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# Effects of short-term exposure to particulate matter on emergency department admission and hospitalization for asthma exacerbations in Brescia district

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## ABSTRACT

**Background:** Rising pollution plays a crucial role in worsening several respiratory diseases. Particulate Matter (PM)-induced asthma exacerbations are one of the most dangerous events.

**Objectives:** To assess the correlation between progressive particulate matter short-term exposure and asthma exacerbations, we investigated the role of PM levels on Emergency Department (ED) admissions and hospitalizations for these events in Brescia, an important industrial city located in northern Italy with high yearly levels of air pollution.

**Methods:** We analyzed 1050 clinical records of ED admissions for suspected asthma exacerbation, starting from January 2014 to December 2017. Daily PM levels were collected from the Environmental Protection Regional Agency. We performed a time-series analysis using a Poisson regression model with single and multiple day-lag. Results were expressed as Relative Risk (RR) and Excess of Relative Risk (ERR) of severe asthma exacerbation over a 10 $\mu$ g/m<sup>3</sup> increase in PM<sub>10</sub> and PM<sub>2.5</sub> concentration.

**Results:** We selected and focused our analysis on 543 admissions for indisputable asthma exacerbation in ED and hospital. The time-series study showed an increase of the RR (CI95%) for asthma exacerbation-related ED admissions of 1.24 with an ERR of 24.2% for PM<sub>2.5</sub> at lag0-1 ( $p < 0.05$ ). We also estimated for PM<sub>2.5</sub> a RR (CI95%) of 1.12 with an ERR of 12.5% at lag0-5 ( $p \leq 0.05$ ). Again, for PM<sub>2.5</sub>, an increase of the RR (CI95%) for asthma exacerbation-related hospitalizations of 1.31 with an ERR of 30.7% at lag0-1 ( $p < 0.05$ ) has been documented. These findings were confirmed and even reinforced considering only the population living in the city.

**Conclusions:** Short-term PM exposure, especially for PM<sub>2.5</sub>, plays a critical role in inducing asthma exacerbation events leading to ED admission or hospitalization.

**Keywords:** Environmental Development, Epidemiology, Prevention, Quality of Life, Morbidity and Mortality

## INTRODUCTION

Asthma exacerbation is one of the most relevant acute complications in patients with bronchial asthma. The main recurring symptoms are chest tightness, wheezing, dry cough, breathlessness due to acute broncho-obstruction [1]. A heterogeneous plethora of etiologic factors can trigger it, and its symptoms can occur at any time, even without significant prodromic signs [2-3]. In patients with asthma, exacerbations are among the most serious and, sometimes, life-threatening events, always requiring the use of the so-called "Emergency Drugs" to revert the diffuse bronchospasm and high doses of topic steroidal drugs. A progressive increase in dosages and concentrations of basal therapies or a shift to other classes of basal and/or control drugs may also be required [4].

In the worst severe exacerbations, treatments available might only be partially or even not effective, and in these cases, systemic and sometimes invasive treatments, provided in the Emergency Departments or during hospitalization, are the only effective therapeutic options [5].

The quality of life of patients with frequent exacerbations may also dramatically compromised [6-7]. From the simplest to the most complex, everyday actions may be impaired by exacerbation-related symptoms or even by the patient's fear of their sudden onset [8-9]. Furthermore, the triggering exacerbating factors are heterogeneous and often devious. Some are associated with pathologic conditions such as bacterial or viral infections, others with accidental expositions to airborne particles or allergens [10].

Among these triggers, airborne pollutants are developing an increasing clinical and epidemiological interest [11]. Both young and older asthmatic populations may manifest exacerbation-related symptoms after a short-term exposition, but these specific etiological triggers are extremely variable in molecular composition, concentration of each pollutant, involved area, and exposure time [12-13].

Particulate Matter (PM) is one of the most diffused and analyzed pollutants. Particulate Matter is a complex of particles classified according to their dimensions: PM<sub>10</sub> for median mass aerodynamic diameter (MMAD) equal or lower than 10  $\mu\text{m}$ , PM<sub>2.5</sub> (also called Fine Particulate Matter) for MMAD lower than 2.5  $\mu\text{m}$ , and PM<sub>0.1</sub> (also called Ultra-Fine Particulate Matter) for MMAD below 0.1  $\mu\text{m}$  [14-15]. Several studies have already demonstrated a strong correlation between Particulate Matter, mainly Fine and Ultra-Fine PM exposure, and the onset or worsening of several clinical conditions. Among them, the respiratory and cardiovascular ones are among the most frequent and clinically relevant [16-20].

Highly industrial, overpopulated, and dust-storm-prone cities are particularly affected by air pollution. Air pollution is associated with a high presence of pollutants emitting sources such as biomass, burning processes, diesel fuel combustion, fossil fuel power plants, vehicles' exhausts, industrial processes, agriculture, and wildfires [21-22].

Most of the studies conducted in these contexts agree with underling the role of airborne pollution in the development and worsening of numerous respiratory conditions [23].

Despite being counted as one of the most representative triggers, only a few studies about the effects of time-dependent exposure to airborne pollutants are available in Italy. Especially in the northern regions, several Italian cities struggle with pollution due to an unfavorable geographic morphology for the pollutants' dispersion and a high population and industrial density [24]. Our work aims to fill

this gap, providing a retrospective analysis of the effects of short-term exposure to Particulate Matter (PM<sub>10</sub>) and Fine-Particulate Matter (PM<sub>2.5</sub>) in the population living in Brescia and its suburbs.

In order to increase the level of informativeness and exclusivity of our work, we opted for the analysis of a city poorly represented in the literature. In addition, we focused on the study of asthma exacerbation as a single complication of a unique clinical event.

Brescia is the district capital of a large-size administrative area ("Provincia di Brescia") in Northern Italy, with an important industrial substrate, a high population density (1,265,954 inhabitants for a surface of 4,785.48 Km<sup>2</sup>, and a population density of 264.5 inhabitants/Km<sup>2</sup>), and one of the highest pollution concentrations in Europe [25].

## **METHODS**

### **Hospital admission data**

We considered the Spedali Civili Hospital of Brescia as a reference health center for our study and collected and analyzed the Emergency Department (ED) patients' admission records due to respiratory-related clinical conditions, from Jan 1, 2014, to Dec 31, 2017, using the PSWEB software. For the analysis, we only considered records related to asthma exacerbations. Through the involvement in the evaluation process of different clinical specialists, for every single record, we conducted a multidisciplinary analysis to selectively enroll only patients affected by exacerbated asthma, regardless of its severity class, the underlying etiological trigger, age, sex, prior illness, and social status. Precisely, asthma exacerbation was defined as the rapid increase of typical respiratory symptoms severity, leading to the increment of usual inhalation treatment and/or assumption of systemic oral corticosteroids without perceived benefit in subjects suffering from asthma.

To ensure the highest possible data quality and to reduce selection bias, we reviewed the ED records with dedicated focuses on ICD-Codes, observed and reported patients' conditions and related color code, medical history, ED physician physical examination, blood sample analysis, X-ray, and/or CT reports (where available), specialists visits, discharge diagnosis with outcomes and hospitalization clinical records. ED records have been collegially analyzed by a multidisciplinary team composed of two pneumology specialists, an ED department physician, an epidemiology specialist, an epidemiology resident doctor, and two trained graduating Medical students. Duplicated records and asthma exacerbation-unrelated respiratory records have been removed from the analysis.

### **Air pollution and meteorological data**

As a measure of air pollution, we used the daily mean concentration for Particulate Matter (PM<sub>10</sub>) and Fine Particulate Matter (PM<sub>2.5</sub>) from Jan 1, 2014, to Dec 31, 2017, as measured by the Regional Agency for the Environment Protection, ARPA Lombardia, database [26]. Particulate Matter daily mean concentrations are expressed as µg/m<sup>3</sup>. According to the WHO recommendations, the PM<sub>10</sub> annual average upper limit is 20 µg/m<sup>3</sup>, while PM<sub>2.5</sub> is set to 10 µg/m<sup>3</sup>. On the other hand, daily mean upper limits are set to higher values: 50 µg/m<sup>3</sup> and 25 µg/m<sup>3</sup> for PM<sub>10</sub> and PM<sub>2.5</sub>, respectively [27].

Three fixed detection stations have been considered for PM<sub>10</sub>: a traffic station (Broletto district, Brescia), an industrial station (Rezzato, Brescia), and a background one (Sarezzo, Brescia). For PM<sub>2.5</sub>, we considered a traffic station (Broletto district, Brescia) and a background station (Villaggio Sereno district, Brescia). Detection stations have been selected following the highest daily and seasonal completeness and continuity monitoring criteria.

Missing data for the monitoring stations have been estimated following the MISA-2 algebraic protocol [28], using values detected in the other monitoring station for the same day and the ratio between the annual mean of the missing data station and the one calculated in the other monitoring stations.

Following the EpiAir and EpiAir protocol, data for confounding factors have also been collected. Mid and long-time temporal trends, summer population decrease, holidays, flu epidemic weeks, Temperature, and Relative Humidity have been considered. The summer population decrease time starts from the second week of July to the end of August, with the most important decrease during the second and third weeks of August [31-32]. We considered the Christmas and Easter periods and the National and Patronal days as holidays. Epidemic flu data have been collected from the Flu Syndrome Surveillance System INFLUNET, hosted by the National Health Ministry [29]. Mean daily Temperature (°C) and Relative Humidity Data (%) from 2014 to 2017 have been collected from the local ARPA Lombardia weather monitoring station.

## Statistical Analysis

We performed a time-series analysis with the Poisson regression model and distributed lag values to correlate short-term exposure to Particulate Matter and ED admissions and outcomes, following the EpiAir and EpiAir2 protocols [30-31]. These are among the most recent and reliable time-series protocols developed to study the clinical effects of short-term exposition on various sets of airborne pollutants. The association analysis has also been adjusted for confounding factors: mid-long temporal trend, summer-related population decrease, holidays, epidemic flu weeks, temperature, and relative humidity. Although relevant, population-related data such as age or sex have been considered only from a descriptive perspective. We aimed to analyze the population involved in the study in its wholesome and heterogeneous nature. To adjust the mid-long term temporal trend model, we added to the Poisson Regression Model a triple interaction for year, month, and day of week.

For the latency intervals, we adopted a time Lag0-1 for estimating the immediate exposure effect and a time Lag0-5 for the prolonged one. Lag0-1 considers the Particulate Matter concentrations of the ED visit day and the previous one, while Lag0-5 accounts for the fifth day.

Results have been expressed as Relative Risk (RR) and percentage Excess of Relative Risk (ERR) with 95% Confidence Intervals, and statistical significance has been considered for a p-value inferior to 0.05.

Exposure has been evaluated for a 10  $\mu\text{g}/\text{m}^3$  daily mean concentration increase for both PM10 and PM2.5. Time series analysis has been conducted using the statistical software R version 3.2.3 (The R Foundation for statistical computing) with the "splines" and "mgcv" packages [32].

## RESULTS

### Population and Hospital admissions

A total of 1050 ED Admission records has been analyzed, and 543 records are included.

Table 1 displays a descriptive analysis of the enrolled population. 64% of the enrolled population were males, and the general mean age was 75 years. 40% of patients came directly from the city and 40% from its District but outside the city. 65% of the visits were triaged as "yellow" and 23% as "red." 76% of the patients were hospitalized.

The monthly trend of Emergency Department admissions over the study period is shown in Figure 1. Most visits occurred in the winter months and at the beginning of the spring.

## **Air Pollutants Exposure**

The daily time trend for PM<sub>10</sub> and PM<sub>2.5</sub> concentration levels for every considered monitoring station are shown in Figure 2.

As for the patients' ED visits trend, the highest detected PM<sub>10</sub> and PM<sub>2.5</sub> concentrations occurred during the cold season and decreased progressively during the warm one.

## **Correlation between Particulate Matters and Asthma exacerbations**

The results of the time-series analysis are shown in Table 2. For ED admission, a significant Relative Risk of 1.24 and a Risk Increase of 24.1% at Lag0-1 for PM<sub>2.5</sub> ( $p < 0.05$ ) was observed. Also, the Risk Increase of Hospitalizations at Lag0-1 for PM<sub>2.5</sub> was statistically relevant with a Relative Risk of 1.31 and a Risk Increase of 33.8% ( $p < 0.05$ ). Again, for PM<sub>2.5</sub>, an almost significant Relative Risk of 1.12 with a Risk Increase of 12.5% at Lag0-5 for ED admission was found ( $p = 0.05$ ).

Considering PM<sub>10</sub>, despite the lack of statistical significance ( $p < 0.1$ ), increases have been documented for both ED Admissions (14%) and Hospitalizations (19%) at lag0-1.

To better understand the impact of the population density, we finally considered the Relative Risk and Risk Increase for ED Admissions regarding the population living exclusively in the city. We observed a statistically significant correlation both for PM<sub>10</sub>, with a Relative Risk of 1.21 and a Risk Increase of 20.8% ( $p < 0.05$ ) at Lag0-1, and PM<sub>2.5</sub> with a Relative Risk of 1.34 and a Risk Increase of 33.7% always at Lag0-1 ( $p < 0.01$ ).

## **DISCUSSION**

Our work firmly suggests that short-term exposure to fine particulate matter plays a key role in inducing asthmatic exacerbations. This relationship has been widely observed and discussed in the literature, especially for other respiratory issues such as COPD [33-34]. However, the novelty of the study is the demonstration that it comes out heavily also in a relatively small town like Brescia where the number of inhabitants is limited, there is not a relevant difference between downtown and suburbs lifestyle, and the cultural and socio-economic gaps are not so wide as in other urban realities in the world. Although recognized is that individual features such as age, prior diseases, peculiar work exposition, unfavorable social conditions, availability of asthma care can influence this relationship, our findings suggest that such a risk is mostly linked to the atmospheric pollution per se, rather than other possible concomitants personal or cohort-related factors. However, to further increase the complexity of these analyses, we cannot forget the heterogeneity of the territorial and geographical location that characterizes every single city and its suburbs [30]. In this case, Brescia is located in a highly industrialized region, close to the Alps, and rarely exposed to windy conditions during the year, all unfavorable conditions that should be considered in judging the analysis results [24].

Other sources instead hypothesize the possibility that the particulate material does not necessarily exert an exclusive direct inflammatory action on the upper and lower airways, but rather that it can enhance or unmask previous conditions of atopy, thus acting as a co-factor for the new onset or the exacerbation of more complex inflammatory processes [35]. In our study, the increased risk of new ED Admissions and Hospitalization can be significantly documented, especially within the 24-48 hours of exposure (Lag0-1). These findings match with what happens from a pathophysiological

aspect, where PM<sub>2.5</sub> particles, due to their reduced diameters, can easily reach and settle into the small airways, promoting the acute worsening of chronic inflammatory processes [36]. By increasing the peripheral ventilation heterogeneity, such preferential small airways inflammation rise may induce an increment of the airway responsiveness degree, leading to the acute symptoms onset that characterizes asthma exacerbations [37].

Even with a weaker statistical significance, PM<sub>10</sub> shows a similar trend. As for PM<sub>2.5</sub>, the Risk Increase for ED Visits and Hospitalization associated with PM<sub>10</sub> is reported after a very short time of exposure, suggesting a role as a co-factor in inducing acute respiratory events after mostly settling in the larger airways.

It should be pointed out that this study is not intended solely as a retrospective analysis, as there are several engaging potential application scenarios available. First of all, this work is proposed as a basis for the development of innovative clinical-environmental monitoring models to support policies aimed at containing the emission of pollutants and, as a direct consequence, to save in terms of health care expenditure for the treatment of clinical events resulting from exposure.

This strategy could be applied to better understand the role of every single pollutant and their relative clinical impact not just on a wide clinical category of disease (i.e., respiratory or cardiovascular), but also to a specific and selective clinical issue, to better characterize its clinical and social impact on different types of population and environments. It might become a useful monitoring tool to establish and check over time innovative and more effective preventive measures inside territories with great environmental issues, such as high and prolonged Particulate Matter concentrations.

The versatility of the model employed and the selectivity for a specific clinical event are the strengths of this study, suggesting a possible pathology-specific application for different specialist clinical areas. Finally, although the proposed objective is to assess the acute clinical effects associated with short-term intervals of exposure, the results obtained may be highly informative in larger studies, for example, to analyze and compare the consequences associated with long-term exposure or even inside prospective studies aimed to assess the clinical consequences several times after the exposure.

We hope that our findings might further sensitize the Brescia citizens and generally raise public awareness about the risk that uncontrolled particulate air pollution poses particularly respiratory health.

## CONCLUSION

The results of our study match with the current literature knowledge for the impact of Particulate Matter and the Increase of ED Visits and Hospitalization for respiratory issues. Differently from other studies, however, we selectively focused on a specific respiratory clinical condition (i.e., asthma-related exacerbations) and a specific category of airborne pollutants (i.e., fine-particulate matter PM<sub>2.5</sub>), showing a direct, significant effect between these two phenomena in a highly polluted area of northern Italy corresponding to the Brescia district.

## DECLARATION OF INTEREST

LP reports no conflicts of interest in this work;

JG reports no conflicts of interest in this work;

CC reports no conflicts of interest in this work;

EZ reports no conflicts of interest in this work;

AP reports no conflicts of interest in this work;

EP reports no conflicts of interest in this work;

EB reports no conflicts of interest in this work;

DDB reports no conflicts of interest in this work;

MC reports no conflicts of interest in this work;

CT reports no conflicts of interest in this work;

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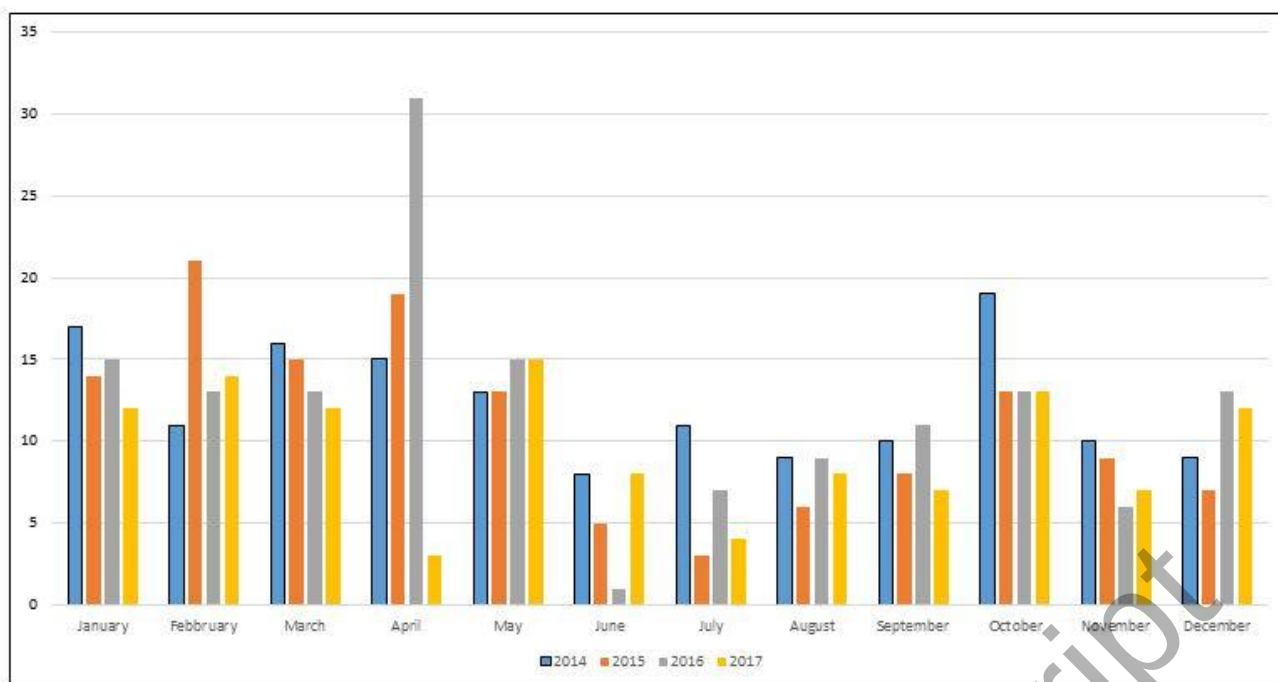


Figure 1. Monthly trend for Emergency Department admissions over the study period.

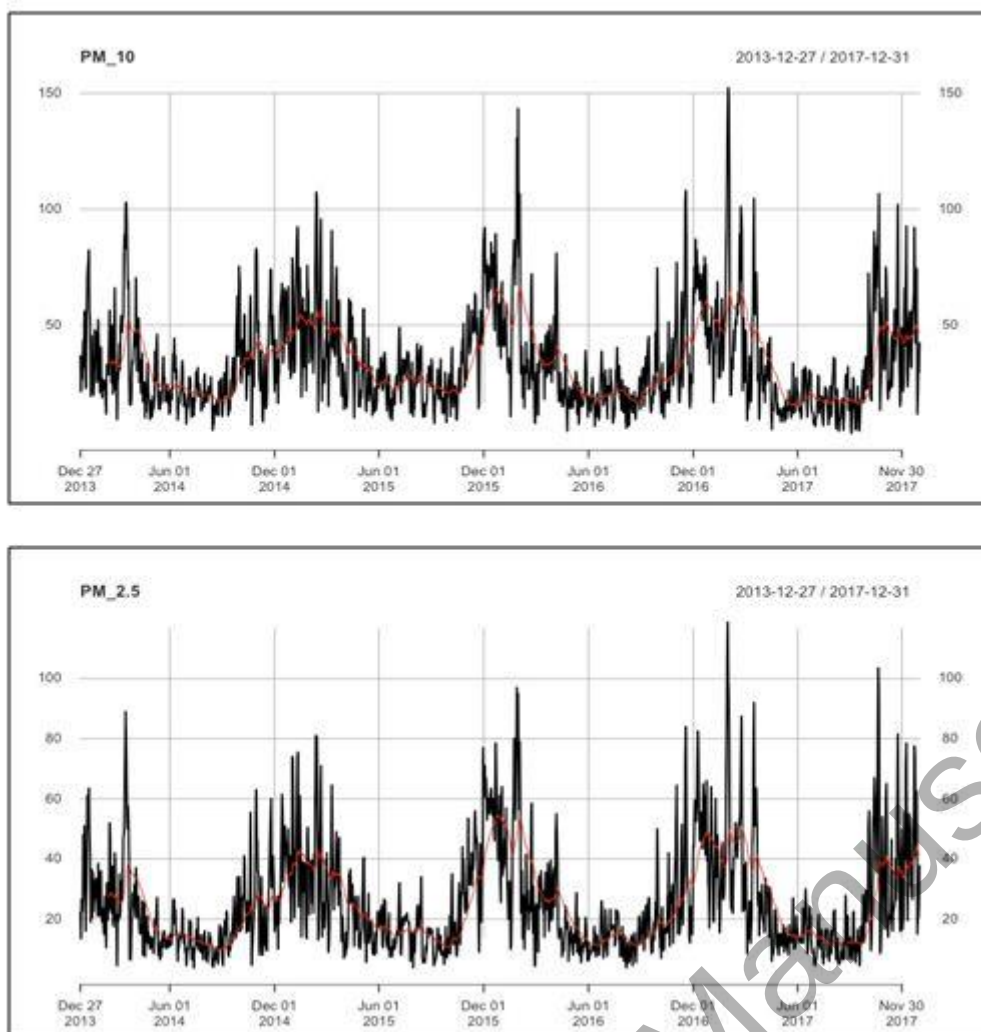


Figure 2. Daily average concentration of PM10 and PM2.5 over the study period.

Table 1: Descriptive analysis of the study population, triage codes, and outcomes after Emergency Department visits

| <b>Population characteristics</b>    | <b>n (%) (Total n=543)</b> |
|--------------------------------------|----------------------------|
| <u>Sex</u>                           |                            |
| M                                    | 227 (41.80 %)              |
| F                                    | 316 (58.20 %)              |
| <u>Mean age (<math>\pm</math>SD)</u> | 46.0 ( $\pm$ 18.19)        |
| <u>Home Address</u>                  |                            |
| Province of Brescia                  | 350 (64.46 %)              |
| Brescia city                         | 193 (35.54 %)              |
| <u>Triage code</u>                   |                            |
| White                                | 5 (0.92 %)                 |
| Green                                | 160 (29.47 %)              |
| Yellow                               | 330 (60.77 %)              |
| Red                                  | 48 (8.84 %)                |
| <u>Outcome</u>                       |                            |
| Hospitalization                      | 172 (31.68 %)              |
| Discharge                            | 371 (68.32 %)              |

Table 2: Relative Risk (RR) and Excess of Relative Risk (ERR%) for ED Admissions and Hospitalizations for a 10  $\mu\text{g}/\text{m}^3$  increase in PM10 and PM 2.5 concentrations

| <i>ED Admissions – Subjects living in the city and nearby districts</i> |             |               |              |                 |                |
|-------------------------------------------------------------------------|-------------|---------------|--------------|-----------------|----------------|
| <b>PM10</b>                                                             | <b>RR</b>   | <b>IC 95%</b> | <b>ERR%</b>  | <b>IC (95%)</b> | <b>p-value</b> |
| <u>Lag 0-1</u>                                                          | 1.14        | 0.98-1.33     | 14.08        | -2.35-33.28     | 0.0971         |
| <u>Lag 2-5</u>                                                          | 1.05        | 0.98-1.13     | 5.47         | -1.67-13.14     | 0.1371         |
| <u>Lag 0-5</u>                                                          | 1.09        | 0.99-1.19     | 8.70         | -1.13-19.50     | 0.0849         |
| <b>PM2.5</b>                                                            | <b>RR</b>   | <b>IC 95%</b> | <b>ERR%</b>  | <b>IC (95%)</b> | <b>p-value</b> |
| <u>Lag 0-1</u>                                                          | <b>1.24</b> | 1.03-1.50     | <b>24.15</b> | 2.92-49.76      | <b>0.0240</b>  |
| <u>Lag 2-5</u>                                                          | 1.07        | 0.98-1.17     | 7.52         | -1.55-17.43     | 0.1073         |
| <u>Lag 0-5</u>                                                          | <b>1.12</b> | 1.00-1.27     | <b>12.53</b> | -0.08-26.73     | <b>0.0519</b>  |

| <i>Hospitalization - Subjects living in the city and nearby districts</i> |           |               |             |                 |                |
|---------------------------------------------------------------------------|-----------|---------------|-------------|-----------------|----------------|
| <b>PM10</b>                                                               | <b>RR</b> | <b>IC 95%</b> | <b>ERR%</b> | <b>IC (95%)</b> | <b>p-value</b> |
| <u>Lag 0-1</u>                                                            | 1.19      | 0.98-1.45     | 19.07       | -2.36-45.20     | 0.0850         |
| <u>Lag 2-5</u>                                                            | 1.03      | 0.95-1.13     | 3.38        | -5.13-12.66     | 0.4479         |
| <u>Lag 0-5</u>                                                            | 1.06      | 0.95-1.20     | 6.39        | -5.35-19.58     | 0.2995         |
| <b>PM2.5</b>                                                              | <b>RR</b> | <b>IC 95%</b> | <b>ERR%</b> | <b>IC (95%)</b> | <b>p-value</b> |
| <u>Lag 0-1</u>                                                            | 1.31      | 1.02-1.67     | 30.67       | 2.42-66.71      | 0.0316         |
| <u>Lag 2-5</u>                                                            | 1.08      | 0.97-1.31     | 7.72        | -3.28-19.97     | 0.1764         |
| <u>Lag 0-5</u>                                                            | 1.13      | 0.98-1.31     | 13.19       | -2.10-30.88     | 0.0946         |
| <i>ED Admissions – Subjects living only in the city</i>                   |           |               |             |                 |                |
| <b>PM10</b>                                                               | <b>RR</b> | <b>IC 95%</b> | <b>ERR%</b> | <b>IC (95%)</b> | <b>p-value</b> |
| <u>Lag 0-1</u>                                                            | 1.19      | 0.98-1.45     | 19.07       | -2.36-45.20     | 0.0850         |
| <u>Lag 2-5</u>                                                            | 1.03      | 0.95-1.13     | 3.38        | -5.13-12.66     | 0.4479         |
| <u>Lag 0-5</u>                                                            | 1.06      | 0.95-1.20     | 6.39        | -5.35-19.58     | 0.2995         |
| <b>PM2.5</b>                                                              | <b>RR</b> | <b>IC 95%</b> | <b>ERR%</b> | <b>IC (95%)</b> | <b>p-value</b> |
| <u>Lag 0-1</u>                                                            | 1.31      | 1.02-1.67     | 30.67       | 2.42-66.71      | 0.0316         |

|                |      |           |       |             |        |
|----------------|------|-----------|-------|-------------|--------|
| <u>Lag 2-5</u> | 1.08 | 0.97-1.31 | 7.72  | -3.28-19.97 | 0.1764 |
| <u>Lag 0-5</u> | 1.13 | 0.98-1.31 | 13.19 | -2.10-30.88 | 0.0946 |

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