Online Supplementary Material

Outdoor air pollution, exhaled 8-isoprostanes and current asthma in adults: the EGEA study

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Methods

Study design and population

Data used for the analyses were collected in the framework of the EGEA study (https://egeanet.vjf.inserm.fr/). EGEA is a French cohort study based on an initial group of asthma cases and their first-degree relatives, and controls (first survey EGEA1, between 1991 and 1995, n=2047). The protocol and descriptive characteristics have been described previously [1, 2].

A 12-year follow-up of the initial cohort was conducted between 2003 and 2007 (EGEA2) [3]. Among the alive cohort (n=2002), 92% (n=1845) completed a short self-administered questionnaire, and among them 1602 (n=1571 adults aged ≥16 years) had a complete examination. All subjects responded to a questionnaire based on international standardized tools to diagnose asthma and to determine respiratory and allergic symptoms, treatments, and environmental exposures.

As a follow-up study of EGEA2, the third survey (EGEA3) was conducted in 2011 using self-completed questionnaire and 1558 questionnaires were returned.

Respiratory phenotypes

Inclusion criteria used to define asthma cases at EGEA1 were based on self-reported positive responses to four questions from the validated and standardized British Medical Research Council, European Coal and Steel Community, American Thoracic Society (ATS) and European Community Respiratory Health Survey (ECRHS) questionnaires: "*Have you ever had attacks of breathlessness at rest with wheezing?*", "*Have you ever had asthma attacks?*", "*Was this diagnosis confirmed by a physician?*" and "*Have you had an asthma attack in the last 12 months?*", or a positive response to at least two questions and a positive review of the

medical records. Asthma in first-degree relatives of asthma cases was defined as a positive answer to at least one of the first two questions [4, 5].

Allergic sensitization was defined by a positive skin prick test (SPT+) with a mean wheal diameter ≥3mm than the negative control for at least one of 12 aeroallergens (indoor: cat, *Dermatophagoides pteronyssinus, Blattela germanica,* outdoor: olive, birch, *Parieteria judaica,* timothy grass, *Cupressus* and ragweed pollen, and molds: *Aspergillus, Cladosporium herbarum, Alternaria tenuis*). Subjects were classified as sensitized if they have one or more SPT+.

Pulmonary function test was assessed by spirometry, performed using a standardized protocol with similar equipment across centers according to the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines [6]. Forced expiratory volume in one second (FEV1) percent predicted value was based on Quanjer et al. reference equations [7]. For subjects with a forced expiratory volume in one second (FEV_1) of > 80% of the predicted value, a methacholine bronchial challenge test was performed (maximum dose 4mg).

Exposure assessment

The ESCAPE assessment used land-use regression (LUR) models, developed to explain the spatial variation of pollutant exposures within each city. Predictor variables were calculated using the site coordinates and digital data thanks to geographical information system [8]. Two indicators of road traffic were also calculated: traffic intensity on the nearest road (vehicles per day), and total traffic load on all major roads within 100-buffer (intensity multiplied by road length). The spatial resolution is 50 meters. In the ESCAPE project, models to estimate back-extrapolated levels of PM and NOx in previous years were based on historic data on land use and road networks, and background levels of PM and NOx. The back-extrapolated concentration was estimated by multiplying the modeled ESCAPE annual mean concentration

by the ratio between average annual concentrations as derived from the routine monitoring site(s) for the period in the past and for the ESCAPE measurement period time: Cextrapolated-ratio = CESCAPE * Ratioroutine, with Ratioroutine = Croutine-baseline / Croutine-ESCAPE [9].

The IFEN assessment used the geostatistical interpolation techniques (kriging-like techniques) to estimate air pollution at unsampled locations, taking account the spatial structure of each pollutant. Interpolation was done for pollution estimates coming from background monitoring stations on a 4kmx4km grid covering France. Land cover was integrated to the interpolation process as well as specific cofactors correlated with the pollutants such as altitude and north-south concentration gradient for O_3.

In summary, the NO_2, NOx and road traffic levels were estimated for 608 participants, the O_3 and $O_{3\text{-summer}}$ levels for 603 participants from Paris, Lyon, Grenoble and Marseille, and the PM levels for 437 participants from Paris and Grenoble.

Exhaled breath condensate collection

Briefly, the RTube (TM) was rinsed with deionized water and dried thoroughly. Participants breathed orally at tidal volumes into a mouthpiece attached to a cold condenser (-20°C). They were seated comfortably with a headrest. All headrests and back seats were tilted slightly to avoid any saliva contamination during breathing maneuvers. Breathing was quiet and regular. After 15 minutes, EBC collection was immediately separated in aliquots and stored at -80·C according to standardized procedures (http://www.afaq.org/certification=262711141114) [10].

Measurement of exhaled 8-isoprostanes

EBC 8-iso concentration was measured with a specific enzyme immunoassay (EIA) kit (8-isoprostanes EIA kit Cayman Chemical, Ann Arbor, MI, USA) according to the

manufacturer's protocol. Fifty microliter of EBC was assayed in duplicate and 8-iso concentration was calculated from a calibration curve obtained from eight calibrator concentrations (0.8 – 500 pg/mL). The intra-assay coefficient of variation for 8-iso was less than 15% and the limit of detection (LD) was 4.0 pg/mL.

Results

Characteristics of participants according to city

The characteristics of participants were heterogeneous across cities (Table E2). In Paris, participants were younger, had more often current asthma and a better controlled asthma. In Lyon, they had more often a BMI ≥30 kg/m^2 and they were more often technicians. In Marseille, the participants were more often current smokers, managers, and they had a lower FEV_1.

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Table E1. Characteristics of participants included and participants not included in the study.

Characteristics	Participants included n=608	Participants not included n=963	p-value
Age (years), mean ± SD	42.5 ± 17.2	43.0 ± 16.1	0.57
Sex, Men, n (%)	288 (47.4)	488 (50.7)	0.20
Status at inclusion, n (%)			
Cases	120 (19.8)	182 (18.9)	
Relatives	313 (51.5)	539 (56.0)	0.22
Spouses	36 (5.8)	60 (6.2)	
Controls	139 (22.9)	182 (18.9)	
Smoking habits, n (%)		n=955	
Never smoker	312 (51.3)	468 (49.0)	0.31
Ex-smoker	168 (27.6)	254 (26.6)	
Current smoker	128 (21.1)	233 (24.4)	
BMI (kg/m²), n (%)		n=784	
<20	70 (11.5)	79 (10.1)	
[20-25[	316 (52.0)	401 (51.1)	0.66
[25-30[	165 (27.1)	218 (27.8)	
>=30	57 (9.4)	86 (11.0)	
Socio-professional category, n (%)	n=605	n=955	
Unemployed	72 (11.9)	86 (9.0)	
Manager	212 (35.0)	324 (33.9)	0.13
Technician	248 (41.0)	402 (42.1)	
Manual worker	73 (12.1)	143 (15.0)	
Asthma, n (%)		n=838	
Current	240 (39.4)	318 (38.0)	0.56
FEV_1 % predicted, mean ± SD	103 ± 18.9	n=779 101 ± 17.3	0.26
Allergic sensitization¶, n (%)	n=602 327 (54.3)	n=701 405 (57.8)	0.21

BMI, body mass index; FEV_1, forced expiratory volume; ¶: defined by at least one weal ≥ 3 mm to 12 tested allergens;

Table E2. Characteristics of participants by city.

Characteristics	Lyon n=122	Marseille n=49	Paris n=224	Grenoble n=213	p-value
Age (years), mean ± SD	48.6 ± 14.5	47.7 ± 17.6	37.6 ± 15.9	42.9 ± 18.3	**<0.0001**¶
Sex, Men, n (%)	53 (43.4)	24 (49.0)	106 (47.3)	105 (49.3)	0.77
Status at inclusion, n (%) Cases	23 (18.9)	9 (18.4)	41 (18.3)	47 (22.1)	**0.0006**¶
Smoking habits, n (%) Never smokers Ex-smokers Current smokers	 63 (51.6) 40 (32.8) 19 (15.6)	 14 (28.5) 21 (42.9) 14 (28.6)	 126 (56.2) 53 (23.7) 45 (20.1)	 109 (51.2) 54 (25.4) 50 (23.4)	**0.01**¶
BMI (kg/m²), n (%) <20 [20-25[[25-30[>=30	 3 (2.5) 60 (49.2) 43 (35.2) 16 (13.1)	 4 (8.2) 29 (59.2) 14 (28.6) 2 (4.0)	 36 (16.1) 118 (52.7) 48 (21.4) 22 (9.8)	 27 (12.7) 109 (51.2) 60 (28.1) 17 (8.0)	**0.005**¶
Socio-professional category, n (%) Unemployed Manager Technician Manual worker	n=120 3 (2.5) 30 (25.0) 67 (55.8) 20 (16.7)	 2 (4.1) 26 (53.1) 15 (30.6) 6 (12.2)	n=223 30 (13.5) 83 (37.2) 97 (43.5) 13 (5.8)	 37 (17.4) 73 (34.2) 69 (32.4) 34 (16.0)	**<0.0001**¶
Asthma (%) Current	35 (28.7)	16 (32.7)	106 (47.3)	83 (39.0)	**0.005**¶
FEV_1 % predicted, mean ± SD	103 ± 19.6	97.8 ± 21.4	102 ± 16.2	106 ± 20.2	**0.04**¶
Allergic sensitization#, n (%)	56 (45.9)	n=48 26 (54.2)	n=223 129 (57.9)	n=209 116 (55.5)	0.19
In all, exhaled 8-iso concentration, pg/mL, GM (q1;q3)	n=67 1.27 (0.82;2.33)	n=28 1.15 (0.65;2.72)	n=217 7.47 (3.93;14.1)	n=119 1.39 (0.83;3.33)	**<0.0001**¶
In participants without asthma, exhaled 8-iso concentration, pg/mL, GM (q1;q3)	n=45 1.21 (0.82;2.32)	n=23 1.09 (0.53;2.82)	n=114 7.71 (3.89;15.0)	n=71 1.10 (0.56;3.15)	**<0.0001**

BMI, body mass index; FEV_1, forced expiratory volume; GM, geometric mean; q1 and q3, the 25th and the 75th percentiles of the GM.
#: defined by at least one weal ≥ 3 mm to 12 tested allergens; ¶Results in bold represent significant results (p-values≤0.05).

Table E3. Associations between exhaled 8-iso concentration and characteristics of participants.

Participants without asthma n=253					
	n	GM	q1	q3	p-value
Sex					
Men	112	2.12	0.98	5.75	**0.01**[#]
Women	141	3.26	1.32	7.98	
Age					
[16-25[	38	4.56	2.19	8.62	
[25-35[	47	3.36	1.14	11.0	**0.01**[#]
[35-45[	29	2.60	1.10	5.83	**0.0007**[#] [¶]
[45-55[	63	2.71	1.33	5.82	
>=55	76	1.82	0.83	4.73	
Smoking habits					
Never smokers	123	123	2.84	2.84	1.14	1.14	7.19	7.19	0.96	0.96
Ex-smokers	87	87	2.30	2.30	1.00	1.00	5.61	5.61		
Current smokers	43	43	3.16	3.16	1.41	1.41	5.43	5.43		
BMI (kg/m²)										
<20	30		2.53		1.00		14.5			
[20-25[	130		2.87		1.00		8.07		0.36	
[25-30[	70		2.37		1.32		4.90			
>=30	23		2.94		1.41		6.12			
Socio-professional category										
Unemployed	21		5.19		2.35		9.88			
Manager	100		3.05		1.11		8.26		0.24	
Technician	98		2.51		1.14		5.61			
Manual worker	33		1.54		0.58		4.88			
Participants with current asthma n=178										
Inhaled corticoids in the 12 last months										
No	89		4.52		2.39		9.54		0.52	
Yes	87		3.49		1.55		8.51			

BMI, body mass index; 8-iso, 8-isoprostanes; GM, geometric means of 8-iso; q1-q3, the 25th and the 75th percentiles of the GM. Adjusted for, age, sex, smoking habits and body mass index. [#] Results in bold represent significant results (p-values≤0.05).
[¶]Trend test.

Table E4. Associations between back-extrapolated outdoor air pollution and current asthma.

		NO_2[#]	NOx[#]	PM_{10}[¶]
Model 1	n	608	608	224
	OR crude (95% CI)	0.99 (0.87,1.12)	1.03 (0.92,1.14)	1.16 (0.62,2.19)
Model 2	n	605	605	223
	OR adjusted (95% CI)	0.98 (0.86,1.12)	1.02 (0.91,1.14)	1.13 (0.58,2.22)
Model 3	n	603	603	223
	OR adjusted (95% CI)	0.97 (0.85,1.11)	1.00 (0.90,1.13)	1.12 (0.56,2.27)

Data are presented as OR and 95% confidence intervals (95% CI) with the participants without asthma as reference. Results are expressed per 20 µg/m^3 increase of NOx exposure, per 10 µg/m^3 increase of NO_2 and PM_{10} exposures.

Model 1: unadjusted; Model 2: adjusted for age, sex, smoking habits, body mass index and socio-professional category; Model 3: adjusted for age, sex, smoking habits, body mass index, socio-professional category and cleaning products.

[#]The logistic models were conducted with random effects on familial dependence (level 2) and city (level 3).

[¶]The logistic models were conducted with random effects on familial dependence because PM_{10} were assessed only in Paris.

Table E5. Associations between back-extrapolated outdoor air pollution and exhaled 8-iso concentration among participants without asthma.

		NO_2[#]	NOx[#]	PM_{10}[¶]
	n	253	253	114
Model 1	β crude (95% CI)	0.05 (-0.001,0.10)	0.03 (-0.02,0.08)	0.10 (-0.15,0.35)
	p-value	0.08	0.22	0.45
	n	253	253	114
Model 2	β adjusted (95% CI)	0.03 (-0.02,0.08)	0.01 (-0.03,0.06)	0.11 (-0.12,0.34)
	p-value	0.24	0.57	0.37
	n	253	253	114
Model 3	β adjusted (95% CI)	0.03 (-0.02,0.08)	0.01 (-0.04,0.06)	0.10 (-0.13,0.33)
	p-value	0.30	0.63	0.43

Data are presented as β and 95% confidence intervals (95% CI). Results are expressed per 20 µg/m^3 increase of NOx exposure, per 10 µg/m^3 increase of NO_2 and PM_{10} exposures. 8-iso concentration was log10 transformed.

Model 1: unadjusted; Model 2: adjusted for age, sex and smoking habits. Model 3: adjusted for age, sex, smoking habits and cleaning products.

[#]The linear regression models were conducted with random effects on familial dependence (level 2) and city (level 3).

[¶]The linear regression models were conducted with random effects on familial dependence because PM_{10} were assessed only in Paris.

Table E6. Associations between O_3 and $O_{3\text{-summer}}$ exposure and exhaled 8-iso concentration by city, among participants without asthma.

O_3 exposure					
		Lyon	Marseille	Paris	Grenoble
Model 1	n	45	23	**111**	71
	β crude (95% CI)	0.12 (-0.35,0.59)	-0.31 (-1.53,0.31)	**-0.27 (-0.48,-0.05)**[#]	0.04 (-0.59,0.67)
	p-value	0.62	0.21	**0.01**	0.91
Model 2	n	45	23	**111**	71
	β adjusted (95% CI)	0.13 (-0.36,0.62)	-0.49 (-1.49,0.51)	**-0.24 (-0.44,-0.04)**[#]	-0.04 (-0.63,0.55)
	p-value	0.66	0.34	**0.02**	0.91
Model 3	n	45	23	**111**	71
	β adjusted (95% CI)	0.04 (-0.45,0.53)	-0.44 (-1.42,0.54)	**-0.22 (-0.42,-0.02)**[#]	0.05 (-0.56,0.66)
	p-value	0.85	0.40	**0.03**	0.88
$O_{3\text{-summer}}$ exposure					
Model 1	n	45	23	**111**	**71**
	β crude (95% CI)	0.17 (-0.67,1.01)	0.69 (-1.52,2.90)	**-0.61 (-1.00,-0.22)**[#]	**-0.99 (-1.93,-0.05)**[#]
	p-value	0.69	0.55	**0.003**	**0.05**
Model 2	n	45	23	**111**	71
	β adjusted (95%CI)	0.20 (-0.68,1.08)	1.44 (-1.11,3.99)	**-0.56 (-0.93,-0.19)**[#]	-0.73 (-1.69,0.23)
	p-value	0.66	0.28	**0.0004**	0.13
Model 3	n	45	23	**111**	71
	β adjusted (95% CI)	0.11 (-0.75,0.97)	1.60 (-0.97,4.17)	**-0.53 (-0.90,-0.16)**[#]	-0.73 (-1.67,0.21)
	p-value	0.81	0.23	**0.007**	0.14

Data are presented as β and 95% confidence intervals (95% CI). The linear regression models were conducted with random effects on familial dependence. 8-iso concentration was log10 transformed. Results are expressed per 10 µg/m^3 increase of O_3 and $O_{3\text{-summer}}$ exposure.
Model 1: unadjusted; Model 2: adjusted for age, sex and smoking habits; Model 3: adjusted for age, sex, smoking habits and cleaning products.
[#]Results in bold represent significant results (p-values≤0.05).

Table E7. Associations between O_3 and $O_{3\text{-summer}}$ exposures and exhaled 8-iso concentration.

	Participants in all cities	With only participants in Paris	Without the participants of Paris
O_3	**250** **-0.20 (-0.39,-0.01)**[#] **0.04**	**111** **-0.22 (-0.43,-0.01)**[#] **0.04**	139 -0.05 (-0.27, 0.17) 0.69
$O_{3\text{-summer}}$	**250** **-0.52 (-0.77,-0.26)**[#] **0.002**	**111** **-0.54 (-0.94,-0.14)**[#] **0.009**	139 -0.08 (-0.29, 0.13) 0.45

Data are presented as β and 95% confidence intervals (95% CI). The linear regression models were conducted with random effects on familial dependence (level 2) and city (level 3). 8-iso concentration was log10 transformed.

Results are expressed per 10 µg/m^3 increase of O_3 and $O_{3\text{-summer}}$

Adjusted for age, sex, smoking habits and cleaning products.

[#]Results in bold represent significant results (p-values≤0.05).

Table E8. Associations between outdoor air pollution and exhaled 8-iso concentration in bi-pollutant models among participants without asthma.

	$PM_{2.5}$	O_3
n	182	182
β adjusted (95% CI)	0.16 (-0.07,0.39)	-0.14 (-0.32,0.09)
p-value	0.21	0.25
	$PM_{2.5}$	$O_{3\text{-summer}}$
n	182	**182**
β adjusted (95% CI)	0.11 (-0.11,0.33)	**-0.59 (-0.71,-0.47)**
p-value	0.33	**<0.0001**[#]

Data are presented as β and 95% confidence intervals (95% CI). The linear regression models were conducted with random effects on familial dependence (level 2) and city (level 3). 8-iso concentration was log10 transformed. Results are expressed per 10 $\mu g/m^3$ increase of O_3 and $O_{3\text{-summer}}$ exposures and per 5 $\mu g/m^3$ increase of $PM_{2.5}$ exposure.

Adjusted for age, sex, smoking habits and cleaning products.

[#]Result in bold represents significant result (p-values≤0.05).

Figures legends

Figure E1. Pollutant levels from ESCAPE by city.
— Value recommended by the World Health Organization.

Figure E2. Road traffic levels from ESCAPE by city.

Figure E3. Pollutant levels from IFEN by city.
The average recommended by the World Health Organization was 100 µg/m^3 over 8 hours.