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Association between modelled traffic related air pollution (NO_2) and asthma score in ECHRS

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Abstract

The aim of this analysis is to study the association between air pollution and asthma among adults. For this goal, a previously developed "asthma score" was used.

Persons aged 25-44 years were randomly selected (1991-1993) and followed up (2000-2002) within the European Community Respiratory Health Survey (ECRHS-I and II). The asthma score was defined from 0 to 5, based on positive answers to symptoms reported for the last 12 months: wheeze/breathlessness, chest tightness, dyspnoea at rest, dyspnoea after exercise, and woken by dyspnoea. Participants' home addresses were linked to outdoor modelled NO_2 estimates for 2001. Negative binomial regression was used to model the asthma score.

The score from ECRHS-II was positively associated with NO_2 (Ratio of the Mean asthma Score (RMS) 1.23, 95% Confidence Intervals (CI): 1.09-1.38 for an increase of 10 $\mu g.m^{-3}$). After excluding participants with asthma and symptoms at baseline, the association remained (RMS 1.25, 95%CI: 1.05-1.51) and was particularly high among those reporting a high score in ECRHS-II. The latter probably reflects incident cases of asthma.

Our results suggest that traffic-related pollution causes asthma symptoms and possibly asthma incidence in adults. The asthma score offers an alternative to investigate the course and aetiology of asthma in adults.

Introduction

It is well known from time-series and other studies that fluctuations in air pollution levels are associated with short-term effects among asthmatics[1]. Evidence of adverse effects of air pollution on asthma outcomes and of a potential asthmogenic role of traffic-related local pollutants are far more often studied in children than in adults[2-4]. In adults, traffic related pollutants have been associated with cough, bronchitis and COPD[5-7] and living close to a major road has been associated with asthma-related symptoms[8]. An Italian study found indications of an association between nitrogen dioxide (NO_2) and asthma prevalence in young adults when stratified by different climates [9]. US veterans residing near a major road had higher prevalence of persistent wheeze [10]. One study found that health care use for asthma in adults was associated with traffic volume [11]. In a recent study, Mc Creanor et al reported that exposure to road traffic air pollution levels was associated with a decrease in lung function and with an increase in biomarkers of neutrophilic inflammation in asthmatics adults[12]. Air pollutants may amplify the inflammatory reactions in the airways, but in addition promote allergic disease in asthmatics[13-15]. Pollutant-induced oxidative stress could promote airway inflammation and, therefore, hyper responsiveness which may be one path to the development of asthma.

The European Respiratory Health Survey (ECRHS) has found a positive association between NO_2 and asthma incidence in adulthood [16]. In that analysis, ‘asthma incidence’ was defined in the traditional way, assuming asthma to be a well defined dichotomous phenotype with a specified time of onset (‘doctors diagnosed asthma’). However, as previously promoted, asthma can be defined as a continuous trait using a

grading scheme based on reported symptoms [17, 18]. Markers of asthma severity and major risk factors of asthma showed a significant linear association with this novel asthma score. Using a continuous measure of a complex disease has some appeal as it improves the power to identify risk factors. The score is also not affected by diagnostic practices, which may grossly vary between regions and also over time within the same area [18]. The aim of this study is to explore the association between the asthma score and traffic related air pollution estimated at follow-up. The concept of asthma taken as a continuous trait is rather novel and has not yet been explored in air pollution epidemiology, thus, the utility and possible interpretations of the score in this field will be discussed.

Methods

Study population

The details of the study are described elsewhere [19, 20]. Briefly, persons aged 25-44 years were randomly selected from the population for the ECRHS I carried out in 1991-1993 [20]. The follow-up (ECRHS II) took place during the period 2000-2002 [19] (mean response rate = 65.3%). Both surveys included an initial screening questionnaire, extensive interviewer led questionnaire, skin prick test, blood test for IgE, spirometry and methacholine challenge test. Ethical approval was obtained for each centre from the appropriate institutional or regional ethics committee, and written consent was obtained from each participant. From the 25 cities (8090 participants from the random sample) included in ECRHSII, 20 (6824 participants) had central air pollution data. Three of those cities were not included in the APMoSPHERE project (Reykjavik, Tartu and Basel,

n=1178). Erfurt (N=282) was excluded due to participant identifier linkage problems occurring during the geocoding procedure while protecting confidentiality of the participants' address data. In total, 4394 participants from the random sample have information on the asthma score and home outdoor modelled NO_2 at follow-up and 2921 participants have full information on all the covariates included in the final multivariate analysis.

Asthma score

The asthma score used in this study is one of the two previously developed [18] scores using data from ECRHS [17]. Two scores were proposed, one based on answers to eight questions, (where three included the term "asthma") and another based on positive answers to just the 5 questions dealing only with symptoms. The five symptoms were: wheeze and breathlessness, feeling of chest tightness, attack of shortness of breath at rest, attack of shortness of breath after exercise, and woken by attack of shortness of breath during the last 12 months.

This simplified score, used in this analysis, ranges from 0 through 5 and is independent of local trends in "asthma labelling" [18].

Covariates

We included in the analysis the following variables collected through a standardized questionnaire: sex, age, social class (in 5 groups based on the ISCO coding of the occupational history at ECRHS II and derived from the longest-held job during the follow-up period between ECRHS I and II), family history of asthma or atopy, smoking (no, former, current), pack years, exposure to second hand tobacco smoke, any exposure to dust, fume or gases at work, gas cooking and season of the interview.

We also included atopy defined as a concentration >0.35 $kU_A.L^{-1}$ for any specific IgE to cat (e1), house dust mites (*Dermatophagoides pteronyssinus* d1), *Cladosporidium* as indicator of mould (g6) or timothy grass determined using the Pharmacia CAP system (Pharmacia, Uppsala, Sweden).

Finally bronchial hyperresponsiveness (BHR) and percent of predicted forced expiratory volume in one second (FEV1) were also taken into account. BHR to methacholine was measured in eligible participants using one of two dosing schedules, one delivering methacholine to a maximum dose of 1 mg and the other to a maximum of 2 mg. Methacholine was delivered via a Mefar dosimeter (Mefar, Bovezzo, Italy), recorded 2 min after each inhalation and the test terminated when either a 20% fall in FEV1 had been achieved or the final dose given.

Modelled NO_2 concentrations with APMoSPHERE

NO_2 has been widely used in epidemiological studies as a marker for traffic-related air pollution.[21-23] As part of the APMoSPHERE project [24], 1km resolution emission maps were developed for the then 15 member states (EU15) by disaggregating national emissions estimates, categorised by sources of air pollution, on the basis of relevant proxies including population density, road distribution and land cover. The NO_x emission map was then used as the basis for modelling mean annual NO_2 concentrations using focal sum techniques, in a geographic information system. The model provides estimates of concentrations by calibrating the distance-weighted sum of the emissions (tonnes/km/year) in concentric rings (annuli) around each monitoring site to the monitored concentrations ($\mu g.m^{-3}$). Models were developed using monitoring data from the EU Airbase database. Models were calibrated using 714 background sites for 2001,

and validated by comparing predictions with observations for a separate set of 228 reserved background sites ($r^2 = 0.60$).

Participant's residential addresses were geocoded manually using an online mapping service (www.multimap.com). NO_2 at the place of residence of each participant at follow-up (ECRHS II) was obtained by intersecting the geographic coordinates of the address with the map of NO_2 concentrations.

Statistical analysis

Due to the score distribution, i.e. being a scale with a majority of zeros, the negative binominal regression model (with a log link) which allows for extra-Poisson variation is the most appropriate for modelling this score[25]. The results are expressed as ratios of the mean asthma scores. For NO_2 the effect for an increase of a 10 $\mu g.m^{-3}$ higher concentration is reported, corresponding approximately to the difference between the 5^{th} and the 95^{th} percentile in the city with lower levels of NO_2 (Umea).

In a first step we analysed the score cross-sectionally; thus in all the participants and adjusting for follow-up characteristics we analysed the association of NO_2 with the score at ECRHS II. The data was analysed pooled for all the centres but adjusted by centre. We report the crude association adjusted only by centre. We then conducted a multivariate analysis retaining all variables significantly associated with the score in the crude model in order to achieve a parsimonious model. Age was forced into the model. Effect estimates were derived for each centre and heterogeneity across the city specific estimates was examined by using standard methods for random-effects meta-analysis [26, 27]. A random-effect meta-analysis was also performed by geographical region: North (Sweden), Centre (Belgium, England, France) and South (Spain, Italy). The analyses

were stratified by sex, asthma, atopy, BHR and smoking status, all defined at baseline. Stratified sub-group analyses were performed by sex and several baseline characteristics such as asthma, atopy, BHR and smoking. The stratified models included all the above covariates except the stratification variable. Wald tests were performed to test the interactions between the variable used for the stratification and the NO_2 and associated p-values were calculated.

In a second step we studied the association between the score and NO_2 concentration, both defined at follow-up, in a sub-population reporting neither symptoms nor asthma at baseline. The same multivariate model and data pooling was adopted as in the above first step. This population may be considered a sample being in all likelihood free of asthma at baseline. Thus, the occurrence of symptoms at follow-up may be interpreted as new onset of symptoms, which may ultimately reflect incidence of asthma. While this notion may be questionable among those reporting only one symptom at ECHRS II, a high asthma score may reflect new onset of asthma. We thus performed a further analysis considering those with only one symptom at follow-up as participants free of symptoms and we compared them with participants reporting at least two symptoms. Next we considered those reporting one or two symptoms as participants free of symptoms, comparing them with participants reporting at least three symptoms.

The analyses were made using STATA 8. The criterion for statistical significance was set at a p value < 0.05.

Results

The study includes 4394 participants with both data on asthma and modelled NO_2 concentration, used as a marker of traffic related ambient air pollution. The distribution of the asthma score was skewed: 70 % of the study participants reported none of the asthma symptoms and scored 0. The mean score was 0.52 and the standard deviation 0.98. Table 1 shows the distribution of the score and NO_2 by centre ordered from North to South.

Table 1: Description of the score and NO_2 per centre

		Score at ECRHS I			Score at ECRHS II			NO_2* percentiles					
	N	% of 0	Mean	SD	% of 0	Mean	SD	5th	25th	50th	75th	95th	Max
Umea	147	80	0.39	0.97	79	0.4	0.97	8	11	12	14	17	19
Uppsala	478	79	0.39	0.91	77	0.45	1	9	11	16	20	33	43
Goteborg	318	73	0.51	1.06	76	0.4	0.87	18	23	27	29	34	41
Norwich	224	66	0.71	1.24	65	0.64	1.08	17	23	25	27	29	33
Ipswich	239	78	0.53	1.17	59	0.75	1.09	19	25	26	28	32	33
Antwerp	633	71	0.49	0.94	75	0.43	0.89	19	23	28	33	36	39
Paris	416	52	0.85	1.18	58	0.7	1.04	19	49	50	53	54	55
Grenoble	380	69	0.52	0.95	66	0.59	1.02	12	25	31	31	32	55
Verona	281	90	0.14	0.44	79	0.34	0.82	16	24	28	29	32	34
Pavia	192	79	0.37	0.87	74	0.42	0.89	12	15	19	24	27	31
Torino	73	86	0.23	0.68	83	0.34	0.92	30	36	38	41	42	44
Oviedo	139	66	0.57	1.01	60	0.7	1.14	13	24	30	32	34	34
Galdakao	360	77	0.34	0.74	80	0.32	0.74	13	20	25	33	36	40
Barcelona	250	79	0.32	0.73	73	0.46	0.88	30	53	57	59	62	63
Albacete	140	61	0.76	1.2	59	0.71	1.03	18	28	30	32	32	32
Huelva	204	74	0.52	1.04	56	0.83	1.23	26	30	33	34	35	44
Total	4394	72	0.49	0.99	70	0.52	0.98	11	21	28	33	54	63

* NO_2 modelled for 2001 (at ECRHS II)

Table 2 describes the distribution of the covariates. 55% of the participants are females. The distribution of the covariates between ECHRS I and II did not vary except for smoking, with a decrease of smokers in ECRHSII.

Table 2: Characteristics* of the participants at both surveys

	ECHRS I		ECHRS II	
N	4394	100	4394	100

Females	2433	55	2433	55
Age				
≤ 30	1467	33	NA**	NA**
30-35	864	19	777	17
35-40	922	21	897	20
40-45	1019	23	879	20
45-50	200	4	926	21
>50	NA**	NA**	998	22
Social Class at ECRHS II¤				
Managers & professionals non-manual	NA**	NA**	1230	27
Others non-manual	NA**	NA**	1912	43
Skilled manual	NA**	NA**	388	9
Semi-skilled or unskilled manual	NA**	NA**	446	10
Unclassified or unknown	NA**	NA**	501	11
Atopy	1046	29	995	29
Family history of asthma or atopy	1533	37	1533	37
Smoking				
Never	1967	44	1931	43
Former	984	22	1275	29
Current	1523	34	1260	28
Pack years (mean; standard deviation)	NA§	NA§	11	17
Exposure to second hand tobacco smoke	2622	59	1825	41
Predicted FEV1‡ (mean; standard deviation)	108	13	108	14

* N and % unless specified otherwise

** NA not aplicable, due to the design of the study

¤ Social class was produced with two different methods at both surveys, social class at ECRHS II takes into account the longest-held job during the follow-up period between ECRHS I and II

§ NA not aplicable, because only available for ECRHSII

‡ Percent predicted of the Forced Expiratory Volume in 1 second

The crude association between the covariates and the score is shown in Table 3. Season and any exposure to gas, dust or fumes at work were not associated with the score. The

RMS for each increase of 10 ug.m^{-3} of NO_2 is 1.15 (95% Confidence Intervals (CI) 1.05-1.25).

Table 3: Crude association (adjusted for centre only) between asthma score (5 items) at follow-up and follow-up characteristics in all the participants, expressed in the ratio of mean asthma score (RMS)

	RMS	95%CI	
NO_2 (per each increase of 10μg.m-3)	**1.15**	1.05	1.25
Females	**1.19**	1.06	1.34
Age at ECRHS II			
≤ 35	1.00		
35-40	1.12	0.93	1.35
40-45	0.97	0.80	1.18
45-50	0.94	0.78	1.14
>50	0.95	0.78	1.14
Social Class at ECHRS II			
I-II	1.00		
III non-manual	**1.27**	1.10	1.46
III manual	0.97	0.76	1.23
IV-V	**1.43**	1.16	1.77
Unclassified	1.16	0.94	1.43
Atopy at ECHRS II	**1.69**	1.48	1.94
Family history of asthma or atopy	**1.50**	1.32	1.70
Smoking at ECRHS II			
Never	1.00		
Former	1.15	1.00	1.32
Current	**1.52**	1.33	1.75
Pack years	**1.01**	1.01	1.01
Exposure to second hand tobacco smoke at ECRHS II	**1.39**	1.23	1.57
Predicted FEV1‡ at ECRHS II	**0.98**	0.97	0.98

Cooking done mainly with gas	1.07	0.93	1.24
Occupational exposure to dust, fumes or gases	0.98	0.90	1.07
Season of the interview			
Spring	1.00		
Summer	1.05	0.88	1.25
Fall	1.14	0.97	1.33
Winter	1.08	0.92	1.27

‡ Percent predicted of the Forced Expiratory Volume in 1 second

In the multivariate analysis the RMS for each increase of 10 ug.m^{-3} of NO_2 is 1.23 (95% CI 1.09-1.38) (Table 4).

Table 4: Multivariate association (adjusted per centre) between asthma score (5 items) at follow-up and follow-up characteristics in all the particiapants, expressed in ratio of means asthma score (RMS)

	RMS	95%CI	
NO_2 (per each increase of 10 μg.m-3)	**1.23**	1.09	1.38
Females	**1.28**	1.10	1.49
Age at ECRHS II			
≤ 35	1.00		
35-40	1.14	0.91	1.43
40-45	1.02	0.81	1.29
45-50	1.00	0.80	1.27
>50	1.13	0.89	1.42
Social Class at ECHRS II			
I-II	1.00		
III non-manual	**1.18**	1.00	1.39
III manual	0.95	0.71	1.26
IV-V	**1.28**	0.99	1.65
Unclassified	1.28	0.96	1.69
Atopy at ECHRS II	**1.64**	1.42	1.89
Family history of asthma or atopy	**1.40**	1.22	1.61
Smoking at ECRHS II			

Never	1.00		
Former	1.17	0.98	1.40
Current	**1.27**	1.04	1.56
Pack years	1.00	1.00	1.01
Exposure to second hand tobacco smoke at ECHRS II	**1.23**	1.06	1.43
Predicted FEV1‡ at ECRHS II	**0.98**	0.97	0.98

‡ Percent predicted of the Forced Expiratory Volume in 1 second

The association was homogeneous among centres (p-value 0.169); after excluding Torino, which had very large confidence intervals, the p-value for heterogeneity was still not significant (p-value 0.244) (Figure 1). We neither observed heterogeneity across the three geographic areas (p-value of homogeneity 0.947) (Figure 2).

After stratifying for baseline characteristics, all the associations were always positive, but the RMS was higher in males, in non-asthmatics, in atopics, in participants with BHR and in non and ex-smokers (Table 5). However, only the p-value for interaction for smoking was significant (RMS in non and ex-smokers: 1.30, 95%CI: 1.11-1.52; RMS in smokers: 1.07, 95%CI: 0.92-1.26; p-value for interaction: 0.005).

In participants with no asthma and no symptoms at baseline, the associations between NO_2 and asthma score was positive (RMS: 1.25, 95%CI: 1.05-1.50). When comparing participants reporting none or one symptom with those reporting a score ≥2 the effect estimates increased (RMS: 1.45, 95%CI: 1.03-2.05). The association became even higher when considering participants reporting a score ≥3 (RMS: 2.57, 95%CI: 1.31-5.04) (Table 5).

Table 5: Ratio of mean asthma score (5 items) at follow-up adjusted by follow-up characteristics per each increase of 10 $\mu g.m^{-3}$ of NO_2 stratified by different groups

	n	RMS	95%CI	p-value for interaction

All participants					
Crude	4394	**1.10**	1.05	1.16	
Adjusted for centre	3494	**1.15**	1.05	1.25	
Adjusted for all characteristics*	2921	**1.23**	1.09	1.38	
According to sex					
In males†	1350	**1.32**	1.12	1.56	
In females†	1571	1.14	0.97	1.34	0.13
Stratified by baseline characteristics					
In participants without asthma*	2696	**1.27**	1.11	1.45	
In participants with asthma*	224	1.07	0.88	1.30	0.176
In participants without atopy ‡	1779	**1.20**	1.02	1.41	
In participants with atopy ‡	728	**1.37**	1.14	1.65	0.628
In participants without BHR**	2165	**1.18**	1.02	1.37	
In participants with BHR**	250	1.27	0.94	1.72	0.634
In never and former smokers ††	2122	**1.30**	1.11	1.52	
In current smokers ††	799	1.07	0.92	1.26	0.005
In participants with no asthma and no symptoms at baseline	**Number of participants with symptoms**				
No symptoms against any symptom*	387	**1.25**	1.05	1.50	
No and one symptoms against 2, 3, 4 or 5 symptoms*	123	**1.45**	1.03	2.05	
No, 1 and 2 symptoms against 3, 4 or 5 symptoms*	44	**2.57**	1.31	5.04	

* adjusted for sex, age, social class, atopy, family history of atopy or asthma, smoking, exposure to second hand tobacco smoke, predicted percent of the forced expiratory volume in 1 second at follow-up

**BHR Bronchial hyperreponsiveness pd20<1 mg of metacholine

† adjusted for all the above except sex

‡ adjusted for all the above except atopy

†† adjusted for all the above except smoking

Discussion

We observed significant associations between traffic related air pollution and the asthma score, with similar findings across Europe.

To put the findings into context we refer to Table 4, showing that a rather modest change in NO_2 of only 10 $\mu g.m^{-3}$ resulted in a similar association to that between the score and being a current smoker. A contrast of 20 $\mu g.m^{-3}$ (a difference well within the range of ambient concentrations within European cities) was associated with a difference in asthma score as strongly as a family history of asthma or atopy, which may be a good proxy for genetic factors. Our estimates are not easily comparable with other studies, as the use of this particular score is rather novel and the ratio of the mean score estimated with negative binomial regression is not directly comparable with Odds Ratios (OR) obtained with logistic regression. Nevertheless, our estimates for well-known risk factors of asthma symptoms such as smoking and family history of asthma or atopy are in the same range as those described in the literature. In a study among young adults, the OR for asthma like symptoms varied from 1.74 (shortness of breath) to 3 (wheezing) for smoking [28]. In a study conducted in Northern Europe the OR of presenting wheezing in the last 12 months ranged from 1.5 to 3.6 depending on the intensity of smoking. In the same study, the OR for wheezing in the last 12 months was 2.24 for family history of asthma [29]. Regarding air pollution, an increase of almost 20 $\mu g.m^{-3}$ in NO_2 levels was moderately associated with tightness in the chest (OR = 1.11) and wheeze (OR = 1.11) in an Italian study [9]. In a Swedish study, NO_2 values above 19 $\mu g.m^{-3}$ measured at the address was associated with a moderate increase in asthma symptoms (OR = 1.21) [30]. Our air pollution estimates seem higher than what has been described, but the association

between air pollution and asthma symptoms in adults has not been frequently studied and comparability with the score is limited.

The score comes with several advantages as compared to a dichotomous definition of asthma. As previously shown, it may be a valuable instrument to reduce misclassification bias due to dichotomization of asthma [17, 18]. The use of a continuous measure increases the power to detect risk factors, a notion supported by our findings. The use of a score is a novel approach to not only characterize asthmatic symptoms but an approach for 'asthma severity' and to investigate related risk factors [17, 18]. Furthermore, the incidence of 'doctors diagnosed asthma' is relatively low, requiring large studies, and the time of onset of asthma is in fact hard to define and participant to diagnostic attitudes of physicians. Moreover, asthma is a complex phenotype and the clinical severity (symptoms) indeed relevant for patients. To study associations between risk factors and a complex disease with all these features, the use of continuous traits is thus appealing. Asthma is a disease that is probably the result of a long process and it is not easy to define the presence or absence of the disease at some definite point in time nor to identify the time of "onset" [31]. These difficulties could lead to misclassifications and the use of the symptoms-based score resolves some of the challenges faced with a dichotomous definition of asthma.

In air pollution epidemiology, the continuous score is appealing as associations with air pollution are usually low across the observed ranges of pollution, thus power is limited for disease incidence (Y/N). Resolving the problem of geographic variation in diagnostic patterns encountered with "doctor diagnosed asthma" is particularly attractive in air

pollution research where the pooling of studies, cities, and countries is in fact attractive not only to increase the power but to also investigate susceptibility factors.

The disadvantage of the score though lays in the challenges of its interpretation, which may be participant to continued debates, in particular in the context of air pollution research. The question emerges whether the score, as used in our analyses, reflects acute effects of air pollution or its long-term chronic contribution to the underlying pathology leading to asthma incidence. We, thus, discuss these two perspectives in more detail.

On the one hand, in a cross-sectional survey of the general population, asking about symptoms experienced during the last 12 months, the score may reflect the cumulated "acute conditions" triggered by air pollution. Among asthmatics, symptoms reflect the inherently variable phenotype of asthma; thus, the score may capture the course and severity/control of asthma, and our finding may be interpreted as a cumulative summary (last 12 months) of acute effects of air pollution on asthma symptoms, which may be a proxy of asthma severity. In fact, in a recent study investigating the cross-sectional relationships between asthma severity and background annual concentrations of air pollutants[32], this score was used as a marker of the activity of asthma along with another asthma severity score, both assessed for the last twelve months. Both scores were associated with ambient home outdoor ozone concentrations, whereas no association was observed with NO_2. This inconsistency may in part be explained by the large spatial scale of the NO_2 model used in that analysis (grids of 4 km^2), thus, spatial heterogeneity may not have been adequately captured.

With this interpretation of "cumulative summary", our findings are in line with the body of evidence suggesting acute effects of air pollution [1]. The score may, thus, be used

efficiently in future studies to evaluate whether acute effects of pollution on asthma performance may change in response to changes in treatments and/or in the composition of pollutants due to changes in engine technology, fuel formulation, or the composition of the vehicle fleets.

On the other hand, the asthma score may also be considered as a tool to identify the incidence of asthma of various levels of severity, if we accept the notion of asthma being a continuous trait. With this interpretation, results ought to be compared with traditional "incidence studies" such as our own analysis of the ECRHS data. In this work, we used the dichotomised definition of new onset of "doctor diagnosed asthma". An increase of 10 $\mu g.m^{-3}$ of NO_2 was associated with asthma incidence (OR 1.43 95% CI 1.02-2.01) [16]. The use of the dichotomous definition, however, presented limitations that could be overcome with the score. In adults, the definition of "asthma" remains a challenge and the score clearly complements attempts to understand better the aetiology of this disease, independent of secular trends in the labelling of "asthma" by the community of physicians. In a previous publication within the ECRHS, Chinn et al have shown that, from ECHRS I to II, the prevalence of asthma increased while the prevalence of symptoms did not, suggesting a change over time in the diagnosis or treatment of asthma [33]. The results shown here using the asthma score are in the same direction as those we found in the previous analysis. Given the inherent variability in symptom occurrence in both asthmatics and non-asthmatics, the mere "onset" of only one symptom among those free of symptoms and asthma at baseline is unlikely to reflect incidence of asthma. This notion may be more acceptable among those presenting a high score at follow-up. Our last analysis were restricted to participants without asthma nor symptoms at baseline and

the particularly strong effects among those presenting at least two symptoms at ECRHS II would be in line with the interpretation of an effect of pollution on onset of asthma in adults. This 'incidence interpretation' of the score comes with a caveat, as Sunyer et al. have shown substantial changes in the score, with many participants losing or gaining one or more symptoms [18]. As a consequence, it may be questionable to consider those with a change from no disease at baseline to a very low asthma score as 'incident cases'. However, a "high score" phenotype has been shown to be particularly strongly associated with doctor diagnosed asthma [18], thus our related finding may indicate a role of pollution in new onset of asthma in adults. This interpretation is consistent with our previous finding based on the more traditional definition of "asthma incidence", using asthma at follow-up among those free of the disease at baseline [16]. That latter approach is less ambiguous in the interpretation regarding acute and chronic effects as "doctor's diagnosis" does reflect a "chronic condition" rather the cumulated acute expression of the disease. Further research on the use and interpretation of the score as a measure of the course but also the incidence of this chronic disease will be useful to enhance our etiologic understanding of asthma.

We characterized exposure to pollution for approximately the same period as the assessment of the score. While a strength in the assessment and interpretation of 'acute effects', the availability of air pollution measurements only for the follow up period is a limitation that may affect the incidence interpretation of this analysis. Pollution levels may have changed differently across cities and participants who moved to another residence would have inherently larger misclassification of exposure. Although trends in air pollution are often spatially correlated across areas, this simplification might be less

true across the very large European geographic area. However, based on network data available in several cities, one can assume that changes in air quality differed across European areas, which may bias toward null findings.

It is important to note that the association between the NO_2 and the asthma score were rather homogenous for all the cities included in this analysis. The homogeneity was even stronger when taking into account geographical area instead of city. This supports a causal interpretation of our findings.

We found a stronger effect of NO_2 in non and ex-smokers compared to smokers. Smoking might be considered as an effect modifier but previous studies have not been consistent and it remains unclear whether smokers are more or less susceptible to the effects of air pollution than non-smokers. In the SAPALDIA study, Zemp et al found that smokers reported more asthma-like symptoms than non-smokers, suggesting an effect modification by smoking status [7]. It was also suggested, however, that smokers have altered lung function and an increase in mucus, decreasing the air pollutant amount in some region of the lungs and decreasing the susceptibility of smokers to air pollution [34].

The strengths and the limitations of the exposure assessment have been discussed previously [16]; by geocoding home addresses of ECRHS participants we were able to assign an ambient NO_2 concentration derived from the APMoPSPHERE map to each participant. Nevertheless, it is also important to take into account that the APMoPSPHERE map has a spatial resolution of one square kilometre which may not capture all the variability, especially in cities with high population density.

In conclusion, NO_2 is associated with asthma score suggesting that traffic related air pollution causes asthma symptoms in adults. The stronger effects among those free of asthma and symptoms at baseline may indicate a role of pollution in the onset of asthma as well. This needs further investigation. The use of the asthma score offers very attractive alternatives to investigate the aetiology of asthma and the course of this disease in adults.

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Figure 1

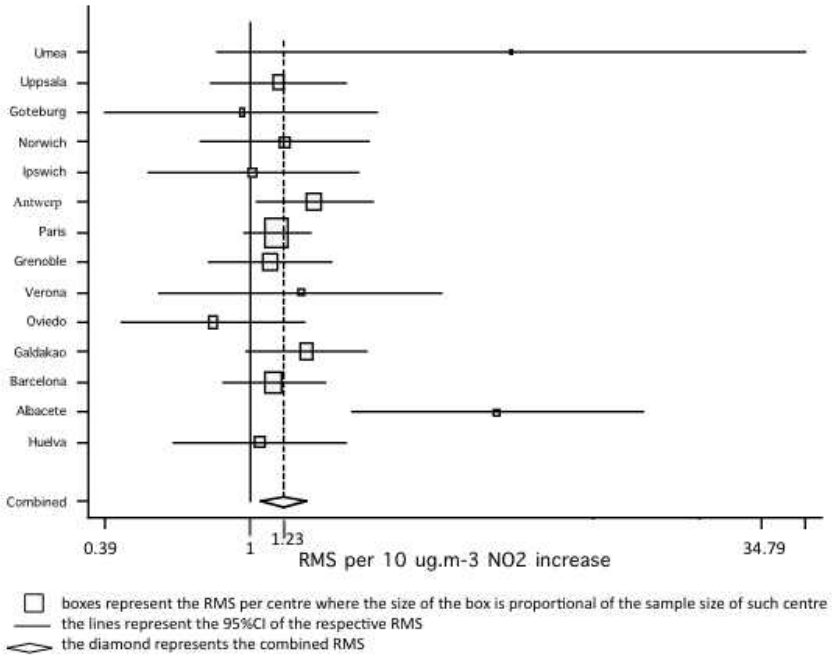
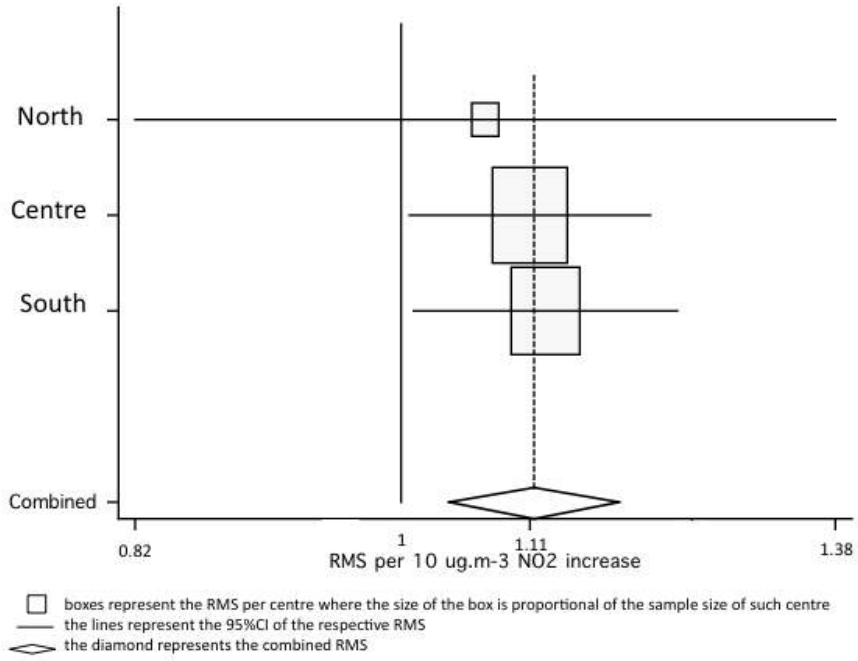


Figure 2


North
Centre
South
Combined
0.82
1
1.11
1.38
RMS per 10 ug.m-3 NO2 increase
boxes represent the RMS per centre where the size of the box is proportional of the sample size of such centre
the lines represent the 95%CI of the respective RMS
the diamond represents the combined RMS