



City housing atmospheric pollutant impact on emergency visit for asthma: A classification and regression tree approach



Julie Mazenq^{a, *}, Jean-Christophe Dubus^a, Jean Gaudart^{b, c}, Denis Charpin^d, Gilles Viudes^e, Guilhem Noel^{e, f}

^a Pediatric Pulmonology Department, Timone Children's Hospital, Aix-Marseille University, Marseille, France

^b Aix Marseille University, IRD, INSERM, SESSTIM, 13005 Marseille, France

^c AP-HM, Timone Hospital, Biostatistics and TICE Service, 13005 Marseille, France

^d Pulmonology and Allergology Department, Hospital Nord, Marseille, France

^e Regional Emergencies Observatory, Provence-Alpes-Cote d'Azur Region (ORU PACA), France

^f Pediatric Emergency Department, Hospital Nord, Marseille, France

ARTICLE INFO

Article history:

Received 24 May 2017

Received in revised form

29 August 2017

Accepted 8 September 2017

Available online 12 September 2017

Keywords:

Asthma

Air pollution

Children

Adults

ABSTRACT

Introduction: Particulate matter, nitrogen dioxide (NO₂) and ozone are recognized as the three pollutants that most significantly affect human health. Asthma is a multifactorial disease. However, the place of residence has rarely been investigated. We compared the impact of air pollution, measured near patients' homes, on emergency department (ED) visits for asthma or trauma (controls) within the Provence-Alpes-Côte-d'Azur region.

Methods: Variables were selected using classification and regression trees on asthmatic and control population, 3–99 years, visiting ED from January 1 to December 31, 2013. Then in a nested case control study, randomization was based on the day of ED visit and on defined age groups. Pollution, meteorological, pollens and viral data measured that day were linked to the patient's ZIP code.

Results: A total of 794,884 visits were reported including 6250 for asthma and 278,192 for trauma. Factors associated with an excess risk of emergency visit for asthma included short-term exposure to NO₂, female gender, high viral load and a combination of low temperature and high humidity.

Conclusion: Short-term exposures to high NO₂ concentrations, as assessed close to the homes of the patients, were significantly associated with asthma-related ED visits in children and adults.

© 2017 Elsevier Ltd. All rights reserved.

1. Introduction

Air pollution harms human health and the environment. Particulate matter (PM), nitrogen dioxide (NO₂) and ground-level ozone (O₃) are now generally recognized as the three pollutants that most significantly affect human health. In Europe, emissions of many air pollutants have decreased substantially in the past decade. However, a significant proportion of the population, especially in cities, still lives in areas where air quality standards set for maximum allowable pollutants are exceeded [1].

Pollutants have a direct irritant and inflammatory effect on neuro-receptors in the airways and bronchial epithelium [2]. NO₂, O₃ and PM induce airway inflammation and airway hyper-responsiveness (oxidative stress, immunology response and

remodeling). According to the World Health Organization (WHO), in 2012, almost 3.7 million persons prematurely died as a result of air pollution in the world [3].

In France, the French Institute of Public Health Surveillance reported that PM_{2.5} were estimated to cause more than 48,000 premature deaths per year, more than half occurring in cities larger than 100,000 inhabitants [4,5].

In recent decades, several epidemiological studies reported an association between short-term exposure to air pollution and adverse health effects, showing an increase in emergency room visits or hospital admissions for asthma as a result of increased pollution levels [6–13]. However, only a few epidemiological studies took into account confounding factors such as meteorological conditions, viral infections and pollen counts according to place of residence [11,14–17]. Moreover, no French study has evaluated the impact of short-term pollution exposure on asthmatic disease in the past decade, despite the lowering of the WHO-recommended threshold values.

* Corresponding author. Pediatric Pulmonology Department, Timone Children's Hospital, 264 Rue Saint Pierre, 13005 Marseille, France.

E-mail address: julie.mazenq@ap-hm.fr (J. Mazenq).

Abbreviations	
CART	Classification And Regression Trees
CNIL	Commission Nationale de l'Informatique et des Libertés
ED	Emergency Department
EEDA	Electronic Emergency Department Abstracts
ICD	International Classification of Disease
ICD-10	International Classification of Disease, Revision 10
INSEE	National Institute of Statistics and Economic Surveys
NO ₂	Nitrogen dioxide
O ₃	Ozone
ORa	adjusted Odds Ratio
ORUPACA	Observatory of Provence-Alpes-Côte d'Azur region
PACA	Provence-Alpes-Cote-d'Azur
PM	Particulate matter
PM ₁₀	Particulate matter with a diameter less than 10 µm
PM _{2.5}	Particulate matter with a diameter less than 2,5 µm
P	Probability values
WHO	World Health Organization

The mediterranean area, including Provence-Alpes-Côte-d'Azur (PACA; south-eastern France) region, has a dry and sunny weather that favors the generation of secondary pollutants. Its spatial heterogeneity is interesting as it includes coastal highly urbanized zones, major road traffic and high-density industrial places but also rural and mountainous ones with forest fires. Moreover, the air quality-monitoring network AIR PACA reported a total of 122 days when PM has exceeded the daily limit, while the national average is 35 days per year [18].

The aim of our study was to measure the impact of air pollution, assessed close to the homes of the patients, on asthma-related hospital visits to the emergency department (ED) within the PACA region in 2013, and to estimate the risks from pollution, meteorological conditions, pollen exposure and viral load.

2. Methods

2.1. Study area

The study was conducted in the PACA region of southeastern France (31,400 km²; 4,937,445 inhabitants or 7.5% of the French population: National Institute of Statistics and Economic Surveys (INSEE 2013)).

This region is an intensively urbanized area with 9 out of 10 inhabitants residing in large urban and metropolitan areas. In 2013, it was the third most populated region of France.

Large urban areas, dense road, motorway networks and industrial zones make it the most significant area in France for air pollutant emissions.

2.2. Population under study

Electronic Emergency Department Abstracts (EEDA), recommended for every patient admitted to an ED in France, are directly available from the patients' computerized medical files. EEDAs are anonymously transmitted daily to "Santé Publique France" (a public health network) and included in the French syndromic surveillance system [19]. EEDAs report the date of the emergency room visit, age of patient, ZIP code of residence and final diagnosis using a national

standardized thesaurus based on International Classification of Disease (ICD) codes validated by the French Society of Emergency Medicine. Since 2008, the ED Observatory of PACA region (ORU-PACA) has collected these data from EDs in the region.

From January 1 to December 31, 2013, EEDAs transmitted by EDs located in PACA were included in this study if they concerned a 3- to 99-year-old patient living in PACA.

We defined 3 age groups: 3- to 17-year-old, 18- to 49-year-old and 50- to 99-year-old. We excluded children under 3 years of age because it is more difficult to be sure about the diagnosis of asthma.

Each factor was recorded on the same day than the ED visit.

The controls were defined as patients consulting for trauma in ED. When the patient was discharge from the ED, the emergency physician had to code the final diagnosis using a national thesaurus of International Classification of Disease, Revision 10 (ICD-10) codes. Visits for an exacerbation of asthma (J45-J46) and for trauma (S00-T98) were defined according to this thesaurus.

This control group was chosen because they are a homogenous group whose attendance at the ED is less likely to be related to air pollution.

Patients' ZIP codes were used to link EEDA to the nearest ("as the crow flies") monitoring station for pollution, pollen and meteorological data.

The study was approved by the "Commission Nationale de l'Informatique et des Libertés" (CNIL), the French data protection authority (n°1,887,366).

This study was purely observational and consent of participants was not required because the research involved no intervention or contact with the patient. Only anonymous data were used.

2.3. Exposure data

2.3.1. Air pollution data

For each ZIP code, respectively, two primary air pollutants and one secondary pollutant were considered and measured in µg/m³: daily average of particulate matter with a diameter less than 10 µm (PM₁₀), daily 1-hour maximum of NO₂, and daily 1-hour maximum of O₃.

The air quality-monitoring network AIR PACA, with 80 stations throughout the PACA region, took these measurements.

A spatial pollution surface model was created from the data for these three pollutants. Data were processed via the deterministic CHIMERE chemistry-transport model over a 4-km grid. Then a communal aggregation mesh was performed, using an average weight by population residing in each mesh.

2.3.2. Meteorological data

For each ZIP code, 4 daily weather indicators were recorded: average temperature (°C); air humidity (%); average wind speed (m/s) and rainfall (mm). These data were obtained from Météo-France (the French national meteorological company) and taken from a total of 237 monitoring stations. Each ZIP code was assigned to the nearest "as the crow flies" measuring station.

2.3.3. Pollen data

The choice of pollens was based upon two criteria: they had to be the most important pollen types causing sensitization and allergic symptoms in this geographic area and they had to be present in relatively high and significant concentrations.

For each ZIP code, the main taxa (*cupressaceae*, *birch*, *ash*, *poaceae* and *urticaceae*) were collected from 7 stationary pollen traps in PACA by the national network for aerobiological monitoring. Each ZIP code was linked to the nearest monitoring station.

2.3.4. Virology data

For each day in 2013, viral load was defined by the ratio of the daily number of visits in each ED of PACA for viral diseases and of the daily number of total visits for each ED.

Viral diseases encoded on the EEDA used to define the viral load were: bronchiolitis (ICD-10: J21), bronchitis (ICD-10: J20), laryngitis (ICD-10: J04), viral pneumonia (ICD-10: J12), influenza (ICD-10: J11), nasopharyngitis (ICD-10: J00) and angina (ICD-10: J02). The viral load was assigned to patients in terms of ED and date of visit.

The grouping of all the codes relating to a seasonal viral pathology is not validated in the literature. However, in France, Public Health France for the epidemiological surveillance of these seasonal viral diseases use the diagnosis of Electronic Emergency Department Abstracts [19]. Syndromic surveillance is the collection, analysis and interpretation of health-related data in near real time. Emergency data using discharge diagnoses are often included in these surveillances. These methods have been applied in EDs for monitoring the three main viral epidemic diseases: influenza, bronchiolitis and gastroenteritis.

2.4. Statistical analysis

First, variables were selected using classification and regression trees (CART) on asthmatic and control population by limiting itself to 3 levels for each category (i.e. 2 splits from the “root” node, the start node of tree). CART is a non-parametric regression approach. The CART method on this population allows having more staff and therefore having more bearing in pollution, pollens and meteorological profiles. That allows taking into account combined effects of several pollutants, pollens or meteorological data, as describe by Gass et al. [20,21]. This analysis provides 3 qualitative variables: pollutant profile, pollen profile and meteorological profile.

For each variable (pollution, meteorological and pollen data), the CART method was carried out for selected multiple categories for the purpose of evaluating the joint effects of exposure mixtures. The referent group contained the lowest concentrations for pollutants, meteorological factors or taxa for pollens. The right-hand

branch of each split always corresponded to the highest concentration. By definition, terminal nodes were located at the end of the tree and so cannot have had off springs. Each terminal node was able to be viewed as a unique mixture. The determination of a cut-off is carried out by a statistical method of binarization (CART). That is, by recursively considering each values of the variable as a potential threshold. The chosen threshold will be that which will optimize a statistical criteria. This method is equivalent to that of clusters in determining the thresholds but adding an explained variable.

Using a nested case control design, a random sampling was performed to improve quality and power of analysis by comparing each asthmatic with 15 controls. Each control was randomly matched on the emergency room visit day, regardless of hospital, and in order by age groups.

The impact of pollution, weather, pollens and virus risk on asthma-related emergency room visits was assessed by conditional logistic regression. For each factor, ORs were estimated regarding their relationship to asthma attacks. Interactions between meteorological factors and pollution or pollen data were also taken into account.

The analysis design used univariate analyses to select variables ($p < 0.20$) via conditional logistic regressions, and to assess interactions between covariates. Multivariate analysis was performed as a stepwise procedure using conditional logistic regression, to accurately estimate the adjusted Odds Ratio (ORa). Probability values (p) of less than 0.05 were considered as significant. This design allowed identical risk exposure to be considered for this large cohort.

Statistical analyses were performed using R3.1.3 software ((C) 2015 The R Foundation for Statistical Computing, Vienna, Austria).

3. Results

Of the 55 EDs in the PACA region, 37 participated in the study and transmitted 1,048,575 EEDAs in 2013. A total of 794,884 visits concerned patients aged from 3 to 99 including 6250 (0.79% of total

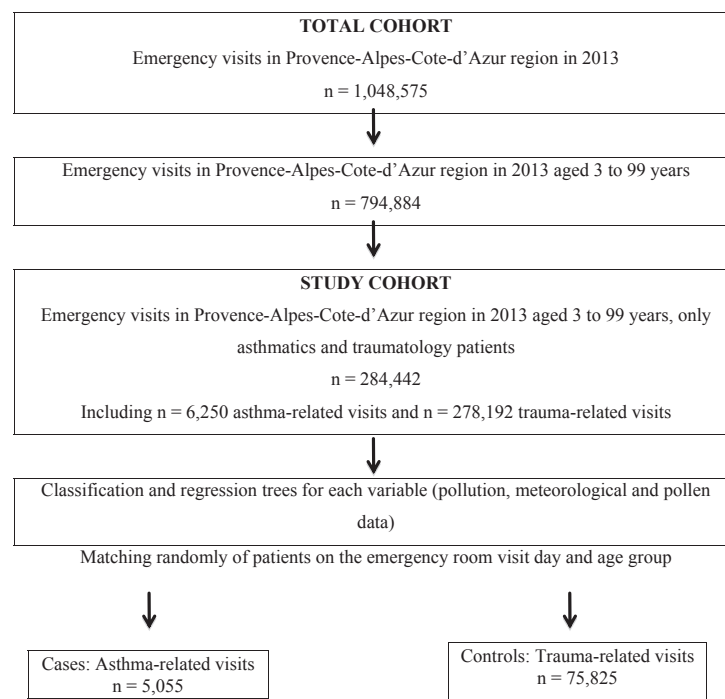


Fig. 1. Flow chart of the study population: nested case control comparing asthma and trauma ED visits in Provence-Alpes-Cote-d'Azur from 1/1/2013–12/31/2013.

Table 1
Distribution of study patients: nested case control comparing asthma and trauma ED visits in Provence-Alpes-Cote-d'Azur from 1/1/2013–12/31/2013.

	Asthmatics	Controls	Total population 3- to 99-years
Number n=	6250 (0.79%)	278,192 (35%)	794,884
Number of patients in age group			
3- to 17-years	3565 (2%)	80,024 (45.69%)	175,156
18- to 49-years	1772 (0.5%)	117,915 (36.12%)	326,487
50- to 99-years	913 (0.3%)	80,253 (27.37%)	293,241
Age (average ± SD) years	22.67 ± 0.8	36.57 ± 11.51	41.49 ± 15.32
Age (median) years	13	31	38
Age (IQR)	30	38	42
Gender			
Male	3130 (0.76%)	157,205 (38.27%)	410,746
Female	3120 (0.81%)	120,987 (31.50%)	384,138

SD: standard deviation.
IQR: interquartile range (from 25th to 75th percentile).

visits) visits for asthma and 278,192 (35% of total visits) for trauma. Fig. 1 shows the flow chart of this study.

Patients visiting for asthma attacks were younger than the total population (average age of 22.67 vs. 41.49 years), but the gender's repartition was the same (50% vs. 51.7% of boys). In total, 75,825 controls were matched to 5055 cases. Table 1 describes the distribution of ED visits in PACA region in terms of age and gender.

3.1. CART method

For pollution data, only NO₂ and O₃ were selected by this method. PM₁₀ was not found a significant variable with CART analysis except for CART analysis with different characteristics: by increasing the number of levels in trees, we found PM10 was only associated with asthma in the youngest patients (3–17 years old). For meteorological data, temperature, humidity and wind speed were selected by CART. As for pollen data, *urticaceae*, *poaceae*, *ash* and *cupressaceae*, were selected by this method. Figs. 2–4 show CART analysis, respectively, for pollutants, meteorological data and

pollens.

3.2. Variables' distribution

Table 2 describes the average daily concentrations in pollutants and average measurements of meteorological and pollen factors.

3.3. Multivariate analysis

Compared to trauma control, women were at higher risk of asthma-related ED visits with $Ora = 1.52$ (95% CI: 1.43–1.61; $p < 0.01$).

Pollution analysis showed that when ground-level O3 concentration was $\leq 25.63\mu\text{m}/\text{m}^3$ and NO2 concentration $> 12.37\mu\text{m}/\text{m}^3$,

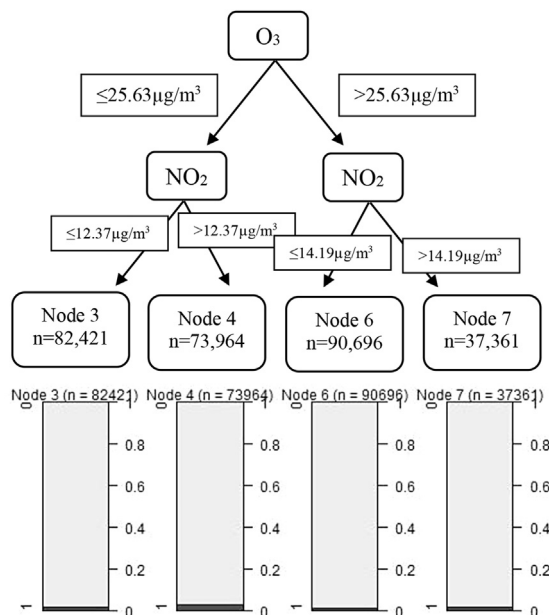


Fig. 2. Tree resulting from CART analysis illustrating the joint effects of pollutants treated as ordinal variables for asthma and trauma ED visits in Provence-Alpes-Cote-d'Azur from 1/1/2013–12/31/2013. (75,825 controls were matched to 5,055 cases) Node x represents terminal node
n = number of patients of each split
In diagram, are stated in boldface the number of asthmatics on the number of total population (asthmatics and traumatology) aged 3- to 99-year-old in each split (expressed in decimal number 0 to 1).

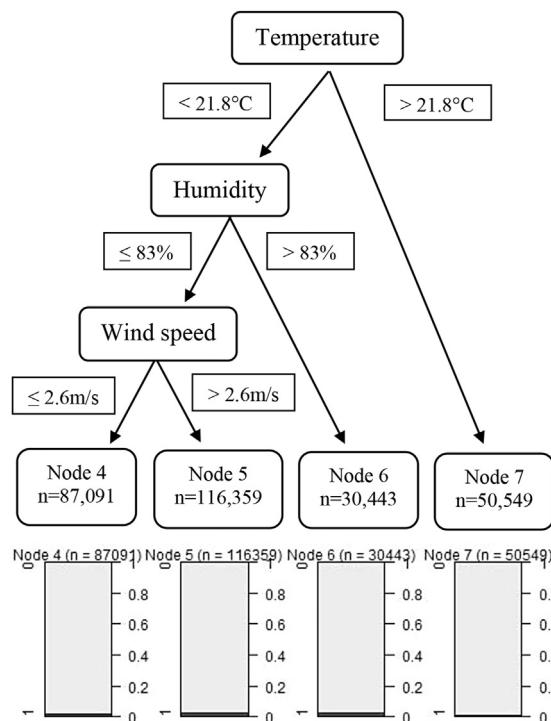


Fig. 3. Tree resulting from CART analysis illustrating the joint effects of meteorological factors treated as ordinal variables for asthma and trauma ED visits in Provence-Alpes-Cote-d'Azur from 1/1/2013–12/31/2013. (75,825 controls were matched to 5,055 cases) Node x represents terminal node
n = number of patients of each split
In diagram, are stated in boldface the number of asthmatics on the number of total population (asthmatics and traumatology) aged 3- to 99-year-old in each split (expressed in decimal number 0 to 1).

there was a statistically significant risk for asthma-related ED visits with an ORa of 1.35 (95% CI: 1.17–1.57; $p = <0.01$) (Fig. 2 and Table 3).

Similarly, when ground-level O₃ was higher ($>25.63\mu\text{m}/\text{m}^3$) and concentration NO₂ remained beyond the limit ($>12.37\mu\text{m}/\text{m}^3$), there was still a risk for asthma-related ED visits with ORa = 1.28 (95% CI: 1.04–1.58; $p = 0.02$) (Fig. 2 and Table 3).

These results showed the NO₂ effect to be independent of ground-level ozone concentration.

Meteorological analysis revealed that low temperatures ($<21.8^\circ\text{C}$) and high humidity ($>83\%$) were statistically linked to asthma-related ED visits, with ORa = 1.28 (95% CI: 1.05–1.57; $p = 0.02$) (Fig. 3 and Table 3).

The association between viral load and asthma-attacks was also statistically significant with ORa = 1.04 (95% CI: 1.04–1.05; $p < 0.01$) (Table 3).

No association between the risk for asthma-related ED visits and pollen was found. Asthma-attacks were not found to increase with meteorological factors and pollution or pollen data either (Table 3).

4. Discussion

Our study shows a significant association between short-term exposure to high concentration of NO₂ measured near patients' home, independent of ground-level ozone, and asthma-related ED visits in 3- to 99-year-old patients in the PACA region in 2013. The study, which took into account viral data, pollens and meteorological conditions, also identifies other risk factors: the female gender, a combination of low temperature and high humidity, and a high viral load.

Our study is original because we evaluated patients' exposure to

atmospheric pollution based on their home ZIP code, rather than on the receiving hospital, and because we used the CART method. Our assessment is more accurate because, according to INSEE, the average commuting distance between home and work in Provence-Alpes-Côte-d'Azur is 10.6 km [22]. Few previous studies have taken into account the patients' place of residence. Shmool and al. reported that, after incorporating residential-level spatial exposure, an excess risk per 10 ppb ozone exposure was significant on lag days 1 through 5, ranging from 7.3 to 9.4% for asthma outpatient in emergency departments in New York City [23]. Regarding statistical method, Gass' study concluded that regression trees can be used to hypothesize about joint effects of exposure mixtures [20,21]. It is one of many statistical tools that can be used to address the challenge of multi-pollutant exposures [24,25].

We used EEDA to define asthma visits in ED. EEDA are validated by the Network OSCOUR® [19] as part of the French Syndromic Surveillance System (SurSaUD®), coordinated by the French Public Health Service [26]. Asthma visits are included in this surveillance system [27]. Of course, asthma diagnosis may be overrepresented because the ICD-10 only permits to code asthma attack regardless of the age of the patient and the number of previous similar episodes. So, in pre-school children, some wheezy episodes may have been wrongly coded as asthma attacks. Similarly, older patients coming to ED for a first wheezy attack may also have been coded as asthma attack. An advantage of our study is to include, for the first time, a specific control group in order to limit the effect of pollution on control case. In our study, we chose patients with trauma because we believe they are less likely to be affected by pollution than other medical conditions. Control group selection bias due to diagnostic coding is more likely. Hence OR in asthmatics are higher in our study than in the literature.

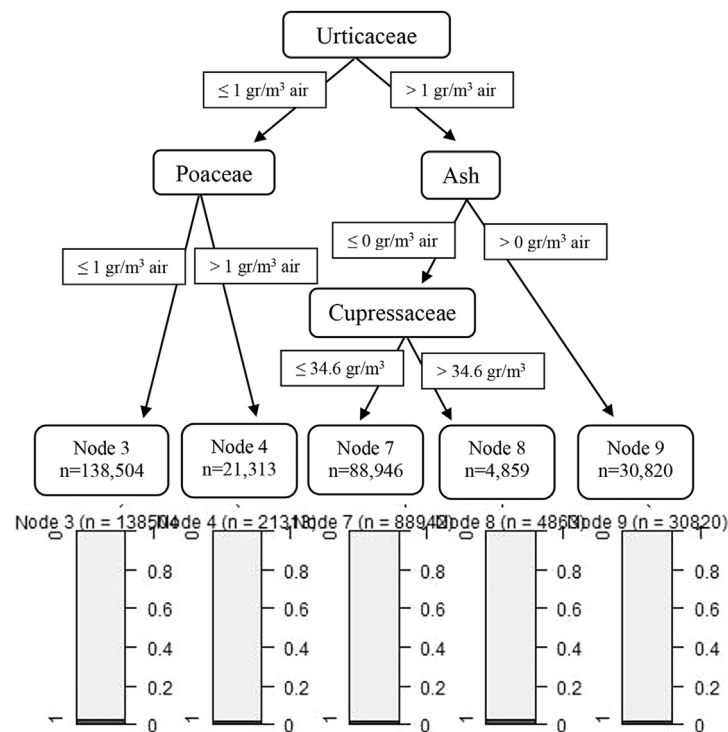


Fig. 4. Tree resulting from CART analysis illustrating the joint effects of pollen treated as ordinal variables for asthma and trauma ED visits in Provence-Alpes-Cote-d'Azur from 1/1/2013–12/31/2013. (75,825 controls were matched to 5,055 cases)

Node x represents terminal node

n = number of patients of each split

In diagram, are stated in boldface the number of asthmatics on the number of total population (asthmatics and traumatology) aged 3- to 99-year-old in each split (expressed in decimal number 0 to 1).

Table 2
Descriptive statistics of pollutants (daily averages PM₁₀ and daily 1-hour maximum of NO₂ and O₃), meteorological, pollens and viral variables for asthmatics cases and traumatology controls during the study period. PACA, France, 2013: n = 5055 cases versus 75,825 controls.

Variables	Pop	Mean	Min	p 25	Median	p 75	Max	IQR
NO ₂ (µm/m ³)	T	12.47	0.002	5.67	10.36	18.39	63.67	12.72
	A	13.83	0.002	6.71	12.38	20.22	57.14	13.51
	Tot	13.15	0.002	6.19	11.37	19.31	60.41	13.12
O ₃ (µm/m ³)	T	24.14	1.61	19.06	23.93	28.51	58.25	9.45
	A	23.82	2.01	18.79	23.68	28.27	51.13	9.48
	Tot	23.98	1.81	18.93	23.81	28.39	54.69	9.46
PM ₁₀ (µm/m ³)	T	24.19	2.63	17.07	22.65	29.55	88.95	12.48
	A	24.89	3.51	17.59	23.26	30.4	88.95	12.81
	Tot	24.54	3.07	17.33	22.96	29.98	88.95	12.65
Rainfall (mm)	T	2.16	0	0	0	0.2	187.7	0.2
	A	2.15	0	0	0	0.2	98.4	0.2
	Tot	2.16	0	0	0	0.2	143.05	0.2
Humidity (%)	T	68.08	14	59	69	78	100	19
	A	68.32	14	60	69	78	100	18
	Tot	68.56	14	59.5	69	78	100	18.5
Temperature (°C)	T	13.9	- 13.1	8.9	13.9	19	31.5	10.1
	A	14.17	- 7.1	9.3	14.1	19.2	31.5	9.9
	Tot	14.04	- 10.1	9.1	14	19.1	31.5	10
Wind speed (m/s)	T	3.45	0	1.9	2.8	4.3	22.5	2.4
	A	3.45	0	1.9	2.9	4.3	21.6	2.4
	Tot	3.45	0	1.9	2.85	4.3	22.05	2.4
Cupressaceae (grains/m ³)	T	37.15	0	0	2.8	15.9	897.3	15.9
	A	39.14	0	0	2.1	15.5	897.3	15.5
	Tot	38.15	0	0	2.45	15.7	897.3	15.7
Urticaceae (grains/m ³)	T	7.92	0	0	0	7	166	7
	A	7.66	0	0	0	6	166	6
	Tot	7.79	0	0	0	6.5	166	6.5
Poaceae (grains/m ³)	T	5.63	0	0	0	3	218	3
	A	5.16	0	0	0	3	147	3
	Tot	5.4	0	0	0	3	182.5	3
Ash (grains/m ³)	T	5.94	0	0	0	1	487	1
	A	6.2	0	0	0	1	456	1
	Tot	6.07	0	0	0	1	471.5	1
Birch (grains/m ³)	T	0.93	0	0	0	0	382	0
	A	0.86	0	0	0	0	382	0
	Tot	0.9	0	0	0	0	382	0
Viral load (%)	T	6.86	0	2.08	4.62	9.8	54.55	7.72
	A	8.39	0	2.78	6.14	12.5	45.57	9.72
	Tot	7.63	0	2.43	5.38	11.15	50.06	8.72

Pop: population.
→ T: traumatology patients – A: asthmatics patients – Tot: Total population (study cohort).
Min: minimum; Max: maximum.
p25: 25th percentile; p75: 75th percentile.
IQR: Interquartile range.

Our study has some limitations because we have not used continuous measurement of personal exposure to air pollutants, which would be considered as the gold standard for exposure assessment [28]. It would be very expensive to measure personal exposure in a large number of participants necessary to satisfy statistical power requirements. Our estimates of pollution exposure are thus based on a series of measurement of pollution from stationary positions. While we cannot rule out coding errors on the ED software, asthma and trauma have easily recognizable clinical presentation, so the potential for errors should be fairly low in this cohort.

Our finding of an association between asthma attacks and elevated concentrations of NO₂ is consistent with the literature. Indeed, NO₂ is the principal pollutant reported to be associated with hospital admissions or consultation for asthma. Outdoors air pollution (NO₂, but also sulfur dioxide SO₂) was associated with increased risk of asthma hospitalization in Shanghai [6]. A positive correlation has been reported between asthma-related ED visits and NO₂, in children but not in adults [10]. Another study found a significant association between short-term increase in NO₂ (for 6-day cumulative mean pollutant concentration) and timing of asthma diagnosis, solely for May to October. This study reported

that a 10-parts per billion increase in NO₂ was significantly associated with an increased rate of asthma diagnosis from 2.7% to 7% [29]. Similarly, a significant positive correlation was found between NO₂ and daily hospital admissions for asthma (r = 0.101, p < 0.001) [30]. A systematic review has reported an association between ambient exposure to NO₂ and a higher prevalence of diagnosis of childhood asthma or increased asthma risk at 3 years [13]. Simons et al. demonstrated that an NO₂ reduction of 10% could potentially decrease respiratory drugs use with an associated direct cost saving of 107.845€ (95%IC: €71.483- €143.823) [31].

We did not find any statistically significant correlation between PM10 level and asthma-related emergency room visits. PM10 has been reported to be a risk factor for asthma attacks but with an interquartile range for PM10 concentration generally higher than that observed in out study [6,13,30,32,33]. We used a CART methodology to select pollutant in order to take into account their combined effect. To our knowledge, no previous study has evaluated the impact of PM10 in asthma with this method. It was only used for PM10 forecast [34,35]. Using the CART method, PM10 was not selected. Upon increasing the number of level in trees, PM10 was only associated with asthma in the youngest patients (3–17 years old), but not in older patients. We have not analyzed the

Table 3

Multivariate analysis, of a case-control nested in a cohort, of different selected variables on the emergency room visits for asthma in Provence-Alpes-Cote-d'Azur region (n = 5055 cases versus 75,825 controls).

Variables	Terminal Node	ORa	95% IC	p
Female		1.52	1.43–1.61	<0.01**
Pollution				
	3: referent			
	4	1.35	1.17–1.57	<0.01**
	6	0.87	0.72–1.05	0.15
	7	1.28	1.04–1.58	0.02*
Meteorology				
	4: referent			
	5	1.11	0.95–1.29	0.20
	6	1.28	1.05–1.57	0.02*
	7	1.28	0.83–1.99	0.26
Pollen				
	3: referent			
	4	0.84	0.66–1.07	0.16
	7	0.87	0.73–1.03	0.11
	8	0.92	0.51–1.65	0.78
	9	0.95	0.79–1.16	0.63
Viral load		1.04	1.04–1.05	<0.01**

Terminal nodes are located at the end of the trees about pollution, pollen and meteorological data. Each terminal node can be viewed as a unique mixture.

The referent group contains the lowest concentrations for pollutants, meteorological factors or taxa for pollens.

ORa: adjusted Odd Ratio.

*: $p < 0.05$ - **: $p < 0.01$.

pollution according to each age group as patients were matched according to age groups. It is possible that other confounding factors could explain the absence of any effect of PM10 e.g. environmental cofactors, or behavioral and socio-economic factors.

We found a link between asthma attacks and viral load, consistent with previous reports. We chose to focus on viral diseases globally rather than on each individual virus. Bonnellyke et al. showed a relationship between asthma attacks and number of respiratory infections, but not the virus itself in their study of 313 children [36]. Another study found a strong association between asthma admission rates and influenza ($r: 0.799$; $p < 0.05$) in Taiwan during the period 2001–2008 [37].

Regarding meteorological factors, we found that a combination of low temperature and high humidity was a risk factor for asthma-related emergency room visits. Zhang reported that a daily mean temperature below the median of 18.7 °C, was linked with an increase in asthma hospital admissions [30]. In Shanghai, outdoor air pollution was associated with an increased risk of asthma hospitalization, particularly in the cold season (from October to March) [6]. In another study, low temperatures were significantly associated with the number of adults transferred by ambulance to ED for asthma attack [9].

Our study differs from the literature because we found no link between pollen exposure and asthma-related emergency room visits. This may be because we only had 7 pollen-monitoring stations distributed throughout the region. This meant that exposure levels for cases and controls were very close. It is possible that the low number of stations adversely affected the multivariate analysis due to the coarse nature of the pollen exposure estimates. In other studies, emergency calls for asthma exacerbation were significantly correlated with pollen exposure, but only between April and August [7]. However, associations have also been reported between mid-spring pollen types (*maple, birch, beech, ash, sycamore/London plane tree and oak*) and both over-the-counter allergy medication sales and ED visits for asthma in children aged (5–17) [38].

Our study did not evaluate the impact of socio-economic factor on asthma-related visits and air pollution. A recent systematic review shed light on the role of socioeconomic status as an effect-modifier of the association between air pollutants (mainly O₃,

followed by NO₂ and PM₁₀) and important asthma-related outcomes, with a strong negative influence on children (3–6 and 12–18 years) living in low socio-economic conditions [39].

It would be interesting to set up an alert system for patients with asthma, using a lower threshold than the current WHO recommendations. A recent quasi-experimental study reported a doubling of emergency admissions for all relevant conditions (asthma, chronic obstructive pulmonary disease or coronary heart disease) and a fourfold increase in admissions for respiratory conditions after implementation for 2 years an alert system automatically triggered by high pollution levels [40]. We might envisage a personalized alert system for each asthmatic patient to trigger an action (for example: to avoid strenuous physical activity, individual adaptation of treatment ...) when daily 1-hour maximum of NO₂ exceeds 12 µm/m³, threshold found in CART method, in the PACA region.

5. Conclusion

Our study shows that short-term local exposure to high concentration of NO₂, as assessed close to the home of the patients, is associated with an increased risk of emergency department visits for asthma exacerbation in patients aged 3–99-years in the PACA region. These findings require further confirmation from other studies, using larger patients' cohorts. Emissions of NO₂ is primarily linked to road traffic. If our data are confirmed, preventative strategies should be implemented to reduce traffic pollutions and vehicles emissions.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Financial disclosure

The authors have no financial relationships relevant to this article to disclose.

Conflicts of interest

None.

Clinical trial registration

“Commission Nationale de l'Informatique et des Libertés” (CNIL) (The French data protection authority): n° 1887366.

Contributor's statement

Julie Mazenq: She conceptualized and designed the study, coordinated and supervised data collection, and drafted the initial manuscript.

Jean-Christophe Dubus: Pr Dubus conceptualized and designed the study, reviewed and revised the manuscript.

Jean Gaudart: Dr Gaudart carried out the statistics analyses, critically reviewed the manuscript.

Denis Charpin: Pr Charpin designed the pollen data collection instruments and critically reviewed the manuscript.

Gilles Viudes: Dr Viudes is the promoter of the study. He conceptualized and designed the study, critically reviewed the manuscript.

Guilhem Noel: Dr Noel conceptualized and designed the study, coordinated and supervised data collection, reviewed and revised the manuscript.

All the authors approved the final manuscript as submitted and

agree to be accountable for all aspects of the work.

Acknowledgments

We thank Mr. Robin Dominique and his staff at the air quality-monitoring network (AirPACA) for collecting the pollution data.

We thank Mrs Boiron who has reviewed the English version of the manuscript.

References

- [1] Air pollution — European Environment Agency. (late updated 3 June 2016). Available online: <http://www.eea.europa.eu/themes/air/intro>. (Late accessed 16 October 2016).
- [2] M. Guarnieri, J.R. Balmes, Outdoor air pollution and asthma, *Lancet* 383 (2014) 1581–1592.
- [3] WHO | Ambient (outdoor) air quality and health. (late updated September 2016). Available online: <http://www.who.int/mediacentre/factsheets/fs313/en/>. (Late accessed 16 October 2016).
- [4] Impacts de l'exposition chronique aux particules fines sur la mortalité en France continentale et analyse des gains en santé de plusieurs scénarios de réduction de la pollution atmosphérique, 2016. Environnement et santé/Rapports et synthèses/Publications et outils/Accueil. Available online: <http://invs.santepubliquefrance.fr/Publications-et-outils/Rapports-et-syntheses/Environnement-et-sante/2016/Impacts-de-l-exposition-chronique-aux-particules-fines-sur-la-mortalite-en-France-continentale-et-analyse-des-gains-en-sante-de-plusieurs-scenarios-de-reduction-de-la-pollution-atmospherique>. Date late updated: June 21 2016. Date late accessed October 16 2016.
- [5] Quelle est la part des pics de pollution dans les effets à court terme de la pollution de l'air sur la santé dans les villes de France?, 2016. Environnement et santé/Rapports et synthèses/Publications et outils/Accueil. Available online: <http://invs.santepubliquefrance.fr/Publications-et-outils/Rapports-et-syntheses/Environnement-et-sante/2016/Quelle-est-la-part-des-pics-de-pollution-dans-les-effets-a-court-terme-de-la-pollution-de-l-air-sur-la-sante-dans-les-villes-de-France>. Date late updated: June 21 2016. Date late accessed October 16 2016.
- [6] J. Cai, A. Zhao, J. Zhao, R. Chen, W. Wang, S. Ha, X. Xu, H. Kan, Acute effects of air pollution on asthma hospitalization in Shanghai, China, *Environ. Pollut. Barking Essex* 2014 (191) (1987) 139–144.
- [7] M.A. Tosca, S. Ruffoni, G.W. Canonica, G. Ciprandi, Asthma exacerbation in children: relationship among pollens, weather, and air pollution, *Allergol. Immunopathol.* 42 (2014) 362–368.
- [8] S. Cakmak, R.E. Dales, F. Coates, Does air pollution increase the effect of aeroallergens on hospitalization for asthma? *J. Allergy Clin. Immunol.* 129 (2012) 228–231.
- [9] T. Abe, Y. Tokuda, S. Ohde, S. Ishimatsu, T. Nakamura, R.B. Birrer, The relationship of short-term air pollution and weather to ED visits for asthma in Japan, *Am. J. Emerg. Med.* 27 (2009) 153–159.
- [10] H.-L. Sun, M.-C. Chou, K.-H. Lue, The relationship of air pollution to ED visits for asthma differ between children and adults, *Am. J. Emerg. Med.* 24 (2006) 709–713.
- [11] G. Cadelis, R. Tourres, J. Molinie, Short-term effects of the particulate pollutants contained in saharan dust on the visits of children to the emergency department due to asthmatic conditions in Guadeloupe (French Archipelago of the Caribbean), *PLoS One* 9 (2014) e91136.
- [12] F.C. Goldizen, P.D. Sly, L.D. Knibbs, Respiratory effects of air pollution on children, *Pediatr. Pulmonol.* 51 (2016) 94–108.
- [13] S. Dick, A. Friend, K. Dines, F. Alkandari, E. Doust, H. Cowie, J.G. Ayres, S.W. Turner, A systematic review of associations between environmental exposures and development of asthma in children aged up to 9 years, *BMJ Open* 4 (2014) e006554.
- [14] J.A. Gleason, L. Bielory, J.A. Fagliano, Associations between ozone, PM_{2.5}, and four pollen types on emergency department pediatric asthma events during the warm season in New Jersey: a case-crossover study, *Environ. Res.* 132 (2014) 421–429.
- [15] K.K. Nishimura, J.M. Galanter, L.A. Roth, S.S. Oh, N. Thakur, E.A. Nguyen, S. Thyne, H.J. Farber, D. Serebrisky, R. Kumar, E. Brigino-Buenaventura, A. Davis, M.A. LeNoir, K. Meade, W. Rodriguez-Cintrón, P.C. Avila, L.N. Borrell, K. Bibbins-Domingo, J.R. Rodriguez-Santana, S. Sen, F. Lurmann, J.R. Balmes, E.G. Burchard, Early-life air pollution and asthma risk in minority children. The GALA II and SAGE II studies, *Am. J. Respir. Crit. Care Med.* 188 (2013) 309–318.
- [16] M. Adam, T. Schikowski, A.E. Carsin, Y. Cai, B. Jacquemin, M. Sanchez, Marcon A. Vierkötter, D. Keidel, D. Sugiri, Z. Al Kanani, R. Nadif, V. Siroux, R. Hardy, D. Kuh, T. Rochat, P.O. Bridevaux, M. Eeftens, M.Y. Tsai, S. Villani, H.C. Phuleria, M. Birk, J. Cyrys, M. Cirach, A. De Nazelle, M.J. Nieuwenhuijsen, B. Forsberg, K. De Hoogh, C. Declercq, R. Bono, P. Piccioni, U. Quass, J. Heinrich, D. Jarvis, I. Pin, R. Beelen, G. Hoek, B. Brunekreef, C. Schindler, J. Sunyer, U. Krämer, F. Kauffmann, A.L. Hansell, N. Kühzli, N. Probst-Hensch, Adult lung function and long-term air pollution exposure. ESCAPE: a multicentre cohort study and meta-analysis, *Eur. Respir. J.* 45 (2015) 38–50.
- [17] M.T. Young, D.P. Sandler, L.A. DeRoo, S. Vedal, J.D. Kaufman, S.J. London, Ambient air pollution exposure and incident adult asthma in a nationwide cohort of U.S. women, *Am. J. Respir. Crit. Care Med.* 190 (2014) 914–921.
- [18] bilan_PM2013_BR.pdf, Available online: http://www.airpaca.org/sites/paca/files/publications_import/files/140100_AirPACA_Bilan_PM_2013_net.pdf. Date late updated: 2013. Date late accessed October 16 2016.
- [19] C. Caserio-Schonemann, J.B. Meynard, Ten years experience of syndromic surveillance for civil and military public health, France, 2004–2014, *Euro Surveill. Bull. Eur. Sur Mal. Transm. Eur. Commun. Dis. Bull.* 20 (2015) 35–38.
- [20] K. Gass, M. Klein, H.H. Chang, W.D. Flanders, M.J. Strickland, Classification and regression trees for epidemiologic research: an air pollution example, *Environ. Health Glob. Access Sci. Source* 13 (2014) 17.
- [21] K. Gass, M. Klein, S.E. Sarnat, A. Winquist, L.A. Darrow, W.D. Flanders, H.H. Chang, J.A. Mulholland, P.E. Tolbert, M.J. Strickland, Associations between ambient air pollutant mixtures and pediatric asthma emergency department visits in three cities: a classification and regression tree approach, *Environ. Health Glob. Access Sci. Source* 14 (2015) 58.
- [22] LA_02139_Mobilites_GSE.p65-LA_02139_Mobilites_GSE.pdf, Available online: http://www.insee.fr/fr/insee_regions/rhone-alpes/themes/syntheses/lettre_analyses/02139/LA_02139_Mobilites_GSE.pdf. Date late updated: March 2011. Date late accessed October 16 2016.
- [23] J.L.C. Shmool, E. Kinnee, P.E. Sheffield, J.E. Clougherty, Spatio-temporal ozone variation in a case-crossover analysis of childhood asthma hospital visits in New York City, *Environ. Res.* 147 (2016) 108–114.
- [24] C. Billionnet, D. Sherrill, I. Annesi-Maesano, GERIE study, Estimating the health effects of exposure to multi-pollutant mixture, *Ann. Epidemiol.* 22 (2012) 126–141.
- [25] Z. Sun, Y. Tao, S. Li, K.K. Ferguson, J.D. Meeker, S.K. Park, S.A. Batterman, B. Mukherjee, Statistical strategies for constructing health risk models with multiple pollutants and their interactions: possible choices and comparisons, *Environ. Health Glob. Access Sci. Source* 12 (2013) 85.
- [26] C. Caserio-Schönemann, V. Bousquet, A. Fouillet, V. Henry, pour l'équipe projet SurSaUD, Le système de surveillance syndromique SurSaUD®, *Bull. Epidémiol. Hebd.* 3–4 (2014) 38–44.
- [27] Bulletin national d'information OSCOUR du 6 septembre, 2016/Tous les numéros/Bulletins SurSaUD (SOS Médecins, Oscour, Mortalité), 2016. Publications et outils/Accueil [Internet]. Available online: <http://invs.santepubliquefrance.fr/Publications-et-outils/Bulletins-SurSaUD-SOS-Medecins-Oscour-Mortalite/Tous-les-numeros/2016/Bulletin-national-d-information-OSCOUR-du-6-septembre-2016>. Date late updated: September 7 2016. Date late accessed October 16 2016.
- [28] F.C. Goldizen, P.D. Sly, L.D. Knibbs, Respiratory effects of air pollution on children, *Pediatr. Pulmonol.* 51 (2016) 94–108.
- [29] J.K. Wendt, E. Symanski, T.H. Stock, W. Chan, X.L. Du, Association of short-term increases in ambient air pollution and timing of initial asthma diagnosis among Medicaid-enrolled children in a metropolitan area, *Environ. Res.* 131 (2014) 50–58.
- [30] Y. Zhang, L. Peng, H. Kan, J. Xu, R. Chen, Y. Liu, W. Wang, Effects of meteorological factors on daily hospital admissions for asthma in adults: a time-series analysis, *PLoS One* 9 (2014) e102475.
- [31] K. Simons, S. Devos, K. Putman, D. Coomans, A. Van Nieuwenhuyse, R. Buyl, Direct cost saving potential in medication costs due to a reduction in outdoor air pollution for the Brussels Capital Region, *Sci. Total Environ.* 562 (2016) 760–765.
- [32] E. Samoli, P.T. Nastos, A.G. Paliatatos, K. Katsouyanni, K.N. Priftis, Acute effects of air pollution on pediatric asthma exacerbation: evidence of association and effect modification, *Environ. Res.* 111 (2011) 418–424.
- [33] J.E. Zora, S.E. Sarnat, A.U. Raysoni, B.A. Johnson, W.-W. Li, R. Greenwald, F. Holguin, T.H. Stock, J.A. Sarnat, Associations between urban air pollution and pediatric asthma control in El Paso, Texas, *Sci. Total Environ.* 448 (2013) 56–65.
- [34] T. Slini, A. Kaprara, K. Karatzas, N. Moussiopoulos, PM₁₀ forecasting for Thessaloniki, Greece, *Environ. Model. Softw.* 21 (2006) 559–565.
- [35] J.-M. Poggi, B. Portier, PM₁₀ forecasting using clusterwise regression, *Atmos. Environ.* 45 (2011) 7005–7014.
- [36] K. Bønnelykke, N.H. Vissing, A. Sevelsted, S.L. Johnston, H. Bisgaard, Association between respiratory infections in early life and later asthma is independent of virus type, *J. Allergy Clin. Immunol.* 136 (2015), 81–86.e4.
- [37] C.-M. Liao, N.-H. Hsieh, C.-P. Chio, Fluctuation analysis-based risk assessment for respiratory virus activity and air pollution associated asthma incidence, *Sci. Total Environ.* 409 (2011) 3325–3333.
- [38] K. Ito, K.R. Weinberger, G.S. Robinson, P.E. Sheffield, R. Lall, R. Mathes, Z. Ross, P.L. Kinney, T.D. Matte, The associations between daily spring pollen counts, over-the-counter allergy medication sales, and asthma syndrome emergency department visits in New York City, 2002–2012, *Environ. Health Glob. Access Sci. Source* 14 (2015) 71.
- [39] L.A. Rodriguez-Villamizar, C. Berney, C. Villa-Roel, M.B. Ospina, A. Osornio-Vargas, B.H. Rowe, The role of socioeconomic position as an effect-modifier of the association between outdoor air pollution and children's asthma exacerbations: an equity-focused systematic review, *Rev. Environ. Health* 31 (2016) 297–309.
- [40] R.A. Lyons, S.E. Rodgers, S. Thomas, R. Bailey, H. Brunt, D. Thayer, J. Bidmead, B.A. Evans, P. Harold, M. Hooper, H. Snooks, Effects of an air pollution personal alert system on health service usage in a high-risk general population: a quasi-experimental study using linked data, *J. Epidemiol. Community Health* 70 (2016) 1184–1190.