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# Air pollution and asthma control in the Epidemiological study on the Genetics and Environment of Asthma

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## Abstract

### Background

The associations between exposure to air pollution and asthma control are not well known. The objective is to assess the association between long term exposure to NO<sub>2</sub>, O<sub>3</sub> and PM<sub>10</sub> and asthma control in the EGEA2 study (2003–2007).

### Methods

Modeled outdoor NO<sub>2</sub>, O<sub>3</sub> and PM<sub>10</sub> estimates were linked to each residential address using the 4-km grid air pollutant surface developed by the French Institute of Environment for 2004. Asthma control was assessed in 481 subjects with current asthma using a multidimensional approach following the 2006–2009 GINA guidelines. Multinomial and ordinal logistic regressions were conducted adjusted on sex, age, BMI, education, smoking and use of inhaled corticosteroids. The association between air pollution and the three domains of asthma control (symptoms, exacerbations and lung function) was assessed. Odds Ratios (ORs) are reported per Inter Quartile Range (IQR).

### Results

Median concentrations (µg.m<sup>-3</sup>) were 32(IQR 25–38) for NO<sub>2</sub> (n=465), 46(41–52) for O<sub>3</sub> and 21(18–21) for PM<sub>10</sub> (n=481). In total, 44%, 29% and 27% had controlled, partly-controlled and uncontrolled asthma. The ordinal ORs for O<sub>3</sub> and PM<sub>10</sub> with asthma control were 1.69(95%CI 1.22–2.34) and 1.35(95%CI 1.13–1.64) respectively. When including both pollutants in the same model, both associations persisted. Associations were not modified by sex, smoking status, use of inhaled corticosteroids, atopy, season of examination or BMI. Both pollutants were associated with each of the three main domains of control.

### Conclusions

The results suggest that long-term exposure to PM<sub>10</sub> and O<sub>3</sub> is associated with uncontrolled asthma in adults, defined by symptoms, exacerbations and lung function. Abstract Word count: 250 Key words: air pollution, asthma, asthma control

**MESH Keywords** Adult ; Air Pollutants ; adverse effects ; analysis ; Asthma ; epidemiology ; etiology ; genetics ; Case-Control Studies ; Cross-Sectional Studies ; Environmental Exposure ; adverse effects ; analysis ; Environmental Monitoring ; Follow-Up Studies ; France ; epidemiology ; Hospitalization ; statistics & numerical data ; Humans ; Logistic Models ; Lung ; physiopathology ; Nitrous Acid ; adverse effects ; analysis ; Ozone ; adverse effects ; analysis ; Residence Characteristics ; Respiratory Tract Diseases ; complications ; epidemiology ; genetics ; Seasons ; Severity of Illness Index

**Author Keywords** air pollution ; asthma ; asthma control

## Introduction

Asthma control reflects disease activity over a short period of time. Achieving and maintaining the control of asthma is a major goal in asthma management. [1, 2] Acute exposure to air pollution is associated with adverse respiratory effects in asthmatic adults including increased respiratory symptoms or hospitalizations, or reduced lung function. [3–5] Evidence showing the effects of chronic exposure to air pollution on asthma incidence in adults is growing. [6–8] However, studies on the effect of chronic exposure to air pollution on asthma control are scant. In two studies, air pollution exposure was associated with the occurrence of asthma-like symptoms in the last three months and with emergency department visits and/or hospitalizations in the last year. [9, 10] In the first survey of the French Epidemiological study on the Genetics and Environment of Asthma (EGEA), higher exposure to  $O_3$  was associated with more severe asthma in adults [11].

Following clinical guidelines, asthma control integrates several dimensions, reflecting both acute and chronic activity of the disease: daytime and night-time symptoms, the need for rescue treatment, exacerbations in the past year and lung function. [1, 2] Although worldwide about half of the patients have poorly controlled disease, [12, 13, 14] few epidemiological studies have been conducted to identify the determinants of asthma control, and even fewer have taken into account such a comprehensive measure of asthma control. [12, 15]

From the data in EGEA2 (follow-up of EGEA), we propose to study the effect of long-term exposure to air pollution, using yearly modeled estimates, on asthma control, assessed by single criteria and by combining several domains of control to follow as closely as possible the Global Initiative for Asthma (GINA) 2006–2009. [15]

## Methods

### Study design

EGEA is an asthma case-control and family study (including spouses and 1<sup>st</sup> degree relatives of the cases), conducted for the first time between 1991 and 1995 on 2047 subjects from 5 French cities. This analysis is based on the cross-sectional data of the follow-up study (EGEA2) conducted between 2003 and 2007 on 1571 adults. [15, 16, 17] (Figure 1, on-line supplement) Written consent was obtained from all participants at both surveys. Ethical approval to carry out the study was obtained for both surveys from the relevant committees (Cochin Royal Hospital, Paris, for EGEA1; Necker Enfants Malades Hospital, Paris, for EGEA2).

### Asthma control

We defined asthma control in this population as previously published [15] following GINA 2006–2009 guidelines. [1, 2] Asthma control was studied in subjects with current asthma, as done in previous publications, [6, 15], based on self-reports of respiratory symptoms over the past 3 months (i.e., any of wheezing, nocturnal chest tightness, attack of shortness of breath following strenuous activity, at rest or at night, asthma attacks), use of short-acting beta2 agonist inhalers in the past 3 months, exacerbation (oral steroid use or hospitalization) in the past 12 months and FEV<sub>1</sub>. Subjects with controlled asthma were those without any of the following features: diurnal symptoms  $\geq 1$ /week in the last 3 months; asthma attack in the last 3 months; nocturnal symptoms (woken due to asthma or by an attack of shortness of breath) in the last 3 months; use of short-acting beta2 agonist inhalers  $\geq 2$ /week in the last 3 months; use of oral corticosteroids in the past year; FEV<sub>1</sub> < 80% predicted. Subjects with partly-controlled asthma were those with 1 or 2 of the above features. Subjects with uncontrolled asthma were those with  $\geq 3$  of the above features or those for whom respiratory problems had caused hospital or emergency admissions in the past year, or had used oral corticosteroids in the past year, or had had 12 asthma attacks in the past 3 months.

### Air pollution

Yearly estimates of outdoor air pollution concentrations at each participant's home address in 2004 for  $O_3$ , PM<sub>10</sub> (available for 481 of the 501 subjects with current asthma), and NO<sub>2</sub> (available for 465 subjects) were derived from a geo-statistical model by the French Institute of Environment (IFEN). Interpolation was done for annual mean concentrations coming from background monitoring stations on a 4km  $\times$  4km grid covering France. The residential addresses of all participants were geocoded to assign estimated annual means for  $O_{3-ann}$ , NO<sub>2</sub> and PM<sub>10</sub> as well as summer ozone ( $O_{3-sum}$ ) assessed from the monthly means from April to September. This has been previously described. [11, 18] (on-line supplement)

### Statistical analysis

First, the association between asthma control and air pollutants was expressed by odds ratios (ORs, reported for one interquartile range (IQR) of the pollutant), derived from multinomial logistic regression. For each factor, the simultaneous assessment of the risk for uncontrolled asthma and for partly-controlled asthma was compared to controlled asthma. Concerning the pollutants for which the proportional odds assumption hypothesis was verified in our data ( $O_{3-sum}$  and PM<sub>10</sub>), we used the ordinal logistic regression leading to the

estimate of a single odds ratio (OR) that gives the risk to go from controlled to partly controlled asthma and from partly controlled to uncontrolled asthma. Generalized linear mixed models were also conducted in order to take into account the family structure and the city dependence of the population. The model integrates that there is a correlation between the subjects living in the same family (i.e. all members of the family sharing genetic background and/or lifestyle determinants) or between the subjects living in the same city (i.e. all participants living in the same city being exposed to the same background concentrations of air pollution). The effect of the family structure or city dependence are random while the other effects of the model are fixed.

All the associations are first reported crude and then followed by the multivariate analysis, for each pollutant separately. Variables taken into account in the multivariate analysis were those known to be associated with asthma control in EGEA [14] (on-line supplement) and another European cohort (ECRHS) [12]. In order to address the independent effect of each pollutant on asthma control, a two-pollutant model was performed, including  $O_{3\text{-sum}}$  and  $PM_{10}$ . Finally, analyses were also conducted on the three domains of asthma control (lung function, symptoms, exacerbations), (on-line supplement). The lack of data on activity limitation in our study did not allow including this domain in the asthma control classification. Analyses were performed with Stata 9.

## Results

Of the 481 subjects included in the analysis, 44%, 29% and 26% had controlled, partly-controlled and uncontrolled asthma. Asthma was more often uncontrolled in women ( $p=0.04$ ) and in older subjects ( $p=0.003$ ). Subjects with uncontrolled asthma used more inhaled corticosteroids (ICS) ( $p=0.001$ ). (Table 1) The IQR (defined by the difference between the third and the first quartiles) was 13 (25–38)  $\mu\text{g.m}^{-3}$  for  $NO_2$ , 11 (41–52)  $\mu\text{g.m}^{-3}$  for  $O_{3\text{-an}}$ , 13 (60–73)  $\mu\text{g.m}^{-3}$  for  $O_{3\text{-sum}}$  and 3 (18–21)  $\mu\text{g.m}^{-3}$  for  $PM_{10}$ . Annual and summer  $O_3$  measurements were highly correlated (Pearson coefficient  $r=0.72$ ).  $NO_2$  was strongly negatively correlated with  $O_{3\text{-an}}$  ( $r=-0.76$ ) and moderately correlated with  $PM_{10}$  ( $r=0.45$ ).  $O_{3\text{-an}}$  and  $PM_{10}$  were not correlated ( $r=-0.08$ ),  $O_{3\text{-sum}}$  and  $PM_{10}$  were weakly correlated ( $r=0.26$ ).

Table 2 shows the results of the crude and adjusted associations between each of the air pollutants and asthma control.  $O_{3\text{-sum}}$  and  $PM_{10}$  were positively associated with partly-controlled and uncontrolled asthma, with a clear gradient from controlled, partly-controlled and uncontrolled. For these two pollutants, the ORs assessed using the ordinal logistic regression were significant (ORs were 1.69 (95% CI: 1.22–2.34) and 1.35 (95% CI: 1.13–1.64) for  $O_{3\text{-sum}}$  and  $PM_{10}$  respectively). Taking into account the family dependence of individuals did not change the coefficients (Table 2). Adding the city of examination as a third level in the model decreased slightly the ORs for  $PM_{10}$  but not for  $O_{3\text{-sum}}$ , and both associations remained significant (ORs were 1.69 (95% CI: 1.21–2.36) and 1.33 (95% CI: 1.06–1.67) for  $O_{3\text{-sum}}$  and  $PM_{10}$  respectively).

In the two-pollutant model, asthma control estimates slightly decreased but remained statistically significant for both air pollutants. Using the ordinal logistic regression, the crude and adjusted ORs for those two pollutants included simultaneously in a unique model were 1.59 (95% CI: 1.16–2.19) and 1.50 (95% CI: 1.07–2.11) for  $O_{3\text{-sum}}$  and 1.25 (95% CI: 1.05–1.49) and 1.28 (95% CI: 1.06–1.55) for  $PM_{10}$  respectively.

Figure 2a and b illustrate the adjusted ORs obtained from the ordinal logistic regression for  $O_{3\text{-sum}}$  and  $PM_{10}$  respectively, stratified by sex, age, current active and passive smoking exposure, use of ICS in the last 12 months, atopy, season of examination, BMI and age of asthma onset. The results from the sensitivity analysis only including subjects who had been living for at least two years in 2004 at their current address are also shown (thus is subjects who had not moved since 2002). All the estimates were above 1, and most of them were significant. No significant interaction was found but the p-value for interaction was borderline significant for sex and  $PM_{10}$  ( $p=0.06$ ), suggesting that the association could be more significant in men.

The study of the associations between air pollution and each one of the three asthma control domains showed that increased levels of  $O_{3\text{-sum}}$  and  $PM_{10}$  were associated with a lower FEV1. However, the association reached the significance level only for  $PM_{10}$  ( $p=0.002$ ) (table 3). For the exacerbations, the ORs for  $O_{3\text{-sum}}$  and  $PM_{10}$  were above 1. Higher exposure to both  $O_{3\text{-sum}}$  and  $PM_{10}$  were positively and significantly associated with higher symptom frequency ( $p=0.013$  and  $p=0.002$ ).

## Discussion

Long-term exposure to  $O_3$  and  $PM_{10}$  is associated with decreased asthma control in adults. This study is innovative since it shows for the first time that long-term exposure to air pollution is associated with uncontrolled asthma.

The associations observed in a large sample of well-characterized adults with current asthma were robust: 1) the associations concern the three domains of asthma control which were studied; 2) the associations were confirmed after adjustment on covariates including sex, age, BMI, smoking and ICS use; 3) the associations remained in a multilevel analysis taking into account the family and the city; 4) the associations were not modified after stratification on several covariates.

Due to the multidimensional approach of the control definition, the results increase the evidence of the combined acute and chronic respiratory effects of air pollution.

A major strength of EGEA is the detailed characterization of subjects with asthma using not only epidemiologically-defined criteria but also extensive clinical characterizations, in a country with homogeneous health care access. Phenotype misclassification is thus unlikely. [17] The detailed EGEA2 questionnaire and examination of the subjects allowed the assessment of asthma control on the basis of the 2006–2009 GINA guidelines. However, EGEA had no information on activity restrictions. The lack of activity data may result in the misclassification of some of the subjects as having ‘controlled asthma’, resulting most likely in a loss of power of the effects of air pollution. In the ECRHSII study, 1032 patients were classified as having “current asthma” and it was found that activity limitation had an impact on the asthma control level in 8.7% subjects (unpublished data). Thus, the lack of this dimension in the EGEA data is expected to impair asthma control classification in a few subjects only. We are aware that the current updated GINA guidelines now include aspects related to future risk, an aspect of importance from a clinical perspective, but difficult to assess clinically and impossible to include in epidemiological studies.

Another strength of our analysis is the robustness and consistency of the findings. For both pollutants ( $PM_{10}$  and  $O_3$ ), all estimates of the stratified analyses by sex, age, smoking, use of ICS, atopy, BMI, season of examination and age of asthma onset were above one and in the same order of magnitude. Furthermore, both pollutants were associated with each of the three domains of asthma control, although the estimates were more stable and significant when using the integrated measure of asthma control. This indicates that results are not driven by one domain.

In the bi-pollutant model, the effect of both pollutants ( $O_{3-sum}$  and  $PM_{10}$ ) remains, suggesting that the effect of both pollutants are independent. This may reflect different mechanisms by which each one affects asthma control. For example  $O_3$  is a potent oxidant [19, 20], while  $PM_{10}$  has oxidant properties and is an irritant producing local inflammation [20, 21].

One of the limitations of our study is the relatively large spatial scale of the air pollution models: 4 km<sup>2</sup> grids. While this is appropriate for secondary or long-range pollutants with a relatively homogeneous distribution over longer distances (e.g.  $O_3$  or  $PM_{10}$ ), this spatial scale cannot capture local traffic-related pollution as small-scale spatial contrasts are substantial for such pollutants [17]. Models with higher spatial resolution have successfully used  $NO_2$  as a marker for local traffic-related pollutants whereas our  $NO_2$  model fails to capture local conditions, resulting in large and most likely random misclassifications of exposure. This could explain why we do not find any association between  $NO_2$  and asthma control.

A limitation of our exposure assignment relates to the use of a model based on measurements taken in 2004 (yearly average) while asthma control data were collected between 2003–2007. However, spatial contrasts of median-range pollutants –relevant in our analyses– are unlikely to vary much from one year to another although the absolute concentrations may differ across years. [22] Results among subjects who had been living for at least two years in the same place as in 2004 were similar, indicating that this issue not to be of major relevance in our study.

Stressful living conditions may confound the observed associations if those correlate both with asthma control and air pollution on the spatial scale used in our analyses. We do not have indicators of stress available, thus, a formal assessment of this concern is not possible. However, the multilevel analyses took into account ‘city’, thus, stressors associated with the city level would have been taken into account. The estimates were similar with and without control for city.

$PM_{10}$  concentrations are quite low in the study. In France, before 2007,  $PM_{10}$  measurements were underestimated because the volatiles particles (such as the ammonium nitrate) were not considered. From 2007 (after the development of our map), the certified air-quality monitoring agencies (AASQA) changed their measurement methods. The difference between the old and the new methods varied from 1.3 to 1.4 fold according to the characteristics of each region. Such scaling of the absolute levels does not affect our estimates of effects.

While there is an extensive literature about the acute effects of exposure to air pollution on different asthma control features, the long term effects of exposure to air pollution on asthma control are unclear. Furthermore, most studies in asthma-air pollution were carried out in children. Hospitalizations or emergency visits for asthma were increased on days with higher air pollution concentrations. [5, 23] Fewer studies have found associations between acute exposure to traffic-related air pollution and lung function in asthmatics. [24]

To our knowledge, only two studies aimed to address the long term effect of air pollution on some measures of asthma control. In a population based study, living close to high traffic density roads was associated with poorer asthma control, assessed by more than one respiratory symptom per week or at least emergency department visit or hospitalization in the last year. [10] They found an association between  $O_3$  and asthma control only in the elderly, and between  $PM_{10}$  and asthma control only in women. [9] In their second study in

adults,  $O_3$ ,  $PM_{10}$  and  $PM_{2.5}$  were significantly associated with symptoms but not with emergency department visits or hospitalizations. [9] Our findings, in which asthma control features were combined with lung function and the use of reliever treatment, are in agreement with these studies.

In our study, the association of  $PM_{10}$  with asthma control seemed to be stronger in men. The existing literature about the difference of the air pollution effects according to sex is quite inconsistent, even if more studies report greater effects in women. [25] As underlined recently, more studies are needed on this aspect to clarify gender differences and assess the role of biological (i.e. men have larger airways allowing larger pollutants such as  $PM_{10}$  to penetrate deeper), socio-cultural, and exposure assessment factors (i.e. women tend to spend more time at home) which may explain such differences. [26]

The association between  $O_3$  and  $PM_{10}$  and asthma control were not modified by smoking, the ICS use, atopy, BMI, age of asthma onset and season; although we did observe some non-statistically significant differences in the point estimates for air pollution exposure between some of these groups. Larger studies may assess whether the apparently higher associations with pollution observed in some of these subgroups may be replicated, while we may conjecture about possible reasons for the observed but non-significant differences. In non-smokers exposed to ETS, stronger associations of pollution with asthma control tended to be shown compared to smokers or non-smokers not exposed to ETS. This could be explained by the fact that ETS and air pollution share similar mechanisms of lung damage. [26, 27] In subjects using ICS, there is also a tendency for higher effects of air pollution, possibly reflecting a subgroup with more severe asthma that could be more susceptible to air pollution effects. [28] In contrast to other findings, subjects with higher BMI are not more susceptible to air pollution in our data. [29] However, most studies showing greater susceptibility of overweight subjects to air pollution were for cardiovascular outcomes. Estimates were also somewhat stronger among non-atopic subjects, while few studies reported atopic subjects to possibly react stronger to air pollution due to interactions between aeroallergens and pollutants. [30] Estimates were also stronger in subjects with childhood asthma, this would suggest that air pollution affects more asthma control in subject who has been asthmatic for a long time. However, our study design is not tailored to address all these questions. The associations with  $O_3$  seemed to be higher for subjects examined during summer rather than winter. Reporting is most accurately recalled for the conditions during the past few weeks and months, thus, participants during summer provide more accurate data for the spring and summer. Furthermore, the exposure metric is the summer condition ( $O_{3-sum}$ ), therefore this finding is expected.

The use of a composite asthma control classification is novel in air pollution research. Whereas air pollution was measured over one year, asthma control was assessed based on acute or subacute asthma events. In this study, the “long-term” expression is used as opposed to day-to-day variations in the air pollutants concentrations. The models used to assess air pollution exposure were developed for the year 2004 which is a reasonable estimate of the longer-term average air quality given that the variation of annual means of background air pollutants is rather limited. An interesting question is whether ‘asthma control’ reflects a summary of the acute effect of air pollution on asthma and how it relates to the chronic development and worsening of the disease. As shown in general populations, a single measure of lung function may be affected independently by the level of pollution on the day of the exam and the long-term exposure. [31, 32] To formally disentangle the chronic from the acute effects of air pollution requires different study designs and estimates of daily levels of air pollution that were not available in our population. Results support an effect of long term exposure to air pollution on asthma control in adulthood in subjects with pre-existing asthma. It remains possible however, that as suggested for occupational asthmogens, environmental insults may also induce directly a more severe form of disease. [33] Increasing evidence suggest that environmental exposures play a role at the various steps of the disease process. However, whether long term exposure to air pollution is at the same time a cause for the development of the underlying chronic asthma pathology is subject to investigations and cannot be addressed with the data used in this analysis.

In summary, our results indicate that both ambient  $O_3$  and  $PM_{10}$  concentrations jeopardize asthma control in adults. The results are robust. The clinically relevant concept of “asthma control” with its integrated assessment of acute and chronic dimensions of the disease offers novel ways to quantify and monitor the public health relevance of air pollution among adults with asthma.

What this papers adds

- What is already known on this subject: Acute exposure to air pollution is associated with adverse respiratory effects in adults with asthma such as the increase in emergency visits, exacerbations, medication intake, symptoms, etc. However, the effect of long-term exposure to air pollution on asthma control, assessed by combining several domains of control reflecting both acute and chronic respiratory conditions, has never been studied.

- What does this study add: Our results suggest a robust association between long-term exposure to  $O_3$  and  $PM_{10}$  and uncontrolled asthma, defined according to international clinical guidelines and combining three different domains (lung function, symptoms and exacerbations), in a large number of well-characterized current asthmatics from the Epidemiological study on Genetics and Environment of Asthma.

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## Footnotes:

**Competing Interest :** None to declare.

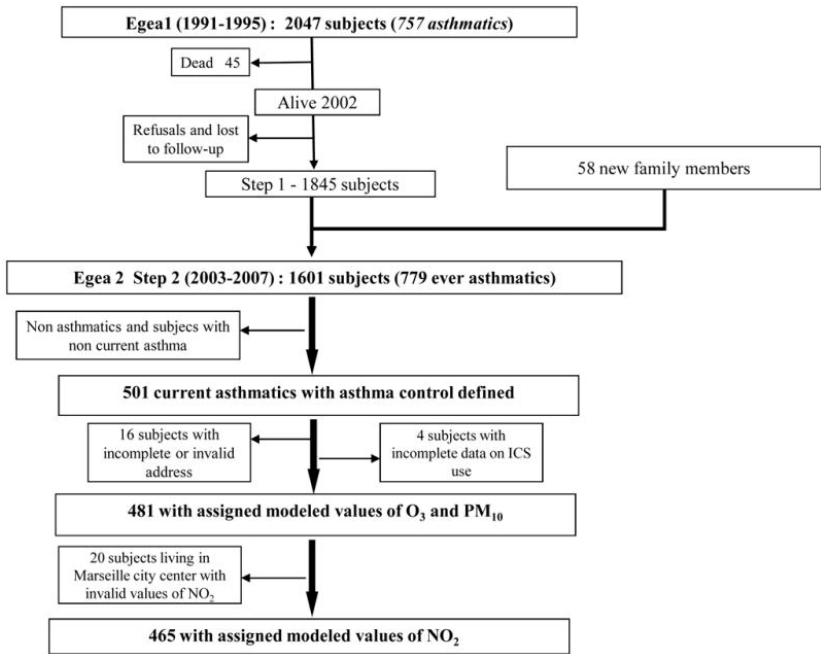
## References:

1. Global Initiative for Asthma . Global strategy for asthma management and prevention . Bethesda (MD) 1995 ; (updated 2006)
2. National Asthma Education and Prevention Program . Expert panel report 3: guidelines for the diagnosis and management of asthma . July 1997 ; (Updated August 2007)
3. Bayer-Oglesby L , Schindler C , Hazenkamp-von Arx ME . Living near main streets and respiratory symptoms in adults: the Swiss Cohort Study on Air Pollution and Lung Diseases in Adults . *Am J Epidemiol* . 2006 ; 164 : 1190 - 8
4. Brunekreef B , Holgate ST . Air pollution and health . *Lancet* . 2002 ; 360 : 1233 - 42
5. Sunyer J , Spix C , Querel P . Urban air pollution and emergency admissions for asthma in four European cities: the APHEA Project . *Thorax* . 1997 ; 52 : 760 - 5
6. Jacquemin B , Sunyer J , Forsberg B . Home outdoor NO<sub>2</sub> and new onset of self-reported asthma in adults . *Epidemiology* . 2009 ; 20 : 119 - 26
7. Kunzli N , Bridevaux PO , Liu LJ . Traffic-related air pollution correlates with adult-onset asthma among never-smokers . *Thorax* . 2009 ; 64 : 664 - 70
8. Modig L , Toren K , Janson C . Vehicle exhaust outside the home and onset of asthma among adults . *Eur Respir J* . 2009 ; 33 : 1261 - 7
9. Meng YY , Rull RP , Wilhelm M . Outdoor air pollution and uncontrolled asthma in the San Joaquin Valley, California . *J Epidemiol Community Health* . 2010 ; 64 : 142 - 7
10. Meng YY , Wilhelm M , Rull RP . Traffic and outdoor air pollution levels near residences and poorly controlled asthma in adults . *Ann Allergy Asthma Immunol* . 2007 ; 98 : 455 - 63
11. Rage E , Siroux V , Kunzli N . Air pollution and asthma severity in adults . *Occup Environ Med* . 2009 ; 66 : 182 - 8
12. Cazzoletti L , Marcon A , Janson C . Asthma control in Europe: a real-world evaluation based on an international population-based study . *J Allergy Clin Immunol* . 2007 ; 120 : 1360 - 7
13. Rabe KF , Adachi M , Lai CK . Worldwide severity and control of asthma in children and adults: the global asthma insights and reality surveys . *J Allergy Clin Immunol* . 2004 ; 114 : 40 - 7
14. de Marco R , Bugiani M , Cazzoletti L . The control of asthma in Italy. A multicentre descriptive study on young adults with doctor diagnosed current asthma . *Allergy* . 2003 ; 58 : 221 - 8
15. Siroux V , Boudier A , Bousquet J . Phenotypic determinants of uncontrolled asthma . *J Allergy Clin Immunol* . 2009 ; 124 : 681 - 7
16. Kauffmann F , Dizier MH , Annesi-Maesano I . EGEA (Epidemiological study on the Genetics and Environment of Asthma, bronchial hyperresponsiveness and atopy)--descriptive characteristics . *Clin Exp Allergy* . 1999 ; 29 : 17 - 21
17. Kauffmann F , Dizier MH , Pin I . Epidemiological study of the genetics and environment of asthma, bronchial hyperresponsiveness, and atopy: phenotype issues . *Am J Respir Crit Care Med* . 1997 ; 156 : S123 - 9
18. Rage E , Jacquemin B , Nadif R . Total serum IgE levels are associated with ambient ozone concentration in asthmatic adults . *Allergy* . 2009 ; 64 : 40 - 6
19. Cieniewicz J , Trivedi S , Kleeberger SR . Oxidants and the pathogenesis of lung diseases . *J Allergy Clin Immunol* . 2008 ; 122 : 456 - 68
20. Bernstein JA , Alexis N , Barnes C . Health effects of air pollution . *J Allergy Clin Immunol* . 2004 ; 114 : 1116 - 23
21. World Health Organisation . Air quality guidelines. Global update 2005 . Germany WHO ; 92 890 2192 6 2006 ; 231 - 46
22. European Environmental Agency . Air Pollution in Europe 1990-2004 . Copenhagen EEA report ; 2007 ; 33 : 46 - 51 -
23. Ponce de Leon A , Anderson HR , Bland JM . Effects of air pollution on daily hospital admissions for respiratory disease in London between 1987-88 and 1991-92 . *J Epidemiol Community Health* . 1996 ; 50 : s63 - 70
24. McCreanor J , Cullinan P , Nieuwenhuijsen MJ . Respiratory effects of exposure to diesel traffic in persons with asthma . *N Engl J Med* . 2007 ; 357 : 2348 - 58
25. Clougherty JE . A growing role for gender analysis in air pollution epidemiology . *Environ Health Perspect* . 2010 ; 118 : 167 - 76
26. Gilmour MI , Jaakkola MS , London SJ . How exposure to environmental tobacco smoke, outdoor air pollutants, and increased pollen burdens influences the incidence of asthma . *Environ Health Perspect* . 2006 ; 114 : 627 - 33
27. London SJ , Romieu I . Gene by environment interaction in asthma . *Annu Rev Public Health* . 2009 ; 30 : 55 - 80
28. Sunyer J , Basagana X , Belmonte J . Effect of nitrogen dioxide and ozone on the risk of dying in patients with severe asthma . *Thorax* . 2002 ; 57 : 687 - 93
29. Dubowsky SD , Suh H , Schwartz J . Diabetes, obesity, and hypertension may enhance associations between air pollution and markers of systemic inflammation . *Environ Health Perspect* . 2006 ; 114 : 992 - 8
30. D'Amato G , Liccardi G , D'Amato M . Environmental risk factors and allergic bronchial asthma . *Clin Exp Allergy* . 2005 ; 35 : 1113 - 24
31. Downs SH , Schindler C , Liu LJ . Reduced exposure to PM<sub>10</sub> and attenuated age-related decline in lung function . *N Engl J Med* . 2007 ; 357 : 2338 - 47

- 32 . Schindler C , Kunzli N , Bongard JP . Short-term variation in air pollution and in average lung function among never-smokers. The Swiss Study on Air Pollution and Lung Diseases in Adults (SAPALDIA) . Am J Respir Crit Care Med . 2001 ; 163 : 356 - 61
- 33 . Malo JL . Asthma may be more severe if it is work-related . Am J Respir Crit Care Med . 2005 ; 172 : 406 - 7

**Figure 1**

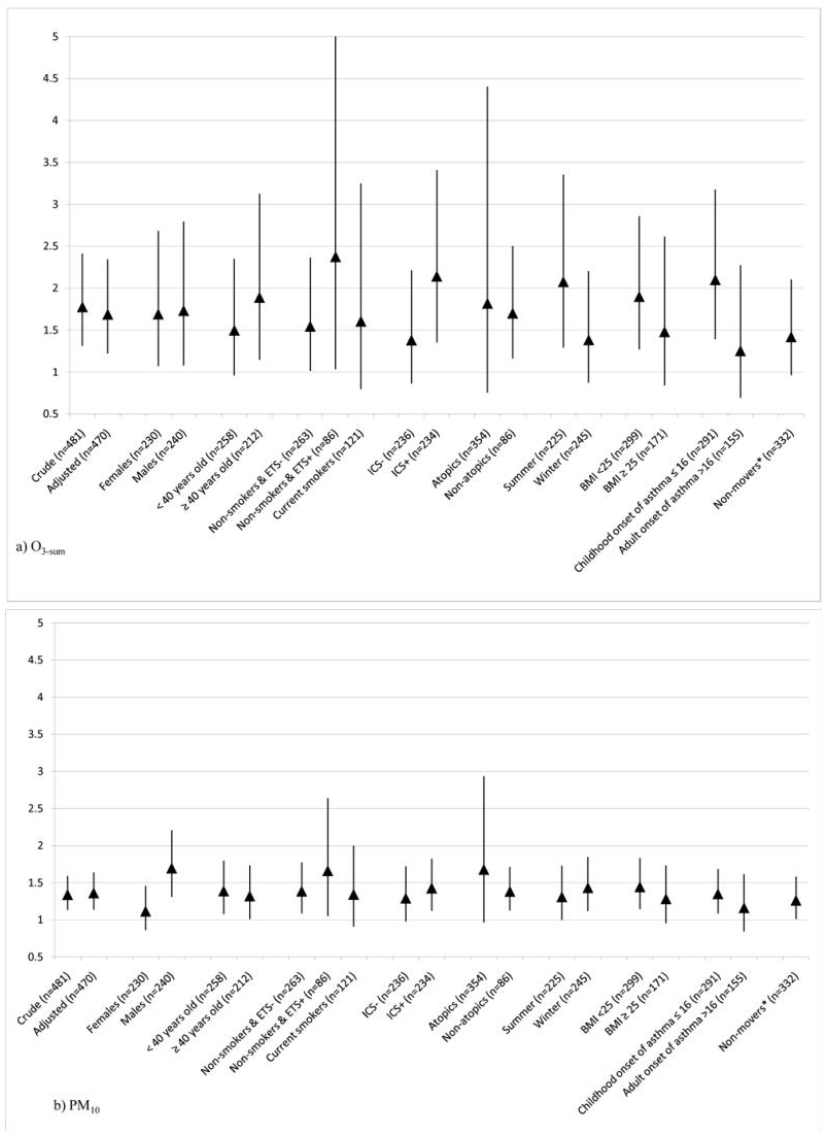
Flow chart of the EGEA population included in this analysis





**Figure 2**

Sensitivity analysis results. Odds ratios (ORs) and 95% confidence intervals (from ordinal regression) showing the associations between each IQR of modelled  $O_3$ -sum a) and  $PM_{10}$  b) and controlled asthma \* Non-movers are those who had been living for at least two years at the same address in 2004 (thus is those who have not moved since 2002)



**Table 1**

Description of health covariates and pollutants, for the total population and then defined by the level of control

	ALL	Controlled	Partly controlled	Uncontrolled
n (%)	481 (100)	216 (44.9)	144 (29.9)	121 (25.2)
<b>General characteristics *</b>				
Females; N(%)	239 (49.7)	103 (47.7)	64 (44.4)	72 (59.5)
Age; mean (SD)	39.5 (16.5)	36.9 (15.5)	40.7 (17.1)	42.9 (16.7)
BMI; mean (SD)	24.4 (4.5)	24.1 (4.2)	24.4 (4.8)	25.1 (4.6)
<b>Educational level *</b>				
Primary; N(%)	105 (22.2)	43 (19.9)	33 (23.4)	29 (25.0)
Secondary ; N(%)	132 (27.9)	67 (31.0)	31 (22.0)	34 (29.3)
University ; N(%)	236 (49.9)	106 (49.1)	77 (54.6)	53 (45.7)
<b>Active/Passive smoking status *</b>				
Non-smoking & ETS-; N(%)	268 (55.7)	115 (53.2)	83 (57.4)	70 (57.9)
Non-smoking & ETS+; N(%)	88 (13.3)	39 (18.1)	30 (20.8)	19 (15.7)
Current smoking; N(%)	125 (26.0)	62 (28.7)	31 (21.5)	32 (26.4)
<b>Clinical characteristics</b>				
Age of asthma onset $\leq 16^*$ : N(%)	297 (65)	140 (69)	88 (63)	69 (61)
Atopy <sup>†</sup> ; N(%)	355 (80.5)	162 (79.0)	106 (80.9)	87 (82.9)
FEV <sub>1</sub> <80% predicted <sup>†</sup> ; N(%)	78 (16.6)	0 (0)	39 (28.1)	39 (33.6)
IgE >100 UI/ml <sup>†</sup> : N(%)	288 (61.5)	114 (53.5)	97 (69.8)	77 (66.3)
BHR <sup>†</sup>	188 (69.4)	106 (65.8)	48 (73.9)	34 (75.6)
At least one symptom <sup>*</sup> ; N(%)	177 (36.8)	0 (0)	85 (59.0)	92 (76.0)
Exacerbations <sup>*</sup> ; N(%)	79 (16.5)	0 (0)	0 (0)	79 (65.3)
Inhaled Corticosteroids <sup>*</sup> ; N(%)	241 (50.1)	68 (31.5)	85 (59.0)	88 (72.7)
<b>Air pollutants in <math>\mu\text{g.m}^{-3}\ddagger</math></b>				
NO <sub>2</sub> ; mean (min-max)	32.1 (7.7–50.2)	32.9 (7.7–50.2)	31.2 (8.8–50.2)	31.9 (11.4–50.2)
O <sub>3-an</sub> ; mean (min-max)	47.3 (35.7–74.1)	46.3 (35.7–66.7)	48.3 (35.7–74.1)	47.9 (35.7–68.1)
O <sub>3-sum</sub> ; mean (min-max)	67.1 (52.4–86.3)	65.9 (54.4–80.8)	67.7 (52.4–86.3)	69.8 (55.4–78.9)
PM <sub>10</sub> ; mean (min-max)	20.2 (12.2–27.6)	19.8 (12.2–27.6)	20.3 (12.2–27.2)	21.0 (1.44–27.6)

**BMI** : Body mass index, **Educational level** : based on highest diploma, **ETS** : Environmental tobacco smoke, **Atopy** : at least one wheal  $\geq 3$  mm to 11 tested allergens, **FEV<sub>1</sub>** : Forced expiratory volume in 1 second, **BHR** : Bronchial hyperresponsiveness pd20<4 mg of metacholine, **At least one symptom** : >1 diurnal symptom per week or an asthma attack in the last 3 months or a nocturnal symptom in the last 3 months, **Exacerbations** : at least 1 hospitalization or emergency room visit or one course of oral corticosteroids in the last year, **ICS** : use of inhaled corticosteroids in the last 12 months

\* collected through questionnaire,

† objectively measured in a hospital setting,

‡ modeled at each subject's address

**Table 2**

Association between an interquartile range of each air pollutant and asthma control. Each line represents a separate single-pollutant model.

	Partly controlled			Uncontrolled		Ordinal		Ordinal (taking into account family dependence)		Ordinal (taking into account family and city dependence)	
	n	OR <sup>*</sup>	95% CI	OR <sup>*</sup>	95% CI	OR <sup>†</sup>	95% CI	OR <sup>‡</sup>	95% CI	OR <sup>§</sup>	95% CI
Crude											
NO <sub>2</sub>	465	0.79	(0.59 – 1.07)	0.88	(0.64 – 1.19)	NA		NA		NA	
O <sub>3-an</sub>	481	<b>1.45</b>	<b>(1.07 – 1.97)</b>	1.35	(0.98 – 1.86)	NA		NA		NA	
O <sub>3-sum</sub>	481	<b>1.60</b>	<b>(1.08 – 2.36)</b>	<b>2.16</b>	<b>(1.41 – 3.30)</b>	<b>1.78</b>	<b>(1.31 – 2.41)</b>	<b>1.73</b>	<b>(1.29 – 2.31)</b>	<b>1.73</b>	<b>(1.29 – 2.31)</b>
PM <sub>10</sub>	481	1.18	(0.95 – 1.46)	<b>1.50</b>	<b>(1.19 – 1.89)</b>	<b>1.34</b>	<b>(1.13 – 1.59)</b>	<b>1.35</b>	<b>(1.13 – 1.61)</b>	<b>1.26</b>	<b>(1.04 – 1.53)</b>
Adjusted <sup>  </sup>											
NO <sub>2</sub>	454	0.84	(0.62 – 1.15)	0.99	(0.71 – 1.40)	NA		NA		NA	
O <sub>3-an</sub>	470	1.33	(0.96 – 1.84)	1.19	(0.83 – 1.70)	NA		NA		NA	
O <sub>3-sum</sub>	470	<b>1.53</b>	<b>(1.01 – 2.33)</b>	<b>2.14</b>	<b>(1.34 – 3.43)</b>	<b>1.69</b>	<b>(1.22 – 2.34)</b>	<b>1.69</b>	<b>(1.21 – 2.36)</b>	<b>1.69</b>	<b>(1.22 – 2.34)</b>
PM <sub>10</sub>	470	1.16	(0.92 – 1.46)	<b>1.60</b>	<b>(1.24 – 2.08)</b>	<b>1.36</b>	<b>(1.13 – 1.64)</b>	<b>1.40</b>	<b>(1.14 – 1.71)</b>	<b>1.33</b>	<b>(1.06 – 1.67)</b>

\* Odds ratios obtained from multinomial logistic regression comparing controlled versus partly-controlled asthma and uncontrolled versus controlled asthma

† Odds ratios obtained from ordinal logistic regression

‡ Odds ratio obtained from generalized linear models taking into account family dependence (level 2) and the ordinal model

§ Odds ratio obtained from generalized linear models taking into account family dependence (level 2) and city (level 3) and the ordinal model

NA not applicable, the ordinal model was not conducted for NO<sub>2</sub> and O<sub>3-an</sub> due to the characteristics of the estimates derived from the multinomial logistic regression that do not suggest a gradual effect from partly-controlled to uncontrolled asthma

|| Adjusted for sex, age, body mass index, educational level, smoking and use of inhaled corticosteroids in the last year

**bold** estimates make reference to estimates with a p<0.05

**Table 3**

ORs derived from logistic regression between a) lung function, b) symptoms and c) exacerbations, and one IQR of each pollutant

<b>a) lung function (defined dichotomically as % predicted FEV<sub>1</sub> value &lt; or ≥ 80)</b>			
	<b>n</b>	<b>OR</b>	<b>95% CI</b>
Crude			
NO <sub>2</sub>	455	1.01	(0.73 – 1.42)
O <sub>3-an</sub>	471	1.23	(0.88 – 1.73)
O <sub>3-sum</sub>	471	1.53	(0.97 – 2.42)
PM <sub>10</sub>	471	<b>1.48</b>	<b>(1.15 – 1.90)</b>
Adjusted *			
NO <sub>2</sub>	453	1.13	(0.78 – 1.65)
O <sub>3-an</sub>	469	1.07	(0.73 – 1.58)
O <sub>3-sum</sub>	469	1.35	(0.80 – 2.28)
PM <sub>10</sub>	469	<b>1.46</b>	<b>(1.10 – 1.92)</b>
<b>b) symptoms (defined as asthma attacks or dyspnea or woken by an asthma attack or shortness of breath in the last 3 months)</b>			
	<b>n</b>	<b>OR</b>	<b>95% CI</b>
Crude			
NO <sub>2</sub>	465	0.91	(0.70 – 1.17)
O <sub>3-an</sub>	481	<b>1.39</b>	<b>(1.07 – 1.81)</b>
O <sub>3-sum</sub>	481	<b>1.63</b>	<b>(1.15 – 2.30)</b>
PM <sub>10</sub>	481	<b>1.36</b>	<b>(1.13 – 1.65)</b>
Adjusted *			
NO <sub>2</sub>	454	0.97	(0.74 – 1.28)
O <sub>3-an</sub>	470	1.29	(0.98 – 1.72)
O <sub>3-sum</sub>	470	<b>1.59</b>	<b>(1.10 – 2.30)</b>
PM <sub>10</sub>	470	<b>1.38</b>	<b>(1.12 – 1.69)</b>
<b>c) exacerbations (defined at least 1 hospitalizations or ER visits in the last year or oral CI in the last 3 months)</b>			
	<b>n</b>	<b>OR</b>	<b>95% CI</b>
Crude			
NO <sub>2</sub>	463	0.91	(0.65 – 1.27)
O <sub>3-an</sub>	479	1.09	(0.78 – 1.54)
O <sub>3-sum</sub>	479	<b>1.69</b>	<b>(1.07 – 2.66)</b>
PM <sub>10</sub>	479	1.21	(0.95 – 1.54)
Adjusted *			

NO <sub>2</sub>	452	1.05	(0.73 – 1.51)
O <sub>3-an</sub>	468	0.94	(0.65 – 1.37)
O <sub>3-sum</sub>	468	1.58	(0.97 – 2.59)
PM <sub>10</sub>	468	1.29	(0.99 – 1.67)

\* Adjusted for sex, age, body mass index, educational level, smoking and use of inhaled corticosteroids in the last year  
**bold** estimates make reference to estimates with a p<0.05