2</sub> for people living close to streets, while the IFEN model, based on background monitors only, and a 4x4 km grid, is less sensitive to proximity to traffic. However, the 4x4 km grid model was refined with network traffic and emission registries of NO<sub>x</sub>. Thus, to investigate effects of traffic emissions on asthma severity, other exposure assignments may be needed such as personal measurements taken with passive samplers, traffic or land use data within narrow buffers around the residence, or geo-spatial models using higher spatial resolution. It is worthwhile to conduct projects targeted at traffic related exposures given the large number of people in Europe living very close to often extremely busy roads.[32] Moreover, we only assigned exposure to residential address as no information on work place or time activity patterns were available, as in most studies conducted in adults.[33] In the first approach using the closest monitor, the maximum distance chosen between residential address and monitor was 40 km and this distance varies among studies with some studies going as far as 80 km,[34] but most of our subjects (93%) lived within 10 km of a monitor. While this rather short distance minimizes the error in assigned exposure for homogeneously distributed pollutants such as O<sub>3</sub> or SO<sub>2</sub>, errors are expected to be larger for spatially heterogeneous pollutants such as NO<sub>2</sub>. We expect these errors to be non-systematic, thus biasing associations toward the null.

The contrast in the assigned exposure was rather low in case of NO<sub>2</sub> and SO<sub>2</sub>, with respectively a 1.5-fold and 1.8-fold change across the inter-quartile range (IQR) of concentrations (31-45 and 15-27 respectively; closest monitor approach), thus affecting the statistical power to observe effects. In case of O<sub>3</sub>, power was clearly better with a 2.8-fold difference (IQR: 20-56). The IFEN model resulted in similar contrasts for NO<sub>2</sub> whereas those for SO<sub>2</sub> were stronger (2.5-fold increase). This may explain why associations became significant in this model. IQR for O<sub>3</sub> was lower in the IFEN model (1.2-fold increase), nevertheless results remained statistically significant and support the interpretation that oxidant pollutants indicated by ambient ozone affect asthma severity.

We found some evidence for heterogeneity of effects across centers with far smaller estimates in some cities. Both analyses performed adding center as a random effect or after exclusion of the centers possibly driving the association in relation to the highest ozone exposure, did not change the main estimate. However, due to the limited sample size within cities, it is not possible to further elucidate whether effects of O<sub>3</sub> to be center specific, driven, for example, by other environmental or population factors present in only a few locations, or whether heterogeneity to be a random finding. It is of note though that the size of the geographic areas was unequal across these cities and that the within-city contrasts of pollutants also differed across cities. These factors may all contribute to heterogeneity.

The question is whether the observed associations reflect an effect of O<sub>3</sub> or whether the latter is a proxy of some other pollutants. Particles measures were not available nor did

we have personal measurements of O<sub>3</sub> exposure. There is some argument that personal O<sub>3</sub> exposure may be more strongly correlated with ambient particles than with ambient O<sub>3</sub> concentrations.[35] This finding, while not universally true, may be due to the well known heterogeneity between indoor and outdoor concentrations of O<sub>3</sub> with usually very low concentrations indoors where people spend 70-80% of their time.[36] Our estimates for O<sub>3</sub> were not sensitive to the inclusion of ambient NO<sub>2</sub> in the three-pollutant model. Based on other studies one may expect substantial correlations between ambient PM and NO<sub>2</sub>[37] thus explaining the O<sub>3</sub> findings with particles does not seem to be very plausible in our study. Air conditioning was not assessed, but was not frequently used in France at the time of the survey. To what extent O<sub>3</sub> may be a marker of other constituents in the toxic mixture of ambient air cannot be answered with our study and the heterogeneity across centers may partly be explained by O<sub>3</sub> indicating in part different characteristics of air pollution across these regions.

In conclusion, we observed significant associations between ambient O<sub>3</sub> concentrations and asthma severity in adults. Results were consistent across two approaches of individual assignment of exposure, as well as for two complementary markers of asthma severity. More studies are needed to elucidate the time sequence of pollution effects and to evaluate the impact of exposure of air pollution on asthma severity. But the present results add to the evidence of adverse effects of O<sub>3</sub> at levels far below current air quality standards among susceptible people, namely those with asthma, supporting more stringent regulations of ambient O<sub>3</sub>, [38] thought to be set to protect public health. The use of asthma severity scores to investigate the contribution of environmental factors to this complex and dynamic disease appears very promising.

**Main messages:**

- Ambient ozone concentrations were significantly associated to asthma severity in adults.
- These effects remained stable with adjustment for urban background pollution.
- Sulphur dioxide - but not nitrogen dioxide - taken as a marker of urban background pollution correlated with asthma severity as well.

**Policy implications:**

- The study suggests that asthmatics are affected by ozone at concentrations far below current standards set to protect public health.
- Asthmatics are expected to benefit from further reductions of summer ozone concentrations.

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### Competing interests

None declared

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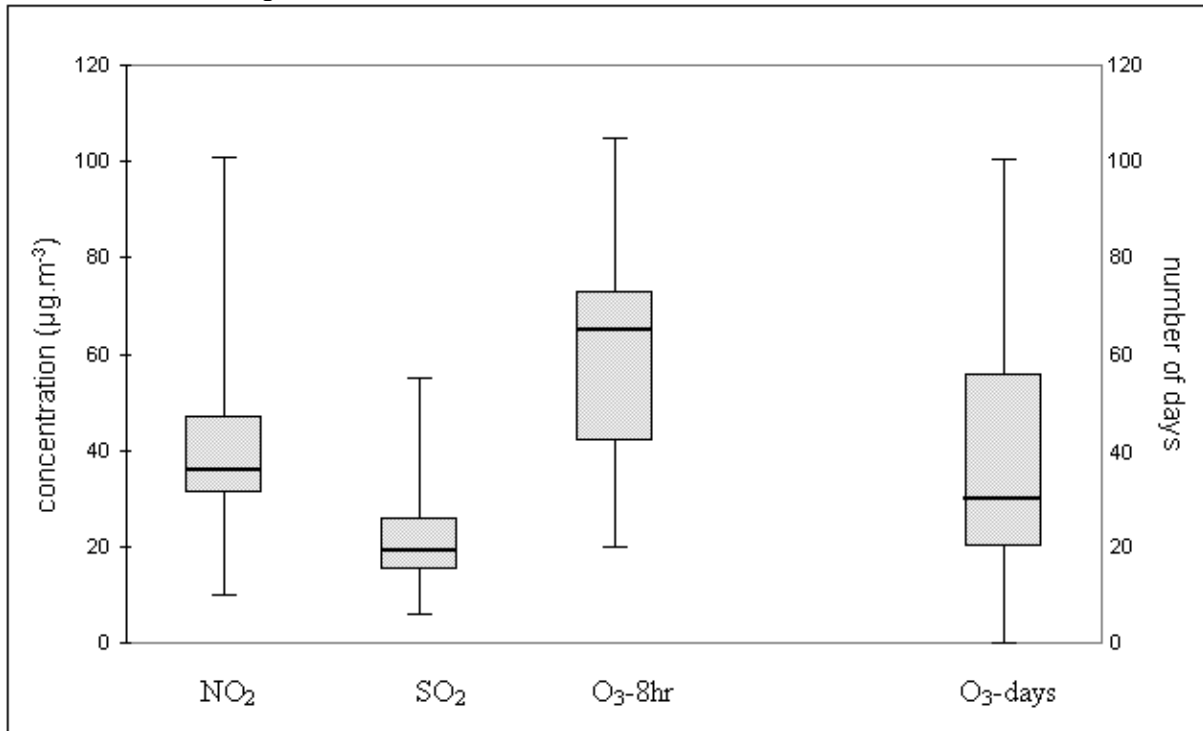
**Figure 1 Legend**

The bottom and top of the box represents the 25<sup>th</sup> and 75<sup>th</sup> percentiles, respectively. The upper and lower whiskers represent the maximum and minimum, respectively.

The horizontal line through the middle of the box is the median.

Median values were 36  $\mu\text{g.m}^{-3}$  for  $\text{NO}_2$ , 19  $\mu\text{g.m}^{-3}$  for  $\text{SO}_2$ , 68  $\mu\text{g.m}^{-3}$  for  $\text{O}_3$ -8hr and 30 days for  $\text{O}_3$ -days.

**Figure 1** - Box plot of assigned pollutant concentrations among the studied asthmatics according to the 1<sup>st</sup> method with annual concentrations based on 1991-1995 nearby background and traffic monitoring stations data.



## APPENDIX

### AIR POLLUTION ASSESSMENT BY THE FIRST METHOD

Air pollution concentrations were derived from the French Agency for Environment and Energy (ADEME) data bank using both background and traffic monitor stations. Air pollution was assigned to subjects residences in two steps. First, the residential address of subjects and air pollution monitors were located on maps by plane coordinates (after transformation of geographical coordinates if needed). Although subjects were recruited through patients consulting in five city hospitals, the residential areas covered a region more than twenty times larger than the city areas. A total of 69 monitors (54 background stations and 15 traffic stations) were used for the assignment of residential concentrations. Second, assignment of the closest monitor to each residence was done in two ways: for subjects living within 100m of main roads, values of the closest NO<sub>2</sub> or SO<sub>2</sub> traffic station were used. 17% of subjects were assigned with data of traffic stations (14% of subjects in Paris area, 12% in Lyon area, 28% in Marseille area, 45% in Montpellier area, and 13% in Grenoble area). Traffic stations do not monitor O<sub>3</sub>. For all other subjects and for O<sub>3</sub>, assignment was based on concentrations recorded at the closest background station (urban, suburban or rural station). A total of 93% of subjects lived within 10 km of a monitor. The maximum distance was 40 km. If more than two monitors were equally distant, the mean value of these monitors was assigned.

Air pollution exposure could not be assessed for 38, 73 and 39 subjects for NO<sub>2</sub>, SO<sub>2</sub> and O<sub>3</sub>-days respectively for whom there was no station within 40 km. For O<sub>3</sub>-8hr, there was no available data for two areas covering the region of Lyon and Montpellier. Air pollution monitoring has been expanded in France during the past years but increased since 1995. If no data was available at the time of the survey, we used the air pollution trends as observed during later years to linearly extrapolate to earlier years. Long-term changes in air quality usually follow similar trends over several years. SO<sub>2</sub> concentrations have dramatically decreased during the 1990's, while NO<sub>2</sub> decreased very slightly and O<sub>3</sub> increased also very little.[1] In this context, back extrapolation was the most accurate approach in presence of missing data, which assumes that a consistent evolution over the period of interest. For O<sub>3</sub> concentrations 70% of subjects got assigned back-extrapolated values, according to a pattern with slight increase of O<sub>3</sub> between 1991 and 1995. In case of NO<sub>2</sub> and SO<sub>2</sub> regular monitoring started earlier, thus 55% and 25% of subjects' locations required back-extrapolation. Health assessments were conducted throughout the year. Therefore, the annual mean concentrations of the same year would poorly reflect past exposure (during the 12 months prior the visit) among subject participating early in the year. Therefore participants during January-June were assigned the annual mean of the previous calendar year and those with assessments during July-December, with the mean of the current calendar year.

### ANALYSIS

Ordinal logistic regression was performed to assess association between air pollution and the 4-class asthma severity score. Tests of the proportional odds assumption were systematically performed. For NO<sub>2</sub>, SO<sub>2</sub> and O<sub>3</sub>-8hr, the hypothesis of proportionality was not rejected. As the test appeared significant for O<sub>3</sub>-days and O<sub>3</sub> summer, we also performed the analysis based using multinomial regression, which does not assume proportional odds ratios. The global association between ozone and asthma severity was significant and all OR were higher than 1, supporting associations between asthma severity and ozone, independently of the model.

Taking into account familial dependence was complex and it was clarified with two analyses: First, mixed logistic regression models were performed considering a dichotomous asthma severity score defining mild asthmatics by the 1<sup>st</sup> or the 2<sup>nd</sup> class and moderate to

severe asthmatics by the 3<sup>rd</sup> or the 4<sup>th</sup> class (Genmod procedure from SAS). Second, both logistic regression models and ordinal logistic regression models were run in a random population of 182 subjects (one subject per family). Familial aggregation had no impact on results.

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**Table S1** Associations between air pollution and the 5-level asthma score per each increase of one IQR in air pollutant concentrations

Air pollutant	First method		Second method	
	n	OR (95% CI)	n	OR (95% CI)
<b>NO<sub>2</sub></b>				
crude model	279	0.96 (0.79-1.17)	295	0.95 (0.77-1.18)
adjusted model*	221	0.92 (0.73-1.17)	238	0.94 (0.74-1.21)
<b>SO<sub>2</sub></b>				
crude model	247	1.06 (0.78-1.44)	295	1.37 (1.01-1.84)
adjusted model*	194	0.98 (0.68-1.41)	238	1.39 (0.98-1.97)
<b>O<sub>3</sub></b>				
	<i>O<sub>3</sub>-8hr</i>			
crude model	201	2.21 (1.48-3.33)		
adjusted model*	171	2.27 (1.41-3.63)		
	<i>O<sub>3</sub>-days</i>		<i>O<sub>3</sub>-summer</i>	
crude model	278	1.93 (1.40-2.65)	295	1.57 (1.26-1.96)
adjusted model*	217	2.09 (1.42-3.09)	238	1.62 (1.26-2.09)
<b>Adjusted three-pollutants models</b>				
<i>O<sub>3</sub> (O<sub>3</sub>-days / O<sub>3</sub>-summer)</i>	179	2.02 (1.26-3.23)	238	2.20 (1.54-3.15)
<i>SO<sub>2</sub></i>	179	1.08 (0.69-1.67)	238	1.41 (0.90-2.23)
<i>NO<sub>2</sub></i>	179	0.79 (0.58-1.08)	238	1.41 (0.93-2.15)

OR: odds ratio; 95% CI: 95% confidence interval.

OR given for one class difference in score and for an increase of 1 inter quartile range in average concentration (or 36 days for O<sub>3</sub>-days).

\*model adjusted for age, sex, smoking habits, occupational exposure and educational level.

**Table S2** Associations between air pollution and the 4-class asthma severity score per each increase of 10 units of air pollutants

Air pollutant	First method		Second method	
	n	OR (95% CI)	n	OR (95% CI)
<b>NO<sub>2</sub></b>				
crude model	290	1.02 (0.88 – 1.17)	308	0.95 (0.76 – 1.18)
adjusted model*	228	1.01 (0.85 – 1.20)	247	0.92 (0.72 – 1.18)
<b>SO<sub>2</sub></b>				
crude model	255	1.20 (0.93 – 1.56)	308	2.06 (1.42 – 3.00)
adjusted model*	200	1.18 (0.87 – 1.62)	247	1.91 (1.24 – 2.96)
<b>O<sub>3</sub></b>	<i>O<sub>3</sub>-8hr</i>			
crude model	210	1.35 (1.18 – 1.55)		
adjusted model*	162	1.35 (1.16 – 1.58)		
	<i>O<sub>3</sub>-days</i>		<i>O<sub>3</sub>-summer</i>	
crude model	289	1.25 (1.14 – 1.37)	308	1.51 (1.24 – 1.85)
adjusted model*	223	1.29 (1.16 – 1.45)	247	1.52 (1.20 – 1.91)
<b>Adjusted three-pollutant models</b>				
<i>O<sub>3</sub> (O<sub>3</sub>-days / O<sub>3</sub>-summer)</i>	184	1.32 (1.16-1.52)	247	1.76 (1.27-2.44)
<i>SO<sub>2</sub></i>	184	1.27 (0.87-1.86)	247	2.71 (1.49-4.94)
<i>NO<sub>2</sub></i>	184	0.95 (0.76-1.20)	247	0.99 (0.64-1.53)

OR: odds ratio; 95% CI: 95% confidence interval.

OR given for one class difference in score and for an increase of 10 µg.m<sup>-3</sup> in average concentration or 10 days of O<sub>3</sub>-days.

\*model adjusted for age, sex, smoking habits, occupational exposure and educational level.

**Table S3** Associations between air pollution and the 5-level asthma score per each increase of 10 units of air pollutants

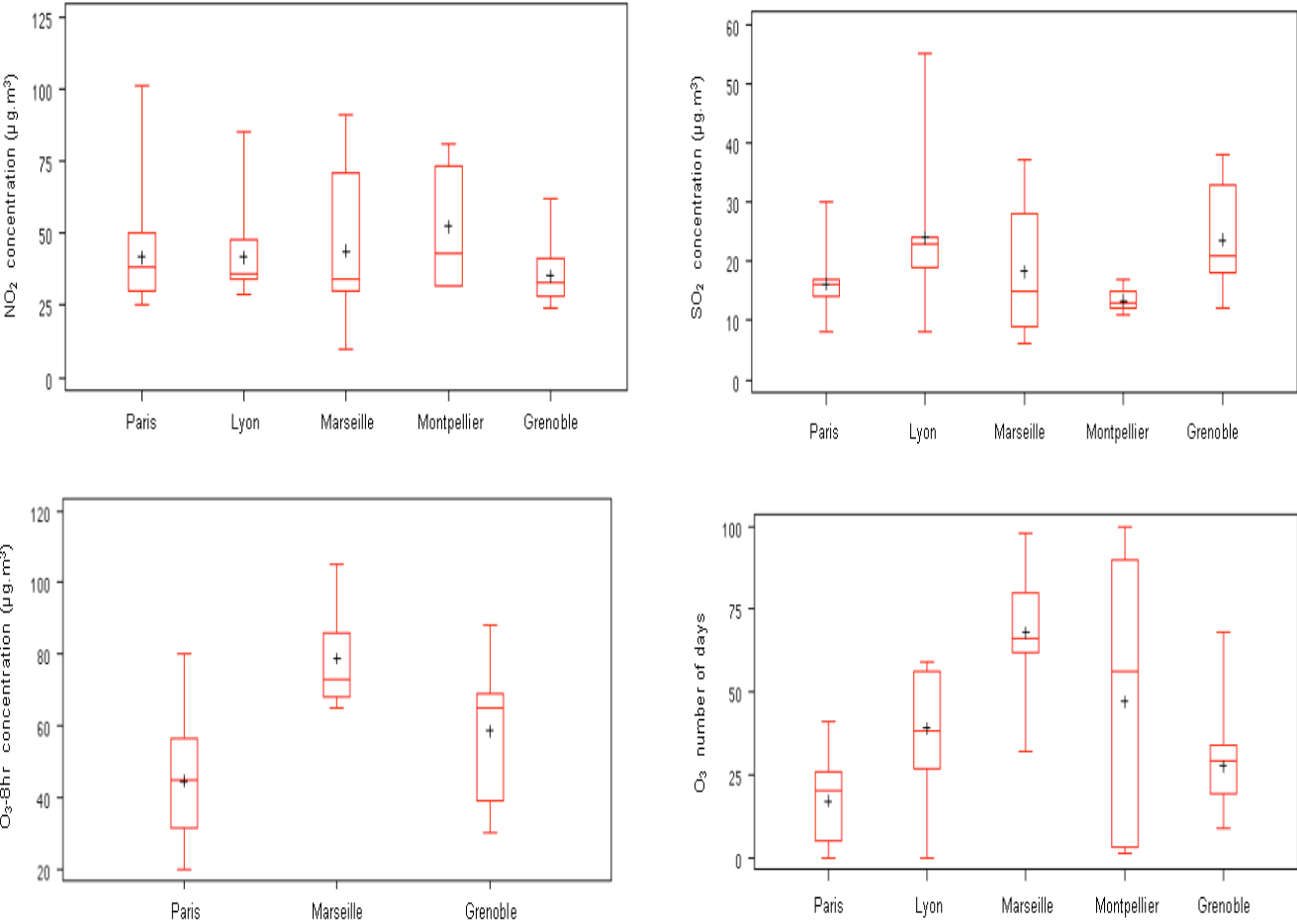
Air pollutant	First method		Second method	
	n	OR (95% CI)	n	OR (95% CI)
<b>NO<sub>2</sub></b>				
crude model	279	0.97 (0.84 – 1.12)	295	0.95 (0.76 – 1.18)
adjusted model*	221	0.94 (0.80 – 1.12)	238	0.94 (0.74 – 1.21)
<b>SO<sub>2</sub></b>				
crude model	247	1.05 (0.81 – 1.35)	295	1.46 (1.02 – 2.10)
adjusted model*	194	0.98 (0.73 – 1.34)	238	1.49 (0.98 – 2.28)
<b>O<sub>3</sub></b>				
	<i>O<sub>3</sub>-8hr</i>			
crude model	201	1.29 (1.13 – 1.47)		
adjusted model*	171	1.30 (1.12 – 1.52)		
	<i>O<sub>3</sub>-days</i>		<i>O<sub>3</sub>-summer</i>	
crude model	278	1.20 (1.10 – 1.31)	295	1.51 (1.23 – 1.85)
adjusted model*	217	1.23 (1.10 – 1.37)	238	1.56 (1.24 – 1.96)
<b>Adjusted three-pollutants models</b>				
<i>O<sub>3</sub> (O<sub>3</sub>-days / O<sub>3</sub>-summer)</i>	179	1.22 (1.07-1.39)	238	2.06 (1.48-2.86)
<i>SO<sub>2</sub></i>	179	1.06 (0.74-1.53)	238	1.53 (0.88-2.65)
<i>NO<sub>2</sub></i>	179	0.85 (0.68-1.06)	238	1.42 (0.93-2.17)

OR: odds ratio; 95% CI: 95% confidence interval.

OR given for one class difference in score and for an increase of 10 µg.m<sup>-3</sup> in average concentration or 10 days of O<sub>3</sub>-days.

\*model adjusted for age, sex, smoking habits, occupational exposure and educational level.

**Figure S1** Box plot of assigned pollutant concentrations among asthmatics according to the centers with the first method.



The bottom and top of the box represents the 25<sup>th</sup> and 75<sup>th</sup> percentiles, respectively. The upper and lower whiskers represent the maximum and minimum, respectively. The full horizontal line through the middle of the box is the median and the cross is the mean.