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## **Fine Particulate Pollution and Asthma Exacerbations**

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### **Abbreviations:**

APHP Assistance Publique Hôpitaux de Paris

ED Emergency Department

NO<sub>2</sub> Nitrogen Dioxide

O<sub>3</sub> Ozone

PM<sub>10</sub> fine Particulate Matter with an aerodynamic diameter smaller than 10µm

PM<sub>2.5</sub> fine Particulate Matter with an aerodynamic diameter smaller than 2.5µm

RSV Respiratory Syncytial Virus

WHO World Health Organization

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Drs Chappuy, Guedj, Carbajal conceptualized and designed the study, and drafted the initial manuscript.

Drs Bouazza, Foissac, Urien, conceptualized and designed the study, carried out the initial analyses, and reviewed and revised the manuscript.

Pr Tréluyer designed the data collection instruments, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

## ABSTRACT

**Objective:** As the results from epidemiological studies about the impact of outdoor air pollution on asthma in children are heterogeneous, our objectives were to investigate the association between asthma exacerbation in children and exposure to air pollutants.

**Methods:** A database of 1,264,585 pediatric visits during the 2010-2015 period to the emergency rooms from 20 ED of “Assistance Publique Hôpitaux de Paris (APHP)” the largest hospital group in Europe was used. A total of 47,107 visits were classified as asthma exacerbations. Concentration of air pollutants ( $\text{NO}_2$ ,  $\text{O}_3$ ,  $\text{PM}_{10}$  and  $\text{PM}_{2.5}$ ) as well as, meteorological data, evolution of RSV infection and pollen exposition were collected on an hourly or daily basis for the same period using institutional databases. To assess the association between air pollution and asthma, mixed-effects quasi-Poisson regression models were performed.

**Results:** The only compound independently associated with asthma ED visits was  $\text{PM}_{2.5}$  ( $p < 10^{-4}$ ). The association between asthma exacerbation and  $\text{PM}_{2.5}$  was not linear, a sigmoid function described satisfactorily the relationship. The  $\text{PM}_{2.5}$  concentration which gives half the maximum effect was estimated to  $13.5 \mu\text{g}/\text{m}^3$ .

**Conclusions:** We found an association between daily asthma exacerbation in paediatric visits to the ED and fine particulate air pollutants.

## INTRODUCTION

The International Study of Asthma and Allergies in Childhood (ISAAC) found that about 14% of the world's children were likely to have asthmatic symptoms in the last year and suggested that pollution is a major cause of asthma in children<sup>1</sup>. Children may be more vulnerable to the health effects of ambient air pollution because of their higher rates of breathing, narrower airways, developing lungs, and frequent exposure to outdoor air<sup>2,3</sup>. Exposure to high levels, but also to recommended levels of air pollutants, has been shown to aggravate symptoms<sup>4,5</sup>.

A recent systematic review of the literature on the relationship between environmental exposures and asthma in young children<sup>6</sup> identified 27 studies including only 2 studies where acute outdoor pollution was the environmental exposure of interest<sup>7,8</sup>.

A more recent study, not included in this review, examined also the relationship between outdoor pollution and pediatric asthma<sup>9</sup>. The results of these 3 epidemiological studies on the impact of air pollution on asthma in children were heterogeneous due to the diversity of air pollution markers and the lack of adjustment to environmental factors possibly linked together to air pollution (temperature, wind, humidity, viral infections, allergens) and asthma.

The aim of the present study is to examine the association between presentation to hospital for acute asthma and short-term exposure to air pollution after controlling for the confounding factors (i.e., weather, viral environment and allergens).

## METHODS

### *Study population*

Data were extracted from a database of 1, 264, 585 pediatric visits to emergency rooms of the 20 ED of "Assistance Publique Hôpitaux de Paris (APHP)" the largest hospital group in Europe receiving children during the 2010-2015 period (see supplemental Figure 1-4). The

total number of children in these hospitals areas is likely between 600,000 and 1,000,000 (statistics from [www.insee.fr](http://www.insee.fr)). A total of 47,107 visits were classified by pediatrician in the emergency department as asthma exacerbations according to the International Classification of Diseases (ICD 10). The extracted variables for each patient were: name of the hospital, date/hour of visit, age, gender, patient's ZIP code, main diagnosis, disposition after ED visit and date/hour of discharge. The study was approved by the Ethical Committee of Necker Enfants Malades Hospital (Paris).

#### *Pollution data*

Pollution data were collected from September 3, 2010 to September 27, 2015 on an hourly basis from the Paris Air Quality Agency (AirParif, <http://www.airparif.asso.fr/>). The following compounds were monitored: NO<sub>2</sub>, O<sub>3</sub> and fine PM with an aerodynamic diameter smaller than 10 $\mu$ m (PM<sub>10</sub>) and 2.5 $\mu$ m (PM<sub>2.5</sub>). Each pollutant concentration was expressed in  $\mu$ g/m<sup>3</sup>. The number of stations that monitored pollution was 33, 22, 18, 4, for NO<sub>2</sub>, O<sub>3</sub>, PM<sub>10</sub>, and PM<sub>2.5</sub> respectively. The hourly recorded pollution data were averaged to obtain a daily mean exposure for each compound ( $\mu$ g/m<sup>3</sup>).

#### *Environmental data*

Meteorological, viral (RSV) and pollen data were collected for the same period (from September 3, 2010 to September 27, 2015) respectively from the French Meteorology Agency (Meteo France, <https://donneespubliques.meteofrance.fr/>), the reference national center (CNR)/ hospital laboratory network ("réseauRENAL") and the "Réseau National de Surveillance Aérobiologique" (RNSA, <http://www.pollens.fr/accueil.php>).

Meteorological data consisted in maximal daily precipitations (mm), temperature (°C), atmospheric pressure (HPA), wind speed (m/s) and relative humidity (%). The viral data was

focused on the respiratory syncytial virus (RSV). The detection of RSV was made by immunological techniques or by molecular biology (PCR). The virus data were collected on a weekly basis as the number of positive cases in all the microbiological labs of APHP. Total pollen taxas ( $\text{g}/\text{m}^3$ ) was the daily sum of all taxas.

### *Statistical analysis*

The primary endpoint was defined as an ED visit with a main diagnosis of asthma exacerbation. Due to the high variations among stations in the measurement of a given pollutant within a same day, the ZIP code of the patient's residency was linked to the closest measurement station. Global Positioning System (GPS) positions were obtained for all ZIP codes collected in the ED database as well as for all pollution stations. Each pollution station was then linked to several ZIP codes defining a geographical area.

Data description was made through usual tools, using counts and proportions for categorical data; mean, standard deviation, median, interquartile range, and minimal and maximal values for other quantitative data. Correlations between continuous variables were calculated using the non-parametric Spearman's rank correlation test.

Data were analyzed using the nonlinear mixed-effect modeling software program Monolix version 2016R1 (available at [www.lixoft.eu](http://www.lixoft.eu)). To assess the association of daily pollution exposure on occurrence of visit for asthma, mixed-effects quasi-Poisson regression models were performed. A random effect was applied on the geographical area to account for the correlation structure within a given area. Based on preliminary known associations of variables with asthma, the following adjustment covariates were selected: meteorological variables (detailed in "environmental data" section), total pollen-taxas, RSV with the addition of public holydays. To account for non-linearity association a sigmoid function was used

according to the following equation:  $\frac{E_{\max} \times COV}{E_{50} + COV}$ , where COV stands for the continuous

covariate, Emax stands for the maximum change on daily asthma visit associated to COV; E<sub>50</sub> stands for the COV value to reach 50% of the maximum change. All parameters were estimated using the stochastic approximation expectation maximization (SAEM) algorithm combined to a Markov Chain Monte Carlo (MCMC) procedure<sup>10</sup>.

## RESULTS

### *Study population characteristics and environmental data*

From 9/3/2010 to 9/27/2015, a total of 1, 264, 585 ED visits for patients under 18 years of age were recorded involving a total of 47 107 visits with a primary diagnosis of asthma exacerbation (3.7%). The median [IQR] age was 3.5 [1.3 - 8.8] years with 55.4% of boys. The median time spent in the ED was higher for patients admitted for asthma diagnosis compared to the general population (203 vs. 114 min). The patient characteristics are provided in Table 1.

Regarding pollution data, the mean (SD) concentrations over the 5-year period for NO<sub>2</sub>, O<sub>3</sub>, PM<sub>10</sub>, and PM<sub>2.5</sub> were respectively 41.8 (26), 45.5 (22), 29.4 (17) and 18.4 (13) µg/m<sup>3</sup>. It is noteworthy that a decreasing trend was observed from 2011 to 2014 for NO<sub>2</sub>, PM<sub>10</sub> and PM<sub>2.5</sub> with a percent decrease of 6.6%, 20.5% and 25.1% respectively. However, an 5% increase of O<sub>3</sub> concentrations was noticed over the 4-year fully recorded period. For NO<sub>2</sub> and O<sub>3</sub>, the annual mean concentrations were higher than the maximum limit indicated by the European Union and WHO guidelines within the 4-year fully recorded period. Whereas, PM<sub>10</sub> and PM<sub>2.5</sub> annual mean levels were slightly below the EU but above the WHO threshold (see supplemental Figures 5 and 6).

The description of all environmental variables including pollution, meteorological, taxes and RSV are provided in supplemental Table 1.

### *Association between asthma emergency department visits and pollution*

The association between each pollutant and asthma emergency visit was evaluated after adjusting for potential confounding factors. A significant association was found between NO<sub>2</sub>, PM<sub><10</sub>µm and PM<sub><2.5</sub>µm levels and daily number of asthma emergency visits ( $p < 10^{-4}$ ). Interestingly, association between particles from 2.5 to 10 µm and asthma emergency visit resulted in a non-significant relationship ( $p = 0.90$ ), suggesting that PM<sub>10</sub> effect was mainly due to particles with a diameter less than 2.5 µm. No significant association was found with O<sub>3</sub> ( $p = 0.98$ ).

A multiple regression Poisson model was thereafter used including both NO<sub>2</sub> and PM<sub>2.5</sub>. In this model, while PM<sub>2.5</sub> remained highly correlated to daily number of asthma emergency visits ( $p < 10^{-4}$ ), NO<sub>2</sub> was not significant anymore ( $p = 0.062$ ) suggesting that particles  $< 2.5$  µm was the only compound independently associated with asthma ED visits. Furthermore, addition of an NO<sub>2</sub> effect to the model including only PM<sub>2.5</sub> compound did not improve the fit and provided a significant increase in the Bayesian information criterion (BIC).

A non-linearity relationship was found between PM<sub>2.5</sub> concentrations and number of asthma exacerbation visits. The use of a sigmoid function provided a significant drop in the BIC (-2916 units). According to the model, the number of daily asthma visits appeared to increase gradually with PM<sub>2.5</sub> up to a plateau (estimated E<sub>max</sub>: +135%). The PM<sub>2.5</sub> concentration which gave half of this plateau was estimated to 13.5 µg/m<sup>3</sup>. Table 2 summarizes the results of the final Poisson regression estimates. Regarding meteorological variables, humidity and RSV were positively associated with number of asthma visits. Figure 1 shows the observed numbers of asthma ED visits per day as a function of time in the overall EDs included in this study. The superimposition of the model prediction, that takes all covariates into account,



upon the observations provides a visual inspection of the goodness-of-fit during the studied period.

The sigmoid function that describes the relationship between number of asthma ED visits and PM<sub>2.5</sub> concentrations is displayed in Figure 2. According to the model, European standards and WHO recommendations (annual mean of 25 µg/m<sup>3</sup> and 10 µg/m<sup>3</sup>) stand for 65% and 42% of the maximum estimated effect for PM<sub>2.5</sub> respectively.

## DISCUSSION AND CONCLUSIONS

Our study has shown a significant association between outdoor air pollution by PM<sub>2.5</sub> and the number of visits for pediatric asthma exacerbations in the largest urban French area. The source of particulate matters is mainly power stations, motor vehicles and domestic coal burning. They include a carbon core surrounded by chemicals (sulfates, metals or polycyclic aromatic hydrocarbons). Fine particles (<2.5 micrometers) can remain suspended longer in the atmosphere compared to the bigger ones and reach the end of the respiratory tract<sup>11</sup>. Currently, in France, emergency procedures in case of pollution peak or persistence of a pollution episode consist on both public recommendations (i.e., vulnerable and sensitive individuals are advised to avoid intense physical activities) and restricting measures (i.e., suspension of activities contributing to pollution such as industries and transport, including vehicle traffic).

The results of our study are consistent with those obtained in Seville that relate hospitalization for acute respiratory diseases including bronchiolitis, pneumonia, asthma, and bronchitis and other causes to PM<sub>2.5</sub> in children<sup>10</sup>.

In our study, no association of O<sub>3</sub> with asthma ED visit was found. A study conducted in New York City in 2010, found that both PM<sub>2.5</sub> and O<sub>3</sub> were associated with an increased risk of asthma hospitalizations<sup>13</sup>. Gass et al.<sup>9</sup> found also a multipollutant joint effects (NO<sub>2</sub>, O<sub>3</sub> and

PM<sub>2.5</sub>) on pediatric asthma emergency department visits. However, in our analysis the overall confounders that could affect the association between pollutants and asthma exacerbations were taken into account: meteorological factors, data for pollen and RSV count. Furthermore, due to a relatively high correlation between NO<sub>2</sub> and PM<sub>2.5</sub> levels in our study (Spearman's rho=0.7), no additional effect of NO<sub>2</sub> was observed after accounting for PM<sub>2.5</sub> concentrations. Other methodological approaches were also previously used in order to assess the association between air pollutant mixtures and clinical endpoints<sup>9,14</sup>. These approaches are based on classification and regression tree methods. Our analysis was based on traditional pollutant regression models which is currently the most commonly used and preferred method in this context.

We observed a non-linearity regarding the association between asthma exacerbation and PM<sub>2.5</sub>. According to the model, the number of daily asthma visits appeared to increase strongly with PM<sub>2.5</sub> up to 20 µg/m<sup>3</sup>, a change in shape was observed thereafter toward an asymptote. PM<sub>2.5</sub> concentration which gave half of this plateau was estimated to 13.5 µg/m<sup>3</sup>. These findings are consistent with the results obtained by Pablo-Romero et al.<sup>12</sup>. The authors report a constant increase of hospital pediatric admission rate specifically for asthma until a value around 20 µg/m<sup>3</sup>.

Our study has several limitations: i) in the Poisson model, we assumed the population at risk was constant throughout the study period, however given the massive pediatric population size in Ile de France district, no substantial variation is expected during the study period, ii) Another limitation is the number of stations measuring specifically particulate matters below 2.5 µm. Only four stations were available in this study for Paris district area. The median distance between patient's home and the nearest pollution station was 4 km, so that individual's PM<sub>2.5</sub> exposure may not be highly accurate. However, it is noteworthy that daily levels recorded by these stations were highly correlated (Spearman's rho>0.7) suggesting that

the trends in PM<sub>2.5</sub> emissions were similar across the different geographical areas. iii) Finally, the observational design of this study cannot lead us to conclude regarding causal effects of pollutants and only associations can be pointed out.

The Air Quality Guidelines (AQGs) set by WHO are stricter than the EU air quality standards for PM<sub>2.5</sub><sup>11</sup>. The WHO and EU target values were 10 and 25 µg/m<sup>3</sup> respectively. The EU target for PM<sub>2.5</sub> is probably too high to reduce significantly the number of visits for asthma in ED. It suggests to take further action to reduce pollutant emissions and improve air quality.

**Acknowledgments:** We thank all participant centers, Sandrine Chipot and Mathias Huitorel from the d-sisif and Laurent Tréluyer, Director of Information Systems from APHP.

### **What is already known on this topic?**

Epidemiological studies on the impact of air pollution on asthma in children are heterogeneous due to the diversity of air pollution markers and the lack of adjustment to environmental factors possibly linked to air pollution and asthma.

### **What this study adds?**

- There is an association with daily concentrations of PM<sub>2.5</sub> particles and asthma ED visits in children.
- These concentrations may be lower than targets recommended by the European Union.

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## LEGENDS FOR FIGURES

### **Figure 1.**

Observed numbers of asthma ED visits per day as a function of time. The blue curve stands for the Poisson model predictions. The area stands for the 95% prediction interval.

### **Figure 2.**

PM<sub>2.5</sub> maximum effect in percent as a function of PM<sub>2.5</sub> concentrations. Blue area stands for the 95% confidence interval.

### **Table 1.**

Characteristics of patients (aged less than 18 years) from 9/3/2010 to 9/27/2015

### **Table 2.**

Poisson regression estimates measuring the association between asthma exacerbation visits to the ED and various meteorological pollen, virus and pollution factors.

### **Supplemental Table 1.**

Description of environmental variables from 9/3/2010 to 9/27/2015.

### **Supplemental Figure 1.**

Map of “Ile de France” region. Red stars stand for public hospital network included in our study and blue circles stand for NO<sub>2</sub> pollution stations.

### **Supplemental Figure 2.**

Map of “Ile de France” region. Red stars stand for public hospital network included in our study and green circles stand for O<sub>3</sub> pollution stations.

### **Supplemental Figure 3.**

Map of “Ile de France” region. Red stars stand for public hospital network included in our study and yellow circles stand for PM<sub>10</sub> pollution stations.

### **Supplemental Figure 4.**

Map of “Ile de France” region. Red stars stand for public hospital network included in our study and black circles stand for PM<sub>2.5</sub> pollution stations.

### **Supplemental Figure 5.**

Annual mean pollutant concentrations from 2011 to 2014. Vertical lines stand for standard deviations. Horizontal red lines stand for Europe Union annual limit for NO<sub>2</sub> (40µg/m<sup>3</sup>), O<sub>3</sub> (30µg/m<sup>3</sup>), PM<sub>10</sub> (40µg/m<sup>3</sup>), PM<sub>2.5</sub> (25µg/m<sup>3</sup>) respectively.

### **Supplemental Figure 6.**

Time series of NO<sub>2</sub>, O<sub>3</sub>, PM<sub>10</sub> and PM<sub>2.5</sub> fluctuations over time from 2010 to 2015. Horizontal lines stand for Europe Union annual limit for NO<sub>2</sub> (40µg/m<sup>3</sup>), O<sub>3</sub> (30µg/m<sup>3</sup>), PM<sub>10</sub> (40µg/m<sup>3</sup>), PM<sub>2.5</sub> (25µg/m<sup>3</sup>) respectively.

**Table 1. Characteristics of patients (aged less than 18 years) from 9/3/2010 to 9/27/2015**

	<b>Total patients n = 1 264 585</b>	<b>Patient visits for Asthma n = 47 107</b>
Age (year)	3.50 [1.25 - 8.75]	3.08 [1.58 - 6.25]
Sex (boys)	996 519 (55.4%)	29816 (63.3%)
Time in ED (min)	114 [66 - 195]	203 [138 - 293]
Total visit (Year)		
2010 (from 9/3/2010)	116093 (6.5%)	3397 (7.2%)
2011	358995 (20%)	8233 (17.5%)
2012	352460 (19.6%)	9694 (20.6%)
2013	349575 (19.4%)	9378 (19.9%)
2014	367967 (20.5%)	10588 (22.5%)
2015 (to 9/27/2015)	254237 (14.1%)	5817 (12.3%)
French department		
75	641 081 (35.6%)	12 060 (25.6%)
77	19 610 (1.09%)	447 (0.95%)
78	34 873 (1.94%)	903 (1.92%)
91	30 352 (1.69%)	722 (1.53%)
92	422 105 (23.5%)	12 958 (27.5%)
93	378 660 (21.0%)	11 501 (24.4%)
94	226 708 (12.6%)	7 318 (15.5%)
95	45 938 (2.55%)	1 198 (2.54%)
Distance between home and pollution station (km)		
NO <sub>2</sub>	1.67 [1.08 - 2.45]	1.72 [1.23 - 2.45]
O <sub>3</sub>	2.81 [1.88 - 3.95]	2.94 [1.90 - 4.14]
PM <sub>10</sub>	2.21 [1.67 - 3.42]	2.30 [1.70 - 3.48]
PM <sub>2.5</sub>	4.39 [3.11 - 5.46]	4.21 [2.91 - 5.46]

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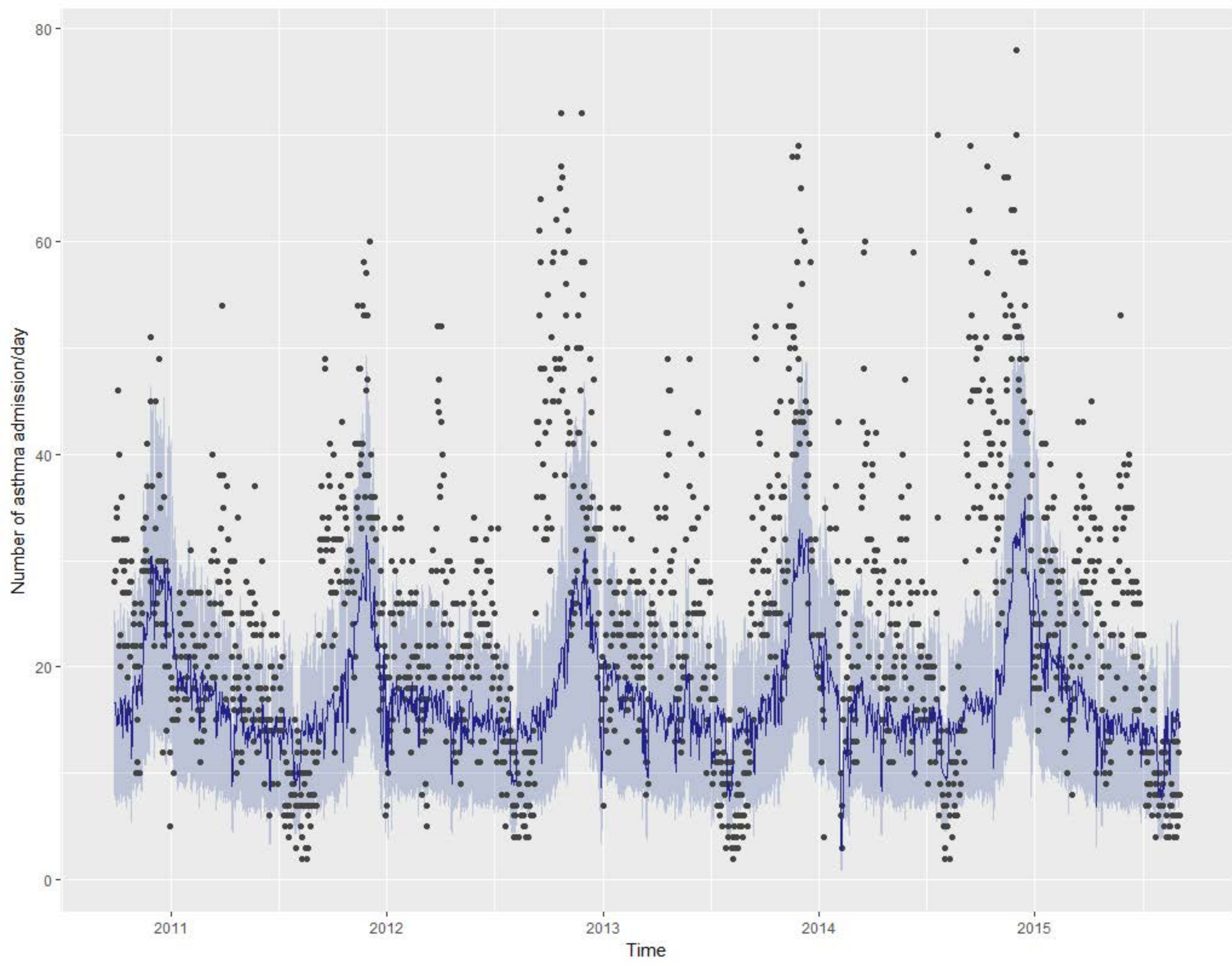
*Median [interquartile range] for continuous variables and count (percent) for categorical variables*

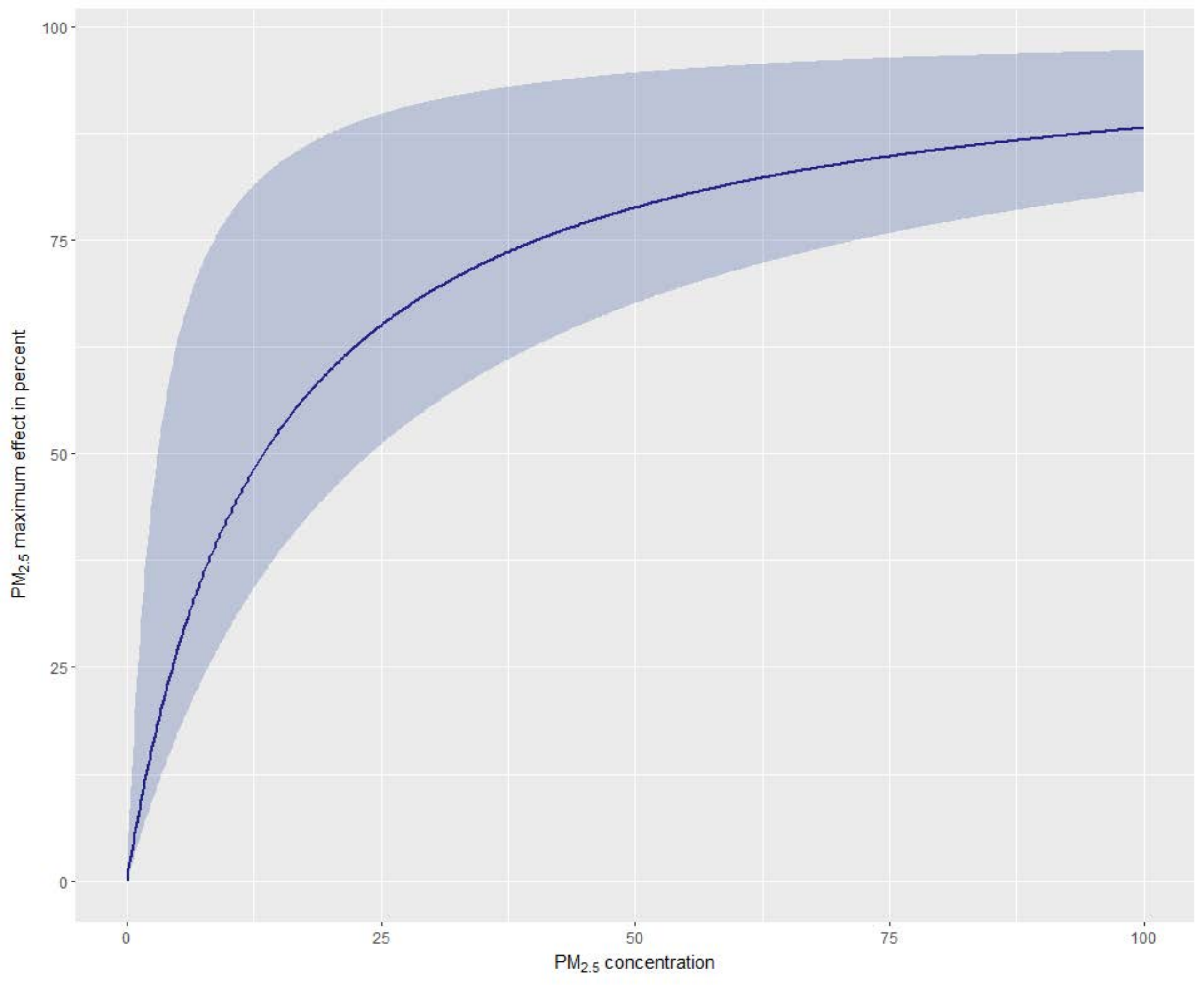
**Table 2. Poisson regression estimates measuring the association between asthma exacerbation visits to the ED and various meteorological pollen, virus and fine particles.**

	Parameter	SE	p-value
<b>Baseline</b>	1.4	0.2	<10 <sup>-4</sup>
$\omega_{Baseline}$	0.37	0.13	0.005
<b>PM<sub>2.5</sub> : E<sub>50</sub> (µg/m<sup>2</sup>)</b>	13.5	5.4	0.012
<b>PM<sub>2.5</sub> : E<sub>max</sub></b>	+139.00%	0.2	<10 <sup>-4</sup>
<b>Precipitations (mm)</b>	+0.02%	0.014	0.99
<b>Temperature (°C)</b>	0.00%	0.0039	0.99
<b>Atmospheric pressure (HPA)</b>	0.00%	0.00033	0.99
<b>Wind speed (m/s)</b>	-0.31%	0.017	0.85
<b>Relative humidity (%)</b>	+1.19%	0.0026	<10 <sup>-4</sup>
<b>Total pollen taxas (g/m<sup>3</sup>)</b>	0.00%	0.00011	0.97
<b>Respiratory syncytial virus (RSV) (n)</b>	+1.30%	0.00091	<10 <sup>-4</sup>
<b>Public holidays</b>	-92.80%	0.081	<10 <sup>-4</sup>

Keynotes: Parameter estimates refer to percentage change on daily asthma exacerbation visit number for one-unit increase of continuous variables (i.e., Precipitations, Temperature, Atmospheric pressure, Wind speed, Relative humidity, Total pollen taxas, Respiratory syncytial virus).  $\omega_{Baseline}$  stands for the standard deviation of inter-geographical-area variability. E<sub>max</sub>, maximum percentage change on daily asthma exacerbation visit number associated to PM<sub>2.5</sub> concentrations; E<sub>50</sub> stands for the PM<sub>2.5</sub> concentration value to reach 50% of the maximum percentage change.





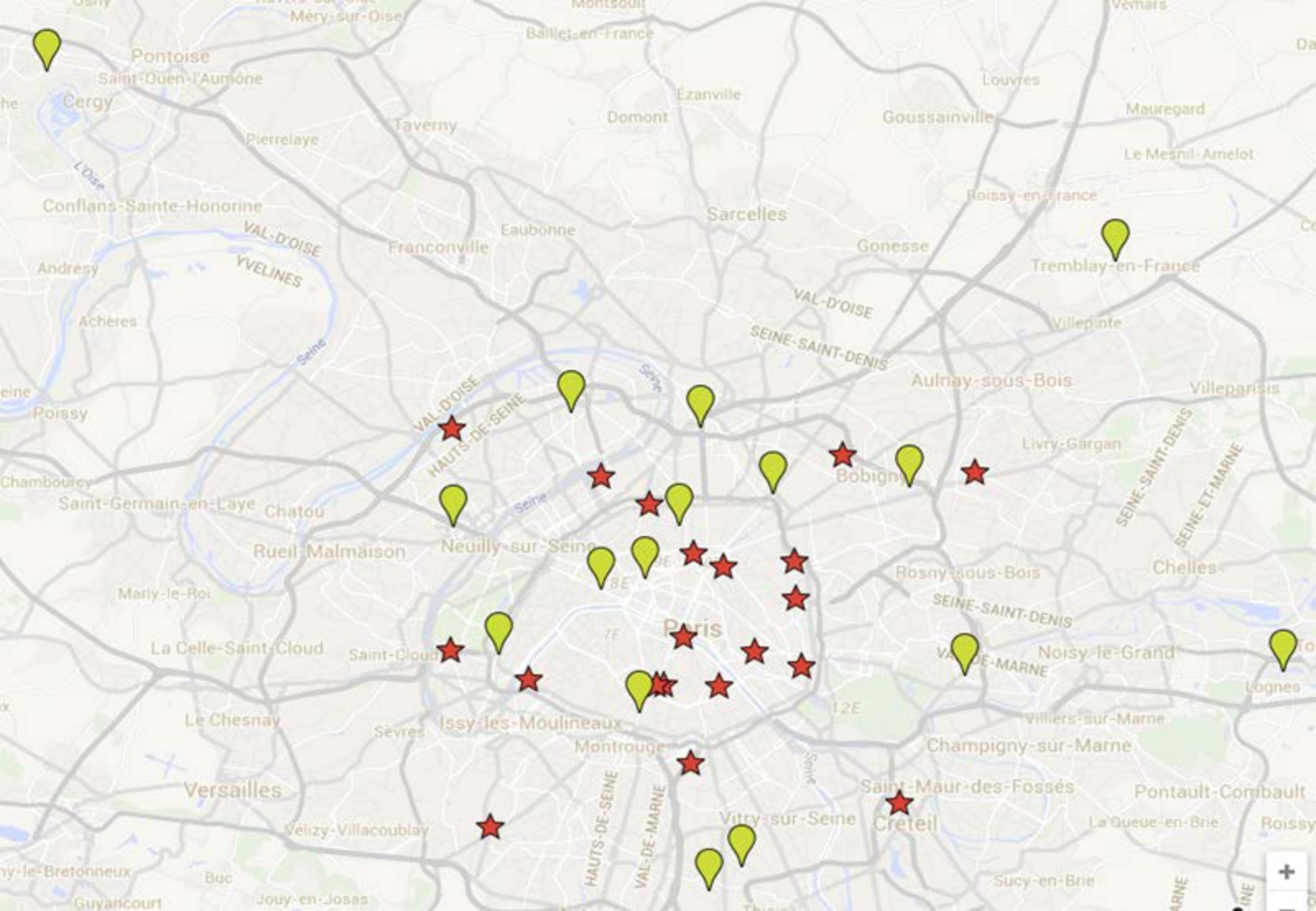


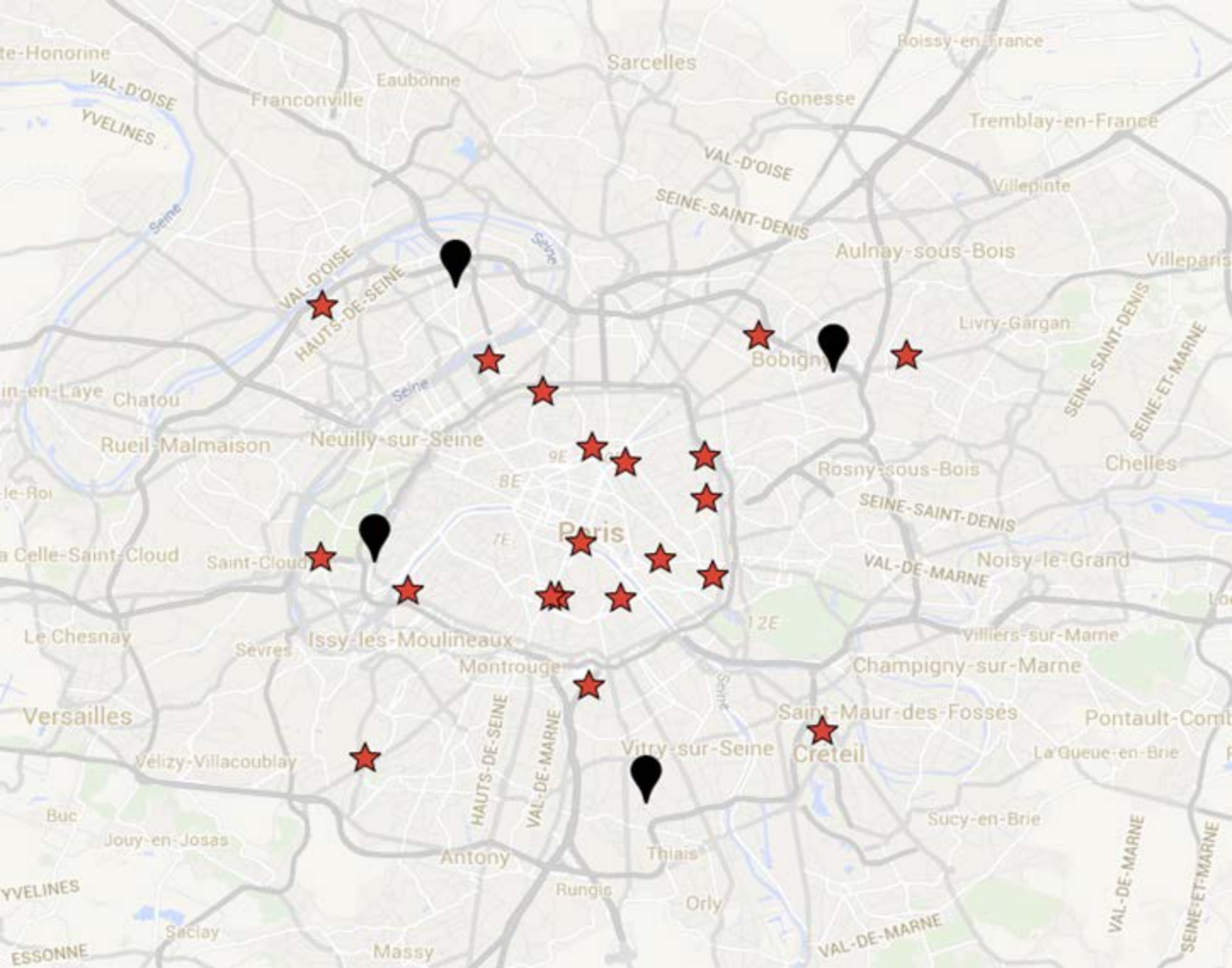
**Supplemental Table 1. Description of environmental variables from 9/3/2010 to 9/27/2015**

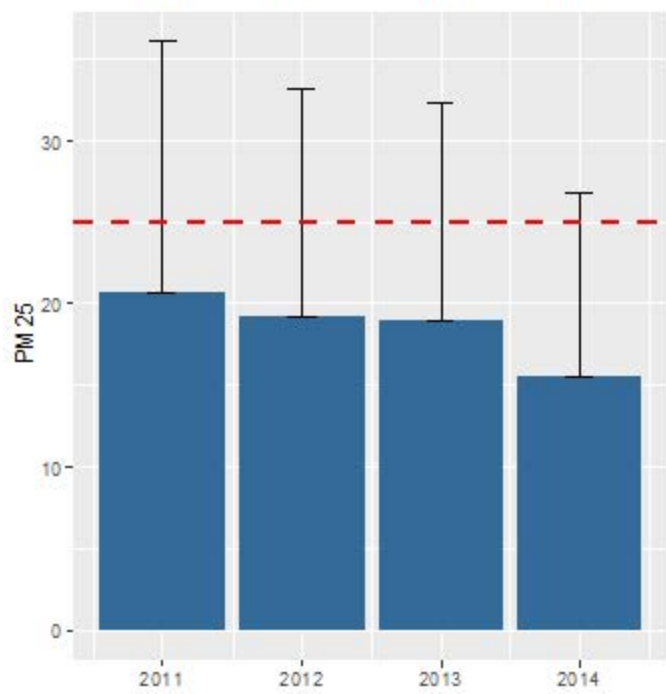
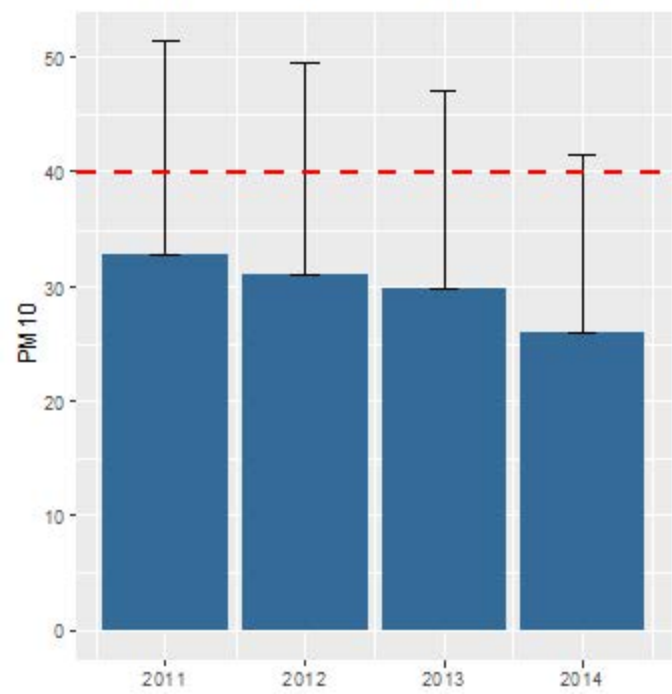
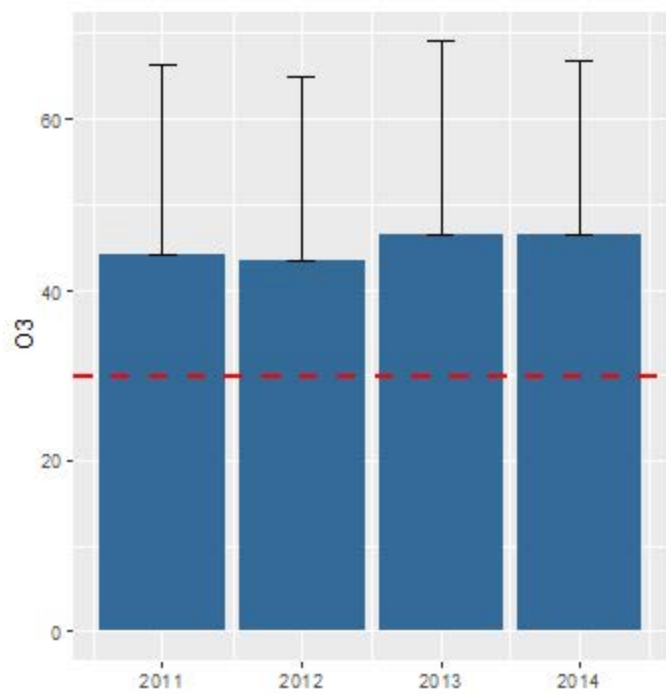
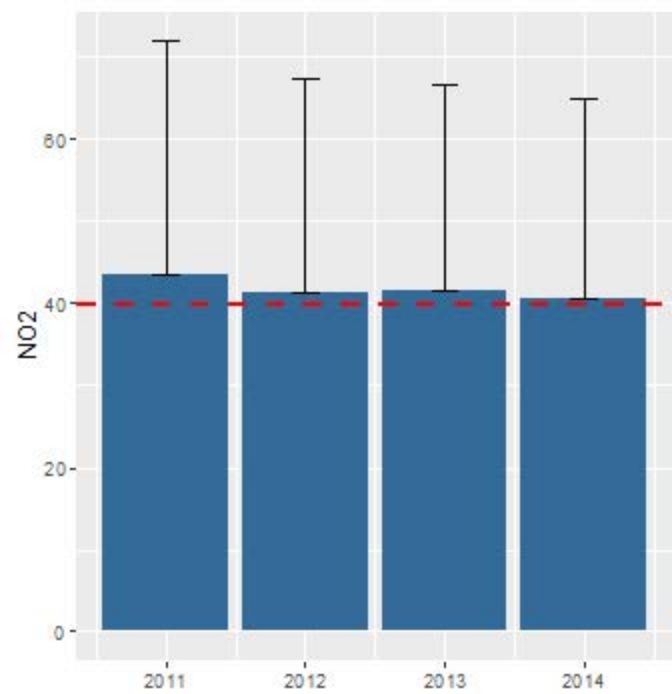
Year		Pollution (µg/m3)				Weather					Pollen	Virus (n)
		NO2	O3	PM10	PM2.5	Precipitations (mm)	Temperature (°C)	Atmospheric pressure (HPA)	Wind speed (m/s)	Relative humidity (%)	Total pollen taxas	Respiratory syncytial virus (RSV)
2010	mean (sd)	48.5 (26.4)	30.1 (17.1)	28.9 (14.4)	20.5 (11.2)	0.7 (1.3)	11.3 (7.5)	1006.7 (9.5)	4.7 (1.5)	87.5 (5.6)	2.3 (8.9)	89.2 (70.7)
	median [IQR]	43.4 [30.3 - 60.6]	29.7 [16.3 - 42.1]	26.4 [17.6 - 37.9]	18.8 [11.2 - 27.2]	0 [0 - 1]	11.1 [4.1 - 17.5]	1007.9 [999.2 - 1013.3]	4.5 [3.6 - 5.7]	89 [85 - 92]	0 [0 - 0]	92 [5 - 170]
	min-max	0.9 - 197.1	0.04 - 94.92	2.7 - 87.5	2.2 - 63.6	0 - 8.9	-0.6 - 26.4	971.1 - 1025.6	2 - 9.2	61 - 94	0 - 86.6	1 - 179
2011	mean (sd)	43.6 (28.3)	44.3 (22.1)	32.7 (18.8)	20.7 (15.4)	0.6 (1.8)	16.8 (6.9)	1011.7 (7.2)	4.6 (1.4)	82.8 (9.3)	107.2 (204.8)	38.2 (51.2)
	median [IQR]	37.0 [22.9 - 56.0]	44.5 [28.2 - 58.8]	28.5 [18.8 - 41.5]	17.3 [8.9 - 27.1]	0 [0 - 0.4]	17 [11.8 - 22.1]	1011.9 [1007.1 - 1016.4]	4.4 [3.6 - 5.4]	85 [79 - 90]	27.3 [0 - 129.3]	16 [1 - 56]
	min-max	1.3 - 203.8	0 - 123	0 - 124	0 - 89.5	0 - 20.2	-0.4 - 36.4	989 - 1029.7	1.4 - 10.1	46 - 95	0 - 1644.1	0 - 212
2012	mean (sd)	41.4 (26.0)	43.4 (21.5)	31.0 (18.5)	19.3 (13.9)	0.7 (1.5)	15.2 (7.3)	1010.8 (8.6)	4.8 (1.5)	84.2 (8.5)	1.5 (9.6)	36.2 (50.6)
	median [IQR]	35.5 [22.7 - 53.5]	44.8 [27.1 - 57.0]	26.1 [17.0 - 40.1]	15.2 [8.7 - 25.8]	0 [0 - 0.8]	14.2 [10.4 - 20.9]	1010.6 [1005.5 - 1017.1]	4.7 [3.7 - 5.7]	86 [79 - 90]	0 [0 - 0]	13 [3 - 51]
	min-max	0.4 - 205.8	0.1 - 173.9	3.5 - 134.4	1.3 - 80.6	0 - 13.4	-2.8 - 38.1	985.4 - 1029.3	2.2 - 10.1	50 - 96	0 - 142.7	1 - 186
2013	mean (sd)	41.6 (24.8)	46.4 (22.8)	29.8 (17.4)	18.9 (13.3)	0.7 (1.8)	14.6 (7.9)	1010.0 (8.4)	4.8 (1.4)	86.0 (8.3)	93.3 (207.8)	41.6 (60.1)
	median [IQR]	36.4 [23.8 - 52.8]	46.4 [29.8 - 61.4]	26.1 [16.8 - 38.8]	15.2 [9.2 - 24.5]	0 [0 - 0.8]	14 [8.6 - 20.2]	1010 [1005.1 - 1016.2]	4.7 [3.7 - 5.8]	88 [81 - 92]	7.8 [0 - 87.3]	12 [2 - 62]
	min-max	0 - 171.1	0.5 - 135.3	3.1 - 134.5	2.1 - 83.8	0 - 18.9	-1.7 - 35.5	981.8 - 1030.8	1.8 - 10.2	57 - 98	0 - 1747.1	0 - 208
2014	mean (sd)	40.7 (24.3)	46.5 (20.4)	26.0 (15.6)	15.5 (11.2)	0.8 (1.7)	16.5 (6.3)	1008.2 (7.7)	4.8 (1.5)	89.2 (7.5)	129.7 (219.5)	44.2 (70.3)
	median [IQR]	35.4 [23.8 - 52.1]	48.0 [32.7 - 61.1]	22.5 [15.2 - 32.9]	12.9 (8.2 - 19.3)	0 [0 - 0.8]	16.2 [11.2 - 21.3]	1008.2 [1003.8 - 1013.5]	4.5 [3.6 - 5.7]	91 [85 - 95]	38.2 [0 - 193.4]	9 [1 - 50]
	min-max	0.8 - 174.0	0 - 124.1	3.8 - 147.8	1.5 - 104.6	0 - 14.7	2.9 - 35.2	985.1 - 1031.1	1.7 - 11.6	61 - 99	0 - 1900.7	0 - 256
2015	mean (sd)	38.8 (25.7)	54.6 (21.3)	26.6 (15.9)	15.8 (12.2)	0.5 (1.7)	17.2 (8.2)	1012.3 (8.4)	5.0 (1.6)	82.7 (9.3)	168.9 (253.0)	26.5 (36.6)
	median [IQR]	32.8 [19.1 - 51.8]	55.9 [40.7 - 68.5]	22.2 [15.33 - 33.9]	12.2 [8.2 - 18.9]	0 [0 - 0.6]	18.3 [10.5 - 22.8]	1012.4 [1007.6 - 1017.7]	4.7 [3.9 - 6.1]	84 [77 - 90]	111.3 [13.3 - 208.3]	6 [2 - 47]
	min-max	1.88 - 185.08	1.3 - 144.5	1.5 - 138.4	2.7 - 100.6	0 - 11.3	1.7 - 39.1	974.3 - 1032.1	2 - 10	55 - 99	0 - 1963.3	0 - 153



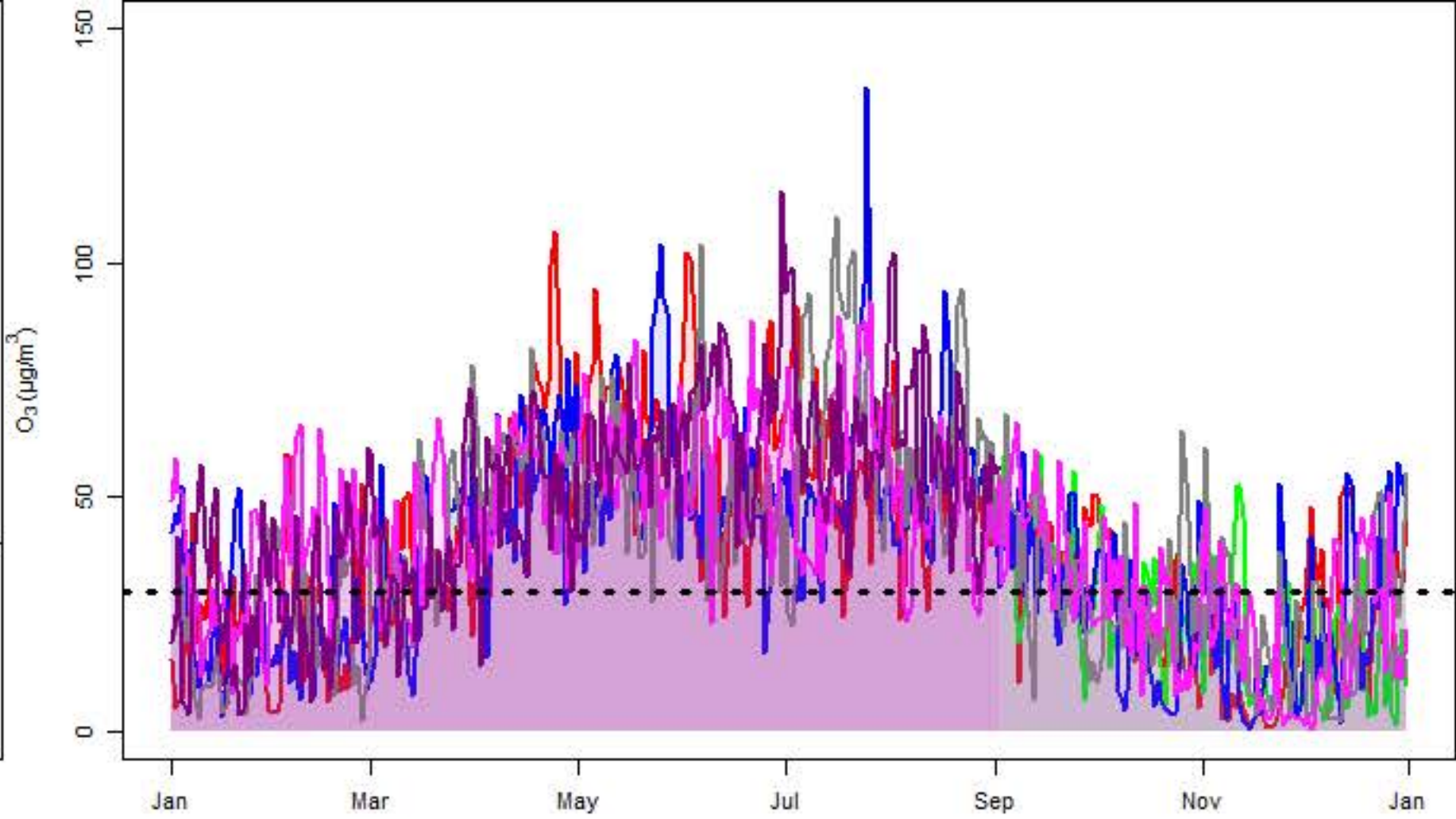
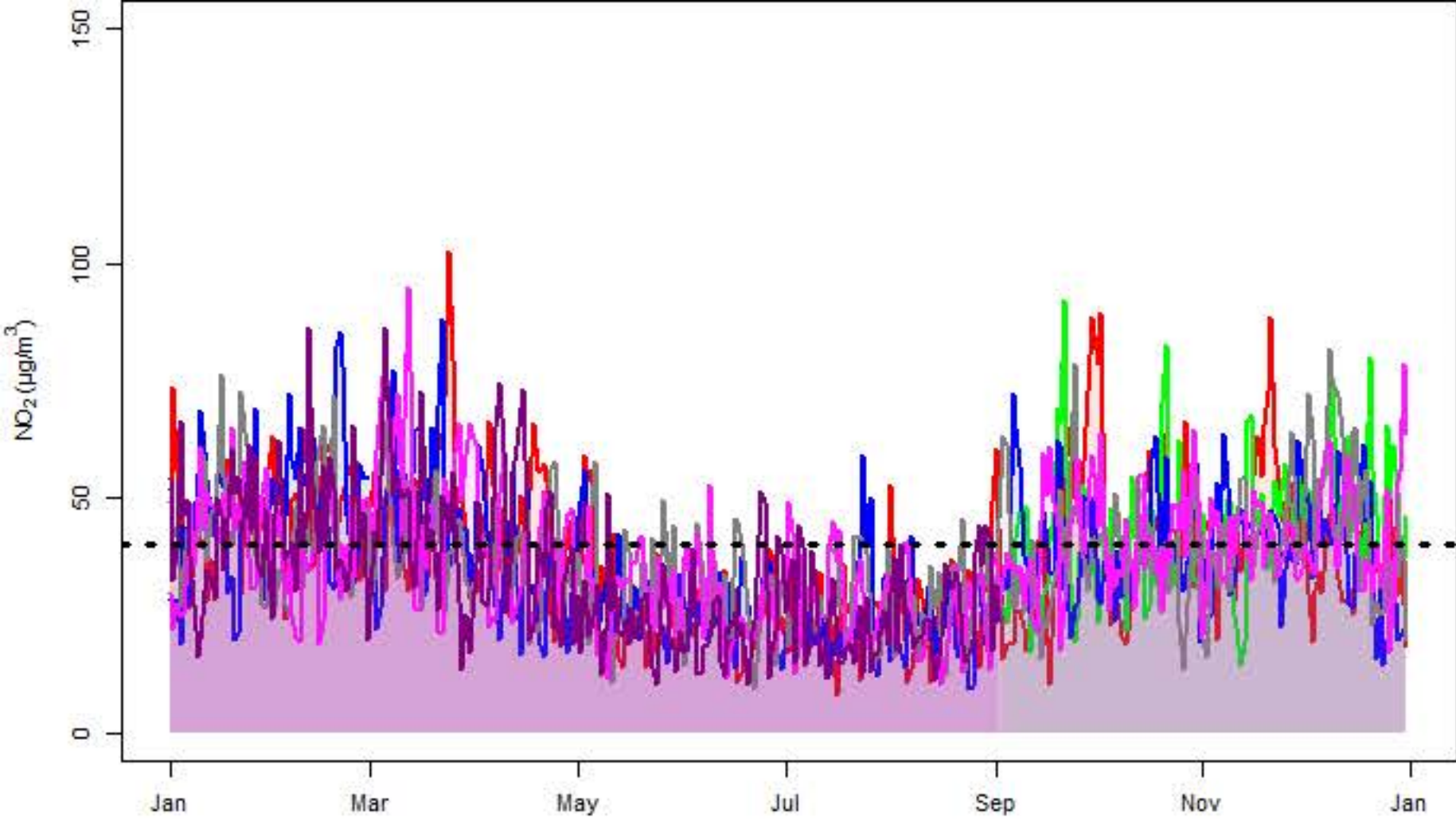












- 2010
- 2011
- 2012
- 2013
- 2014
- 2015

