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Revised version – Allergy

Total serum IgE levels are associated with ambient ozone concentration in asthmatic adults

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

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ABSTRACT

Background: Effects of air pollution exposure on IgE-mediated response in asthmatics are poorly investigated. The aim was to examine the relationship between air pollution concentrations and total IgE levels in adult asthmatics.

Methods: The present study relates to the 369 asthmatic adults from the French Epidemiological study on Genetics and Environment of Asthma (EGEA), with both available total serum IgE measurements and air pollution concentrations. Geo-statistical models were performed on 4km x 4km grids to assess individual outdoor air pollution exposure. Annual outdoor concentrations of ozone (O₃), nitrogen dioxide (NO₂), sulphur dioxide (SO₂), and particles smaller than 10µm size (PM₁₀), and concentrations of summer ozone were assigned to subject's home address.

Results: The geometric mean of total IgE was 161 IU.mL⁻¹ and the average of ozone exposure was 44.9 ± 9.5 µg.m⁻³. Ozone concentrations were positively related to total IgE levels and an increase of 10 µg.m⁻³ of ozone resulted in an increase of 20.4% (95% CI = 3.0-40.7) in total IgE levels. Adjustment for age, sex, smoking habits and previous life in the countryside did not change the results, and an increase of 19.1% (2.4-38.6) in total IgE was observed with ozone. Negative associations observed between NO₂ and total IgE levels disappeared after including ozone in the models. Neither SO₂ nor PM₁₀ were correlated with total IgE levels.

Conclusions: Results suggest that ozone or related ambient pollutants may up-regulate total IgE levels among asthmatic adults.

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INTRODUCTION

Ambient air pollutants are well known causes of symptom exacerbations among asthmatics (1,2). However, the role of air pollution in the onset of asthma and allergic diseases is far less clear and increased incidence in these diseases across the past decades is usually assigned to other environmental factors and 'western life style' (3).

Despite the strong association of total IgE with asthma over the life span (4), the literature on the potential association of air pollution with total IgE is scanty. One study conducted in adults observed higher total IgE related to more polluted area (5), whereas two studies showed inconsistent results in children exposed to NO₂, PM_{2.5} and soot (6,7). None of them assessed ozone exposure. The strong tracking of IgE over the life span evidenced by longitudinal studies suggests that it may be a useful indicator to focus on the investigation of long-term effects of ambient air pollution. Whereas direct adaptive immune response does not explain the role of air pollutants in allergic diseases, various mechanisms may be involved, especially oxidative stress with consequences on innate immunity (8), and up-regulation of the T helper type 2 (Th2) response (9,10), characterized by high IgE production. Further, modification of responses to allergens by gaseous pollutants has also been suggested, but results are debated (8,11). Similarly to smoking for which the role on total IgE is well known (12,13), it is biologically plausible that particles and gaseous air pollutants, such as ozone, may result in increased total IgE levels.

The purpose of this analysis is to investigate the relationships between the levels of total serum IgE and modelled home outdoor air pollution concentrations among adult asthmatics of the French Epidemiological study on the Genetics and Environment of Asthma (EGEA).

METHODS

Population study

EGEA is a case-control and family study. The protocol has been described elsewhere (14). Briefly, asthmatic cases, living in pre-defined geographical areas were recruited from hospital chest clinics in five French cities (Paris, Lyon, Marseille, Montpellier, and Grenoble) between 1991 and 1995. Due to recruitment constraints, the number of asthmatic probands varied according to cities from 36 to 121. Asthmatic relatives were recruited from cases. Subjects answered to a detailed questionnaire regarding respiratory symptoms, environment and treatment. The present study includes the 369 asthmatic adults with available IgE measurement and available modelled air pollution concentrations. Within each city, subject's residences spread across large geographic areas, ranging from 300 km² (for the area of Lyon) to 9300 km² (for the area of Marseille).

Health assessment

Total serum IgE (in international units (IU) per millilitre) were measured by immunoassay (Phadebas PRIST technique; Pharmacia Diagnostics, AB, France). All determinations were performed in one central laboratory (Lyon Pasteur Institute). Skin Prick Tests (SPT) were performed for 11 allergens: cat, *Dermatophagoides pteronyssinus*, *Cladosporium herbarum*, *Alternaria tenuis*, timothy grass, olive, birch, *Parietaria judaica*, ragweed, *Aspergillus*, and *Blatta germanica*. Negative (uncoated) and positive (histamine) SPT controls were used. Atopy was defined as having a positive skin test (≥ 3 mm than the control) to at least one of the 11 allergens. Methacholine bronchial challenge test was performed, except for those with a forced expiratory volume in 1 second (FEV_1) $< 80\%$ predicted or post-diluent $FEV_1 < 90\%$ at baseline. Bronchial hyperresponsiveness (BHR) was defined as $\geq 20\%$ decline of FEV_1 for a methacholine cumulative dose ≤ 4 mg ($PD_{20} \leq 4$ mg).

Air pollution exposure assessment

Residential addresses of participants were geo-coded. Home outdoor air pollution levels for each subject were assigned by deriving concentration estimates from a geo-statistical model carried out by Geovariances for the French Institute of Environment (IFEN) and the French Agency for Environment and Energy (ADEME) for the year 1998 for ozone (O_3), nitrogen dioxide (NO_2), and sulphur dioxide (SO_2) (15). Additional data were explored for particulate matter smaller than $10\mu m$ in size (PM_{10}) from concentrations of the year 2004 since the number of monitors recording PM_{10} concentrations was insufficient in 1998. Common geostatistical interpolation techniques (cokriging-like techniques) (16) have been applied to estimate air pollution at unsampled locations (17); the estimation process, based on measured concentrations, took into account the spatial structure of each pollutant. The interpolation was performed for annual mean concentrations from background monitoring stations of the ADEME network on a $4km \times 4km$ grid covering entire area of France. Land cover was integrated to the interpolation process and cofactors specific to each pollutant taken into consideration. Road network, population density and emission registries were used in the assessment of NO_2 , industrial emissions of sulphur oxides for SO_2 , emission inventory of black smokes for PM_{10} , and altitude for ozone. Annual means for O_3 , NO_2 , SO_2 and PM_{10} as well as summer ozone (summer O_3) assessed from the monthly means from April to September were assigned to each individual's home address.

Environmental factors

Pollen season was assessed for each French geographic department of the subject's home addresses. Pollen counts were assessed by a volumetric monitor located in each of the five cities. The data were collected by the National Network for Aerobiological Monitoring (RNSA) and were available on the RNSA website (18). Subjects were classified as exposed to the pollen season when their blood samples were drawn in months with mean pollen count greater than 480 pollen grains per cubic metre. Smoking habits (never / ex / current smokers) and country living (having lived at least one year in the country side), previously shown to be associated with total IgE levels in the EGEA study were considered in the analyses (12,19).

Data analyses

Analyses have been performed on \log_{10} (IgE) and descriptive results are expressed in geometric means (GM). Statistical methods included χ^2 test, analyses of

variance and correlations coefficients. Relationships between IgE levels and air pollution exposure were assessed with multiple linear regressions on logIgE. For a better understanding, results are expressed in IgE percent change, for a 10 $\mu\text{g.m}^{-3}$ increase in O₃, summer O₃, NO₂ and SO₂ and for a 2 $\mu\text{g.m}^{-3}$ increase in PM₁₀ corresponding to the inter quartile range percentile 75th minus percentile 25th) of these pollutants, according to the formula $(10^{(\beta)} - 1) \times 100$ (where beta (β) is the regression coefficient). Due to the familial aggregation of the data, generalized estimated equations (GEE) were systematically performed to take into account dependence between observations, using MIXED procedures. Significance was assessed at the 5% two-sided level. All statistical analyses were done using SAS version 9.1 (SAS Institute, Inc., Cary, NC).

RESULTS

Characteristics of the population are presented in table 1. The average age of the 369 asthmatic adults was 37.2 years. The geometric mean for the total serum IgE level was 161 IU.mL⁻¹. Nearly 75% of the subjects were atopic. Total serum IgE levels in asthmatics decreased significantly with age and were significantly higher in men than in women, in current smokers than in never smokers or ex-smokers (237 IU.mL⁻¹ vs. 146 IU.mL⁻¹, p=0.007), in atopics than in non-atopics, and in bronchial responsive subjects than in non-responsive subjects (table 2).

Air pollution exposure

Home outdoor air pollution concentrations are described in table 3. Exposure contrasts, expressed as the ratio between the 75th percentile and 25th represented a 2.3-fold spatial difference for SO₂, a 1.3-fold difference for NO₂, a 1.2-fold difference for annual O₃ and summer O₃, and 1.1-fold difference for PM₁₀ concentrations. The range of exposure was 0.6-28.3 $\mu\text{g.m}^{-3}$ for SO₂, 15.4-60.7 for NO₂, 27.8-80.7 for O₃, 39.3-99.2 for summer O₃, and 14.0-28.3 for PM₁₀. O₃ and NO₂ were negatively associated (r=-0.72) while both ozone indicators were positively correlated (r=0.97). The distribution of the air pollution concentrations in each centre is shown in table 4.

Association of total serum IgE levels with air pollution exposure

Total serum IgE levels were positively and significantly associated to both indicators of ozone. Crude results were similar to those adjusted for age, sex, smoking habits, and country living (table 5). The negative association between IgE and ambient NO₂ concentrations disappeared in the two-pollutant models including both NO₂ and O₃. Compared to the single pollutant models, the effect size of NO₂ on IgE decreased in the two-pollutant (NO₂ and summer O₃) model by 57%, whereas the estimate of summer O₃ only decreased by 25%. No interaction was observed between ozone and NO₂ for the relation with total IgE (p interaction = 0.64 and 0.57, respectively for O₃ and summer O₃). After exclusion of subjects with high exposure to NO₂ (\geq 75th percentile), total IgE levels remained associated with ozone (table 6). No association was observed between total IgE levels and SO₂ or PM₁₀.

The observed relationship between ozone and total IgE level did not differ significantly according to sex, smoking habits or participation during pollen season (table 5). Effects of ozone remained significant in some subgroups, namely in men and in subjects examined out of the pollen season. Models adjusted for centre (city) indicated heterogeneity of effects across cities. Effect estimates remained unchanged with adjustment for centre but the confidence interval widened and included the no-

effect level. None of the city-specific estimates reached statistical significance (data not shown).

DISCUSSION

The present results show a positive association between home outdoor annual ozone concentrations assessed with geostatistical methods and total IgE levels in adult asthmatics. Associations were not sensitive to adjustment for neither covariates nor the season of IgE measurements. As the observed association is biologically plausible, the present findings may contribute to a better understanding of the effects of air pollution on asthma.

Strengths and weaknesses

A major strength relates to the well characterized asthmatics included in the EGEA, which leads to minimize misclassification biases. Total serum IgE measurements were available for most of the subjects and underwent a strict quality control. Another strength of the study is to have individual home-based modelled concentrations of various air pollutants. However, the grid size of 4 x 4km was rather crude. This comes with some inherent albeit non-systematic misclassification of exposure. While this is less the case for secondary pollutants, such as ozone, the spatial scale is too crude for primary pollutants, and for markers of traffic related pollution such as NO₂ with substantial spatial heterogeneity (20). Thus, our study does not fully capture traffic related exposure, although NO₂ models took into account land cover, emission registries, road network and population density. As a consequence, our estimates of NO₂ may underestimate the associations of traffic-related to IgE. Further studies are needed with more precise estimates of NO₂. The grid size may be sufficient for O₃. The residential areas covered a region more than twenty times larger than the city areas, resulting in considerable contrast in ambient O₃ concentrations within each centre.

Pollen exposure may be a source of confounding if correlated with ambient air pollution or if IgE increase related to pollen may interact with the investigated association between pollution and IgE. It has been shown that O₃ may amplify the response to aeroallergens (21). However, we used total IgE rather than specific IgE. It is known that the non specific IgE constituting the non sensitive fraction of the total IgE (22) could not be sensitive to pollens. We had no individual pollen data available to adjust for acute exposure. However, the analysis stratified by the season of participation showed that the relation between O₃ and IgE was similar among those who participated during the pollen season and the others. This suggests that acute pollen exposure is unlikely to bias our main findings. A formal assessment of the acute effects of pollen and its interaction with O₃ would require another study design such as panel study.

The substantial North-South gradient of ozone concentrations in France may partly explain the observed heterogeneity of ozone effects across centres. Adding centre in the model may lead to some over-adjustment. As none of the city-specific estimates reached statistical significance, it is impossible to evaluate the reasons for the heterogeneity.

The positive association with ozone and the negative association with NO₂ are consistent with the previous study from the French 6C study conducted in more than 9000 children (23) where O₃ concentrations were positively related to positive SPT, whereas NO₂ concentrations were inversely associated to SPT. This can be explained with the strong negative correlation between O₃ and NO₂. In two-pollutant models, this

'protective' effect of NO₂ disappeared while the associations of O₃ remained rather strong. This suggests the NO₂ findings to be spurious due to confounding by O₃. The O₃ models do not account for local scavenging of O₃ in proximity to streets as an important primary source of NO_x emissions (24), thus the assigned O₃ concentrations may be systematically overestimated among subjects living close to busy roads. Results, however, showed that the association of ozone with IgE remained after exclusion of high exposure to NO₂, further supporting an effect of ozone.

Epidemiological evidence

While no epidemiological study has investigated the relationship between ambient ozone and total IgE, few studies have evaluated IgE associations with other urban air pollutants. Studies examining air pollution effects on human immunological response found inconsistent results. A geographic comparison of IgE levels across two German cities, namely Erfurt in former Eastern Germany and Hamburg, reported lower IgE in the western city (5). While Erfurt had clearly higher levels of SO₂ and suspended particles at that period, many other factors differed between East and West Germany as well, limiting the interpretation of these findings. Among Dutch children of the ISAAC study, total serum IgE was positively associated with ambient NO₂ and soot, but not with PM_{2.5}, measured at school (6). In another Dutch study, total IgE of young children aged of four years from a prospective birth cohort, were not associated with cumulative exposure of NO₂, PM_{2.5} or soot (7). However, results observed in children cannot be extrapolated to adults, due to the immaturity of the immune system in children.

There is some evidence that particles or diesel exhaust particles could increase IgE levels (11,25) and our null findings for PM₁₀ contrast with this literature. Unfortunately we had no information regarding the smaller size fractions such as diesel particles or PM_{2.5}, which may be more relevant. Moreover, it should be noted that contrasts in PM₁₀ exposure were rather small within our population. No effect of SO₂ - known for its irritant and bronchoconstrictive effects - on IgE levels was observed in our sample.

Biological plausibility

It is well known that ozone, through its oxidative properties leads to airways inflammation. Ozone generates reactive oxygen species, directly or indirectly following to peroxidation of the polyunsaturated fatty acids in the lipidic membrane, leading to activation of transcription factors such as NF-κB (26,27). Increased expression of pro-inflammatory interleukins then occurs, including Th2 cytokines such as IL-4 (9,10). The increased respiratory mucosal permeability related to peroxidation could also facilitate the penetration of inhaled allergens (26,28,29). Ozone is an innate immune stimulus, which significantly up-regulates cell surface molecules such as mCD14 and increases antigen presentation, favouring then a Th2 profile (30). While increased expression of eosinophilic cationic protein (31) or production of IL-5 (32) have been observed following acute exposure to ozone in asthmatics, the long-term immunologic effects of chronic exposure to ozone have not been studied. As previous observations have shown increased in IL-4 in relation to the oxidative exposure to cigarette smoking, it can be hypothesized, that among asthmatics, already IL-4 up-regulated, chronic exposure to ozone increases total IgE by a mechanism similar to smoking (33). Our observational study cannot distinguish direct effects of O₃ from indirect effects due to O₃ reaction products. As suggested in a simulation of indoor air chemistry, ozone may enhance the formation of secondary reaction products of volatiles organic compounds which in turn

play a role in sensitization (34). Overall, the findings support the potential role of ozone in the up-regulation of IgE.

In conclusion, results suggest that exposure to ozone may increase total IgE in adult asthmatics. Further research, in particular longitudinal studies, is needed to replicate this finding and to assess the potential role of chronic exposure to oxidants in the general or occupational environment on IgE, besides smoking or ozone.

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Table 1: Population characteristics of the asthmatic adults

	Asthmatic adults
Number of subjects	369
Familial status	
asthmatic cases (family probands), %	53.1
asthmatic relatives of probands, %	46.9
Sex, males, %	51.2
Age, mean ± sd	37.2 ± 13.2
IgE, GM [95% CI], (IU.mL⁻¹)	161 [10-2554]
Atopy, yes, %	72.6
Smoking habits	
never smokers, %	51.2
ex-smokers, %	27.5
current smokers, %	21.3
Educational level	
primary, %	31.1
secondary, %	26.7
university, %	42.2
Country living during ≥ 1 yr, %	50.8
Pollen season at time of blood draw, %	36.6

sd: standard deviation; GM: geometric mean.

Table 2: Association of various individuals' characteristics with total IgE levels

	IgE (IU.mL ⁻¹) GM (95% CI)	p value
Number of subjects	369	
Sex		
men (n=192)	206 (20-2140)	
women (n=177)	123 (6-2682)	< 0.001
Atopy		
no (n=99)	71 (4-1351)	
yes (n=262)	215 (19-2472)	< 0.001
BHR		
no (n=42)	67 (4-1173)	
yes (n=137)	192 (12-3126)	< 0.001
Smoking habits		
never smokers (n=188)	152 (9-2632)	
ex-smokers (n=101)	134 (11-1588)	
current smokers (n=78)	237 (14-3943)	0.02
Educational level		
primary, % (n=92)	162 (3-2518)	
secondary, % (n=79)	141 (9-2122)	
university, % (n=125)	137 (7-2768)	0.69
Country living during ≥ 1 yr		
no (n=181)	172 (10-2928)	
yes (n=187)	150 (10-2254)	0.35
Pollen season at time of blood draw		
no (Aug-Jan) (n=234)	160 (10-1460)	
yes(Feb-July) (n=135)	163 (10-2752)	0.90
Centres		
Paris (n=82)	150 (11-2109)	
Lyon (n=83)	153 (9-2650)	
Marseille (n=49)	193 (15-2509)	
Montpellier (n=41)	241 (19-3101)	
Grenoble (n=114)	140 (8-2587)	0.23

GM: geometric mean

Table 3: Description and correlation coefficients of home outdoor assigned air pollution concentrations assessed in asthmatic adults from the EGEA study

	mean ± sd, µg.m ⁻³	median (p25-p75), µg.m ⁻³	Pearson coefficients				
			O ₃	summer O ₃	NO ₂	SO ₂	PM ₁₀
O₃	44.9 ± 9.5	43.1 (39.3-48.1)	1	0.97**	- 0.72**	- 0.32**	0.12*
summer O₃	62.3 ± 10.9	61.4 (56.9-67.6)		1	- 0.69**	- 0.26**	0.32**
NO₂	35.6 ± 9.5	35.4 (29.3-39.1)			1	0.56**	0.20*
SO₂	9.9 ± 5.5	8.6 (5.8-13.5)				1	0.59**
PM₁₀	20.8 ± 2.5	20.8 (19.8-21.6)					1

* p ≤ 0.01, **p ≤ 0.001

sd: standard deviation; p25 - p75: 25th-75th percentiles.

Table 4: Distribution of the air pollution concentrations in each centre

	Paris n=82	Lyon n=83	Marseille n=49	Montpellier n=41	Grenoble n=114
O₃ (µg.m⁻³)					
mean ± sd,	36.7 ± 6.3	44.2 ± 2.8	55.1 ± 8.1	61.0 ± 3.7	41.0 ± 4.6
median(p25-p75)	37.2 (30.9-42.6)	44.2 (42.9-46.2)	50.8 (48.1-61.3)	61.8 (59.2-62.9)	40.7 (38.2-42.1)
Summer O₃(µg.m⁻³)					
mean ± sd,	48.9 ± 6.3	63.0 ± 3.0	74.5 ± 7.9	78.8 ± 4.0	60.1 ± 4.8
median(p25-p75)	50.0 (43.5-53.1)	62.9 (62.0-64.7)	71.8 (68.3-80.9)	79.8 (76.8-80.9)	60.3 (56.9-60.7)
NO₂(µg.m⁻³)					
mean ± sd,	41.8 ± 12.2	39.5 ± 6.8	29.5 ± 7.4	27.7 ± 6.9	33.6 ± 5.5
median(p25-p75)	37.4 (33.4-54.7)	38.7 (34.4-46.9)	28.0 (22.6-34.8)	27.0 (22.4-32.6)	35.4 (29.4-38.7)
SO₂(µg.m⁻³)					
mean ± sd,	10.9 ± 4.7	10.9 ± 3.9	15.5 ± 8.0	4.8 ± 2.7	8.1 ± 3.6
median(p25-p75)	11.7 (6.8-14.8)	11.8 (7.3-13.7)	16.1 (8.6-22.1)	4.2 (2.9-5.9)	7.7 (4.6-10.7)
PM₁₀(µg.m⁻³)					
mean ± sd,	18.6 ± 1.9	21.1 ± 1.3	24.7 ± 2.9	20.4 ± 1.5	20.5 ± 1.2
median(p25-p75)	18.8 (17.1-20.2)	21.2 (20.5-22.3)	25.4 (23.2-26.7)	20.6 (19.4-21.3)	20.8 (20.1-21.4)

sd: standard deviation; p25 - p75: 25th-75th percentiles

Table 5: Percent change in total IgE for home outdoor assigned air pollution concentrations among asthmatic adults

	n	IgE % change*	Lower 95% CI	Upper 95% CI
Single-Pollutant Model				
O₃				
crude model	369	20.4	3.0	40.7
adjusted model [†]	367	19.1	2.4	38.6
summer O₃				
crude model	369	17.0	2.2	33.9
adjusted model [†]	367	16.9	2.5	33.2
NO₂				
crude model	369	-14.4	-26.7	-0.0
adjusted model [†]	367	-14.4	-26.4	-0.4
SO₂				
crude model	369	-0.6	-24.0	30.0
adjusted model [†]	367	-6.7	-27.9	20.8
PM₁₀				
crude model	369	3.5	-8.1	16.7
adjusted model [†]	367	2.4	-8.7	14.7
Two-pollutant model				
crude model				
O ₃	369	16.3	-6.8	45.2
NO ₂	369	-4.7	-23.6	18.9
adjusted model[†]				
O ₃	367	13.8	-7.9	40.6
NO ₂	367	-6.3	-24.2	15.7
Two-pollutant model				
crude model				
summer O ₃	369	12.9	-6.2	35.8
NO ₂	369	-5.9	-23.9	16.4
adjusted model[†]				
summer O ₃	367	12.6	-5.5	34.3
NO ₂	367	-6.2	-23.4	15.0

* Percent change in total IgE, expressed for an increase of 10 µg.m⁻³ of O₃, summer O₃, NO₂ and SO₂ and for an increase of 2 µg.m⁻³ of PM₁₀, corresponding to the inter quartile range (percentile 75th minus percentile 25th) of these pollutants.

[†] Models were adjusted for age, sex, smoking habits, and country living and took into account familial dependence.

Table 6: Percent change in total IgE per 10 $\mu\text{g.m}^{-3}$ increase in home outdoor O_3 among subgroups of asthmatic adults

	O_3				summer O_3			
	IgE % change*	Lower 95% CI	Upper 95% CI	p_i	IgE % change*	Lower 95% CI	Upper 95% CI	p_i
All subjects	19.1	2.4	38.6		16.9	2.5	33.2	
Sex				0.45				0.39
men (n=190)	21.0	1.0	45.0		17.8	0.6	37.9	
women (n=177)	13.7	-11.5	46.0		12.7	-9.3	40.0	
Smoking habits				0.75				0.91
never smokers (n=188)	22.6	-0.22	50.6		19.1	-0.6	42.8	
ex-smokers (n=101)	19.6	-7.6	54.8		14.6	-8.0	42.6	
smokers (n=78)	14.7	-17.2	58.8		17.4	-10.8	54.3	
Pollen season at time of blood draw				0.71				0.60
during pollen season (n=134)	21.1	-4.3	53.3		17.0	-5.1	44.2	
out of pollen season (n=233)	21.5	-0.4	48.1		19.5	1.0	41.4	
NO_2 exposure				0.69				0.84
$\text{NO}_2 < 75^{\text{th}}$ percentile (n=273)	20.2	1.2	42.8		18.1	1.7	37.0	
$\text{NO}_2 \geq 75^{\text{th}}$ percentile (n=94)	28.7	-11.6	87.4		19.1	-11.6	60.6	

p_i : p interaction

Except for the variable of stratification, models were adjusted for age, sex, smoking habits and country living and took into account familial dependence.