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ORIGINAL ARTICLE

Air pollution and children's asthma-related emergency hospital visits in southeastern France

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Abstract Children's asthma is multifactorial. Environmental factors like air pollution exposure, meteorological conditions, allergens, and viral infections are strongly implicated. However, place of residence has rarely been investigated in connection with these factors. The primary aim of our study was to measure the impact of particulate matter (PM), assessed close to the children's homes, on asthma-related pediatric emergency hospital visits within the Bouches-du-Rhône area in 2013. In a nested case-control study on 3- to 18-year-old children, each control was randomly matched on the emergency room visit day, regardless of hospital. Each asthmatic child was compared to 15 controls. PM_{10} and $PM_{2.5}$, meteorological conditions, pollens, and viral data were linked to ZIP code and analyzed by purpose of emergency visit. A total of 68,897 visits were recorded in children, 1182 concerning asthma. Short-term exposure to PM_{10} measured near children's homes was associated with excess risk of asthma emergency visits (adjusted odds ratio 1.02 (95% CI 1.01–1.04; $p = 0.02$)). Male gender, young age, and temperature were other risk factors. Conversely, wind speed was a protective factor.

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Conclusion: PM_{10} and certain meteorological conditions near children's homes increased the risk of emergency asthma-related hospital visits in 3- to 18-year-old children in Bouches-du-Rhône.

What is Known:
• *A relationship between short-term exposure to air pollution and increase in emergency room visits or hospital admissions as a result of increased pollution levels has already been demonstrated.*

What is New:
• *This study confirms these results but took into account confounding factors (viral data, pollens, and meteorological conditions) and is based on estimated pollution levels assessed close to the children's homes, rather than those recorded at the hospital.*
• *The study area, the Mediterranean, is favorable to creation of secondary pollutants in these sunny and dry seasons.*

Keywords Asthma · Children · Air pollution

Abbreviations

BdR	Bouches-du-Rhône
ED	Emergency department
EEDA	Electronic Emergency Department Abstracts
INSEE	Nation Institute of Statistics and Economic Surveys
ORa	Adjusted odds ratio
ORU	Emergency Department Observatory of
PACA	Provence-Alpes-Côte d'Azur region
PM	Particulate matter
WHO	World Health Organization

Introduction

In both developed and developing countries, outdoor air pollution constitutes a major environmental health concern [30]. Pollutants have a direct irritant and inflammatory effect on neuroreceptors in the airways and bronchial epithelium. Particulate matter (PM) induces airway inflammation and airway hyperresponsiveness (oxidative stress, immunology response, and remodeling). Genetic predisposition and atopy are also important factors [10, 17–19]. In Europe, a significant proportion of the population, especially in cities, still lives in areas where air quality standards set for maximum allowable pollutants are exceeded (ozone, nitrogen dioxide, PM) [2]. The air quality monitoring network AIR PACA (Provence-Alpes-Côte-d'Azur: south-eastern France) reported a total of 122 days when the daily limit value for PM is exceeded, while the national average is 35 days per year [4]. In the period from 2004 to 2006, 19,000 deaths per year could have been prevented if 25 European cities had met the guide values set by the World Health Organization (WHO) for annual average concentrations of $PM_{2.5}$. For Marseille, a reduction in life expectancy of 7.5 years was computed [22].

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 as a result of increased pollution levels [1, 7, 8, 26, 27]. In a recent review, all 25 included studies reported an association between outdoor air pollution and asthma incidence in children [28]. It has been shown that average rates of pollutants (PM_{10}, ozone, nitrogen dioxide, carbon monoxide, and benzene) vary; similarly, rates of nasal eosinophils, values for the fraction of exhaled nitric oxide, and peak flow charts have been found to vary over a week in asthmatic children [23]. However, few epidemiological studies take into account confounding factors such as meteorological conditions, viral infections, and pollen counts according to place of residence [6, 14, 27]. For a decade, no French study has evaluated the impact of pollution on asthmatic disease, despite the lowering of the WHO-recommended threshold values.

The aim of our study was to measure the impact of PM, assessed close to the homes of the children, on asthma-related pediatric hospital visits to the emergency department (ED) within the Bouches-du-Rhône area (BdR) (France) in 2013 and to estimate risks from pollution, meteorological conditions, pollen exposure, and level of respiratory virus circulation.

Methods

Study area

The study was conducted in the BdR area of southeastern France (5087 km^2; 2.01 million inhabitants: National Institute of Statistics and Economic Surveys (INSEE 2011)).

Large urban areas, dense road and motorway networks, and industrial zones make it the most important area for air pollutant emissions in the Provence-Alpes-Côte d'Azur region.

Population under study

Electronic Emergency Department Abstracts (EEDA), mandatory for every patient admitted to an ED in France, are directly available from the patients' computerized medical files. Collected via an ED terminal, EEDAs are anonymously transmitted daily to the French Institute of Public Health Surveillance. EEDAs report date of emergency room visit, age of patient, ZIP code of residence, and final diagnosis (using a national standardized thesaurus based on ICD codes). Since 2008, the ED Observatory of Provence-Alpes-Côte d'Azur region (ORUPACA) has collected these data from 55 EDs in the region (1.5 million ED visits reported in 2013).

From January 1 to December 31, 2013, EEDAs transmitted by EDs located in BdR were included if they concerned a 3- to 18-year-old child living in BdR. Visits for an exacerbation of asthma were defined according to ICD-10 codes included in the national thesaurus (J45–J46).

Patients' ZIP codes were used to link pollution, pollen, and meteorological data.

The study was approved by "Commission Nationale de l'Informatique et des Libertés" (CNIL), the French data protection authority (n°1887366), and by the ethics committee of the French Pediatrics Society (CER_SFP 2015-005).

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.

Exposure data

Air pollution data

For each ZIP code, daily averages were considered for two primary air pollutants measured in micrograms per cubic meter: PM_{10} (particulate matter with a diameter less than 10 μm) and $PM_{2.5}$ (particulate matter with a diameter less than 2.5 μm). These measurements were taken by the air quality monitoring network AIR PACA at 17 stations throughout BdR (including five stations measuring $PM_{2.5}$). For PM_{10} data, a spatial pollution surface was created. PM_{10} 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.

For $PM_{2.5}$, each ZIP code was assigned to the nearest "straight line distance" measuring station.

Meteorological data

For each ZIP code, five daily weather indicators were recorded: average temperature (°C), air humidity (%), average sea pressure (hPa), average wind speed (m/s), and rainfall (mm). These data were obtained from the monitoring network Météo-France and taken from a total of 151 monitoring stations. Each ZIP code was assigned to the nearest "as the crow flies" measuring station.

Pollen data

For each ZIP code, the main taxa of BdR (*cypress*, *birch*, *ash*, *grass pollen*, and *urticaceae*) were collected from two stationary pollen traps in BdR by the national network for aerobiological monitoring. The maximum distance between BdR communes and measuring stations was roughly 100 km (roof of Hospital Nord and roof of Hospital of Aix-en-Provence). Each BdR ZIP code was linked to the nearest monitoring station.

Virological data

For each day in 2013, the daily level of respiratory virus circulation was defined by the total number of positive specimens (nasopharyngeal swabs or aspirates) found in the Virology laboratory of the public hospitals of Marseille for each of the following viruses: respiratory syncytial virus, rhinoviruses, influenza A virus, influenza B virus, and human metapneumovirus. The daily level of respiratory virus circulation was used as a proxy of daily viral exposure in BdR.

Other data not available

On Electronic Emergency Department Abstracts, no information about smoke exposure, familial asthma, atopy, and/or prematurity were available.

Statistical analysis

First, variables were selected using principal component analysis (for each continuous variable). Each control was randomly matched on the emergency room visit day, regardless of hospital. Then, the nested case-control design used univariate analyses to select variables ($p < 0.20$) via conditional logistic regressions and to assess interactions between covariates. Multivariate analysis was performed with a stepwise procedure using conditional logistic regression, to accurately estimate the odds ratio (OR). Each asthmatic child was compared to 15 controls, to improve the quality and analytical power. The impact of pollution, weather, pollen, and virus risk on asthma-related emergency room visits was assessed by taking day 0 to the exposure (i.e., the same day: air pollution exposition and visits to emergency department) and evaluated interactions pollution and asthma attacks at day 0 and average pollution over the previous 2 to 7 days, by taking average for each day into logistic regression model. For each factor, ORs were estimated depending on their relationship to asthma attacks. Interactions between meteorological factors and pollution or pollen data were also taken into account. A p value of less than 0.05 was considered significant.

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

Results

Of the 17 EDs in the Bouches-du-Rhône, 12 participated in the study via their EEDAs. A total of 68,897 visits recorded for children aged from 3 to 18 years showed that 1182 concerned asthma (1.7% of total visits). Figure 1 shows the monthly frequency of visits due to asthma during the study period. Figure 2 shows the monthly variation in PM over the period. Table 1

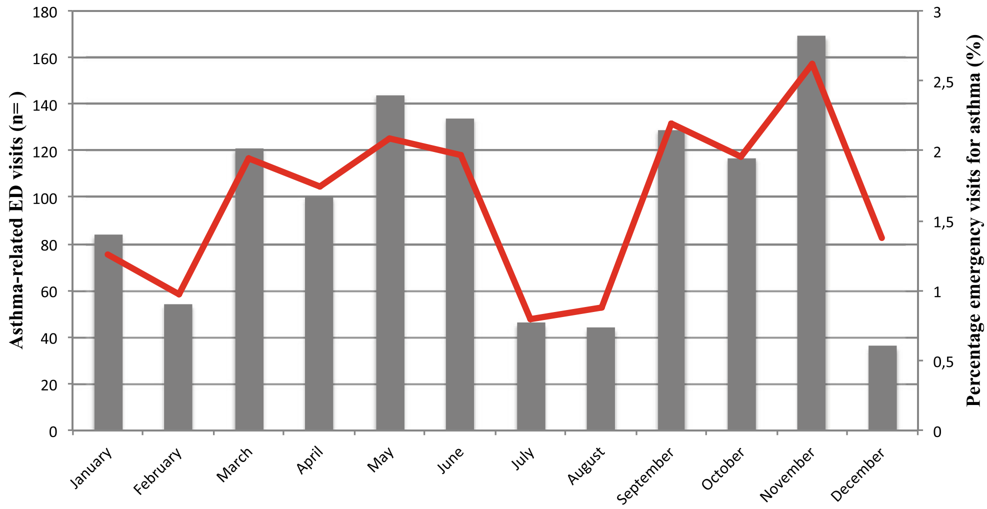

Fig. 1 Frequency of asthma-related visits (n = 1182) by children aged 3 years to 18 years to emergency departments (ED) during the study period and % emergency visits for asthma out of total visits (n = 68,897) (*red line*). Bouches-du-Rhône, 2013

describes the study population with children visiting for asthma attacks and controls.

The impact of pollution on asthma visit was assessed on 1182 cases matched to 18,903 controls.

Quantitative variables selected by principal component analysis for meteorological data were rainfall, temperature, and wind speed; for pollen data, variables were *grass pollen-urticaceae* paired, *birch-ash* paired and *cypress*; for respiratory virus circulation, variables were rhinovirus and total virus.

Clinical data

Males were at higher risk of asthma-related ED visits with an adjusted OR (ORa) of 1.14 (95% CI 1.01–1.28; p = 0.04). Older children had a lower risk of asthma-related visits ORa of 0.89 (95% CI 0.88–0.90; p < 0.001) (Table 2).

Impact of PM

In multivariate analysis, average daily PM_{10} were a statistically significant risk factor for asthma-related ED visits in BdR with ORa 1.02 (95% CI 1.01–1.04; p = 0.02) (Table 2). However, $PM_{2.5}$ were not found to be a risk factor for asthma attacks (ORa 1.00; 95% CI 0.99–1.02; p = 0.52). These results were exactly the same when considering the average pollution over the previous 2 to 7 days for both for PM_{10} and $PM_{2,5}$.

Impact of meteorological data

In multivariate analysis, wind speed was a protective factor for asthma, with ORa 0.90 (95% CI 0.87–0.94; p < 0.001) (Table 2), whereas temperature was statistically linked to asthma attack risk, with ORa 1.09 (95% CI 1.01–1.17; p = 0.02). A trend toward increased risk of

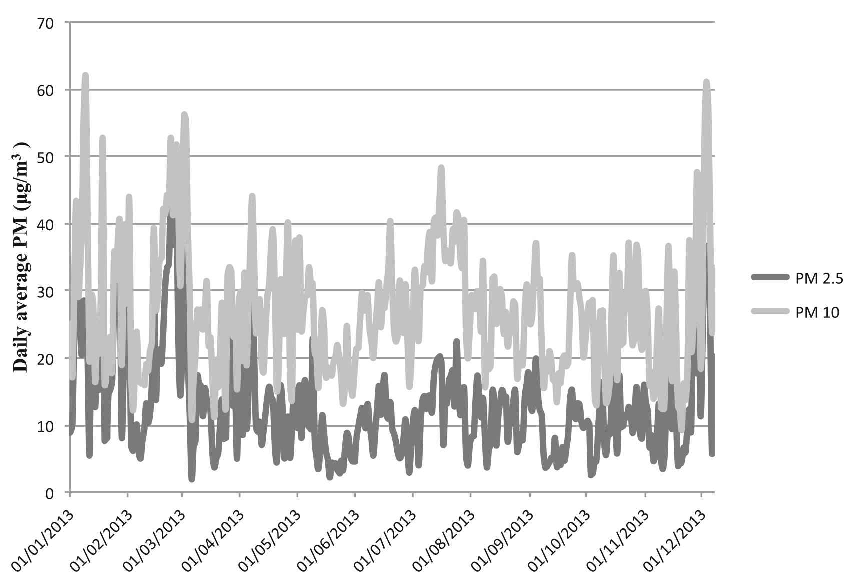

Fig. 2 Temporal evolution of pollutants ($PM_{2.5}$ and PM_{10}) during the study period (daily average measured in µg/m^3). Bouches-du-Rhône, 2013

Table 1 Description study population for asthma-related emergency room visits and controls to emergency departments in Bouches-du-Rhône (n = 1182 cases versus 18,903 controls)

	Asthma (n = 1182)	Controls (n = 18,904)	p
Age (median) (years)	7.7	9.9	<0.001*
Male sex (%)	55	59	0.004*

*$p < 0.005$

asthma was found for rainfall (ORa 1.03; 95% CI 1.00–1.06; p = 0.07) (Table 2). Interactions between wind speed and PM were not significant.

Impact of pollen data

In univariate analysis, *birch-ash* paired was statistically linked to asthma-related ED visits (ORa 0.99; 95% CI 0.98–0.99; p = 0.03). In multivariate analysis, exposure to different taxa was not a risk factor for asthma-related ED visits. Interactions between wind speed and the different taxonomic groups were not statistically significant.

Impact of level of respiratory virus circulation

No association with the risk of asthma-related ED visits was found.

Table 2 Multivariate analysis, by conditional logistic regression, in a case-control nested in a cohort, of different selected variables on asthma-related emergency room visits to emergency departments in Bouches-du-Rhône (n = 1182 cases versus 18,903 controls)

Variables	ORa	(95%) CI	p
Gender	1.14	1.01–1.28	0.04
Age (years)	0.89	0.88–0.90	<0.001
PM_{10} (μg/m^3)	1.02	1.01–1.04	0.02
$PM_{2.5}$ (μg/m^3)	1.00	0.99–1.02	0.52
Rainfall (mm)	1.03	1.00–1.06	0.07
Temperature (°C)	1.09	1.01–1.17	0.02
Wind speed (m/s)	0.90	0.87–0.94	<0.001
Cypress (grains/m^3)	0.99	0.99–1.00	0.33
Urticaceae and grass pollen (grains/m^3)	0.99	0.99–1.01	0.66
Ash and birch (grains/m^3)	0.99	0.99–1.00	0.27
Rhinoviruses	NA	NA	NA
Total virus	NA	NA	NA

Only quantitative variables selected using principal component analysis are represented

ORa adjusted OR, *NA* non-applicable

Discussion

Our study shows a statistically significant association between short-term exposure, from the day of the ED visit up to 1 week before the ED visit, to PM_{10} measured near children's homes and asthma-related ED visits in 3- to 18-year-old children in the Bouches-du-Rhône area in 2013. Exposure to PM_{10} increases the risk of an asthma-related ED visit by 2%. The study, which took into account viral data, pollens and meteorological conditions, also identifies other risk factors: male gender, young age, and higher temperature. Conversely, in this study, higher wind speed is a protective factor for asthma.

Our study has some limitations. Ideally, performing direct personal measurements of exposure would provide a more reliable assessment of the effects of pollutants on asthma symptoms or asthma attacks. Continuous measurement of personal exposure to air pollutants is the gold standard for exposure assessment. However, it is impractical and very costly to measure exposure in the large number of participants necessary to satisfy statistical power requirements [16]. Our assessment of PM exposure levels is thus based on a collective measurement of pollution from stationary positions. While we cannot rule out coding errors on the ED software, asthma has an easily recognizable clinical presentation, so the potential for errors was low on this cohort. Moreover, any coding errors would not be linked to pollution levels. Five EDs did not transmit medical data because they were not equipped with the ED software. The relative gravity of asthma exacerbations was not taken into account, because we compiled diagnostic codes "asthma" and "status asthmaticus" according to only one criterion. Moreover, information on other confounding factors such as tobacco smoke exposure or atopy were impossible to evaluate due to our mode of data collection.

Our study is original in that it evaluates children's exposure to PM based on their home ZIP code. Indeed, many other studies look at exposure levels at the receiving ED hospital. Our assessment is more accurate because, according to INSEE, the average home-school distance in Provence-Alpes-Côte-d'Azur is less than 9 km [13]. Moreover, children are more susceptible than adults to the effects of air pollution because of environmental, behavioral, and physiological factors [18]. Children breathe at a faster rate than adults and spend more time outside engaged in physical activity, so they are exposed to larger doses of ambient air pollution [24].

Despite differences in methods of assessing the PM_{10} rate, our results are consistent with those reported in the literature. The epidemiological study Air Monitoring and Health Programme (PSAS-9) phase II on nine cities in France found a 0 to 1.7% excess risk, statistically significant for all respiratory diseases, of hospital admissions related to PM_{10} exposure level. In this study, PM_{10} data were missing for six towns and asthma-related morbidity was not studied [20]. The APHEA 2 study examined hospital morbidity from 1989 to 1996 in eight European cities, including Paris: a statistically significant link was found between increased PM_{10} values and hospital admissions for asthma. An increase of 10 $\mu g/m^3$ in PM_{10} was associated with a 1.2% increased risk of hospitalization for asthma (95% CI 0.2–2.3) before the age of 14 and 1.1% (95% CI 0.3–1.8) between the ages of 15 and 64. However, this study did not take into account factors such as pollen density or the “circulating viral load,” except for the influenza epidemic period. Furthermore, it covered only Paris, which does not have the same demographic characteristics as the Bouches-du-Rhône area [3]. Samoli et al. studied 3601 asthma-related admissions in 0- to 14-year-old children and found a 2.54% increase mainly in winter and on days of exposure to PM_{10}, with a higher risk of admissions for children aged between 5 and 14 [25]. Sun’s study also found a positive correlation between children’s asthma-related ED visits and exposure to PM_{10} [26]. To note, PM_{10}, but also ozone and nitrogen dioxide, are also found associated with pulmonary exacerbation in other respiratory disease: cystic fibrosis [15].

When considering lags of exposure up to 7 days and asthma-related ED visits, we find the same results than at day 0 exposure. Several studies evaluated lags of exposure for pollutants. Samoli et al. analyzed exposure periods (lag 0, 1, 2) and cumulative exposure for 3 days (lag 0–2) and asthma admissions for 0 to 14 years. For PM_{10}, the highest effect was observed on the same day as the admission but significant result was found for all lags [25].

We did not find a statistically significant correlation between $PM_{2.5}$ level and asthma-related emergency room visits. Contradictory data are found in the literature, probably due to the fact that $PM_{2.5}$ levels are linked to other pollutants through a cocktail effect [11]. In addition, exposure to $PM_{2.5}$ was here evaluated at day 0 and in the previous week at five sites; however, such exposure has been found to be a risk factor for asthma-related ED visits up to 5 days before the medical consultation [12, 14, 17, 29]. Numerous other factors may also affect assessment of the $PM_{2.5}$ effect on asthma, especially when exposure measurements are aggregated.

Regarding meteorological factors, Tosca’s study found a positive association between emergency calls for asthma exacerbation in children, wind speed, and amount of rainfall [27]. In our study, ambient temperature was a risk factor for asthma-related emergency room visits. Wind speed was a protective factor, perhaps by dispersing pollutants. In contrast, our results did not confirm the influence of rainfall, with a trend to a statistically nonsignificant increase in emergency room visits.

Our study differs from the literature in not finding a link between pollen exposure and asthma-related emergency room visits. This may be related to the fact that we had only two pollen-monitoring stations, and that the maximum distance between the BdR municipalities and the measuring stations was roughly 100 km. This meant that exposure levels for cases and controls were similar. In other studies, emergency calls for asthma exacerbation were significantly correlated with pollen exposure between April and August [27].

We did not find a link with the level of respiratory virus circulation. Bonnelyke et al. in their study of 313 children showed a relationship between asthma attacks and number of respiratory infections, not the virus itself [5]. Similarly, Lee’s study found no difference in the detection of viruses among children aged 6 to 14 with asthma exacerbation and those with non-asthma respiratory illness [21]. But our result could also be due to the nested case-control design, as cases and controls showed similar exposure. The present study used data from the Electronic Emergency Department Abstracts mandatory in France and used by the French Institute of Public Health Surveillance for syndromic surveillance, including for asthma [9]. This method could be replicated on a national level, allowing a more accurate evaluation of the effect of viral diseases on asthma-related ED visits.

Conclusion

Our study shows that short-term local exposure to PM_{10}, assessed close to the homes of the children, is responsible for an increased risk of emergency department visits for asthma exacerbation in 3- to 18-year-old children in the Bouches-du-Rhône. These findings require further confirmation from other studies on larger cohorts. Such confirmation would suggest that reinforced preventive or therapeutic strategies should be implemented for children with asthma when air pollution levels exceed the regulatory thresholds for PM_{10}.

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Authors’ contribution 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 and 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.

Antoine Nougairede: Dr. Nougairede designed the virology 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, and 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.

Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflict of interest.

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