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# Respiratory medication sales and urban air pollution in Brussels (2005 to 2011)☆

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ABSTRACT

*Background:* We investigated the associations between daily sales of respiratory medication and air pollutants in the Brussels-Capital Region between 2005 and 2011.
*Methods:* We used over-dispersed Poisson Generalized Linear Models to regress daily individual reimbursement data of prescribed asthma and COPD medication from the social security database against each subject's residential exposure to outdoor particulate matter ($PM_{10}$) or $NO_2$ estimated, by interpolation from monitoring stations. We calculated cumulative risk ratios (RR) and their 95% confidence intervals (CI) for interquartile ranges (IQR) of exposure for different windows of past exposure for the entire population and for seven age groups.
*Results:* Median daily concentrations of $PM_{10}$ and $NO_2$ were 25 μg/m$^3$ (IQR = 17.1) and 38 μg/m$^3$ (IQR = 20.5), respectively. $PM_{10}$ was associated with daily medication sales among individuals aged 13 to 64 y. For $NO_2$, significant associations were observed among all age groups except >84 y. The highest RR were observed for $NO_2$, among adolescents, including three weeks lags (RR = 1.187 95%CI: 1.097–1.285).
*Conclusion:* The associations found between temporal changes in exposure to air pollutants and daily sales of respiratory medication in Brussels indicate that urban air pollution contributes to asthma and COPD morbidity in the general population.



## 1. Background

Exposure to urban air pollution increases overall mortality, as well as respiratory mortality and morbidity, as manifested by hospital admissions or emergency room visits (Atkinson et al., 2014). Although these are reliable indicators of acute exacerbations of respiratory conditions, they only capture the more severe cases of asthma and COPD. In contrast, medication use provides reliable information on a wider range of severity of exacerbations and affected population (Samet and Krewski, 2007). Panel studies indicate that increased levels of air pollutants are positively associated with asthma or COPD medication intake in asthmatic and COPD populations (Segala et al., 1998; Gent et al., 2009; van der Zee et al., 1999; Slaughter et al., 2003; Escamilla-Nuñez et al., 2008; Hiltermann et al., 1998; Silkoff et al., 2005). These observations have been confirmed by a few studies that used registries of medication sales or prescriptions in small/medium size French and Italian cities (Sofianopoulou et al., 2013; Pitard et al., 2004; Laurent et al., 2009; Zeghnoun et al., 1999; Vegni et al., 2005).

In Belgium, the levels of ambient air pollutants in the last decade have been close to or above the European standards. The air pollution in Brussels is strongly influenced by traffic related pollutants (Fierens et al., 2011), and compliance with the European limit for $NO_2$ remains problematic. Here, we present a time-series study in seven groups of age where we combined air pollution information with reimbursement data of prescribed asthma and COPD medication from the Belgian social security for the period 2005 to 2011 in the Brussels-Capital Region. We hypothesize that increases in the levels of air pollution result in increases in medication sales specific to age groups.

## 2. Methods

### 2.1. Study area, population, and period

The Brussels-Capital Region occupies a territory of 161.4km$^2$ comprising 19 municipalities in the center of Belgium. With slightly more than one million inhabitants, it is almost entirely urbanized and the most densely populated region in Belgium. Our study is based on daily

☆ **Take home message:** Urban air pollution increases the sales of prescribed asthma and COPD medication from birth to young elderly ages.

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data on air pollutants and prescribed respiratory medications reimbursed in the Brussels-Capital Region, between the 1st of January 2005 and the 31st of December 2011 (i.e. 2556 days). The geographical unit of observation was the whole region. We considered seven population age groups defined based on the natural history of obstructive airway diseases (Martinez et al., 1995; Viegi et al., 2007): pre-school children and infants (0 to 5 y), school-age children (6 to 12 y), adolescents (13 to 18 y), young adults (19 to 39 y), adults (40 to 64 y), young elderly (65 to 84 y), and elderly population (≥85 y).

### 2.2. Exposure: environmental pollutants

In the Brussels-Capital Region, the air concentrations of various pollutants are measured by the Brussels Environment Agency (http://www.ibgebim.be) and transferred to the Belgian Interregional Environment Agency, where daily levels of pollutants are estimated for $4 \times 4$ km grids using a land use regression model. The interpolation is based on a detrended kriging interpolation model that uses land cover data obtained from satellite images (Janssen et al., 2008). It accounts for the local variations of pollutant concentrations at locations where no monitoring stations are available. During the study period, $PM_{10}$ and $NO_2$ were monitored in the Brussels-Capital Region. $SO_2$ was also monitored, but because of the very low concentrations achieved in the last 10 years, we show the $SO_2$ results as complementary information in the online supplement.

### 2.3. Health outcome: Sales of respiratory medication

In Belgium, the entire residing population is enrolled in the social security system. Most health care expenditure (i.e. prescribed medication, medical procedures, etc.) is reimbursed by seven sickness funds and this information is centralized by the “Intermutualistisch Agentschap – Agence Inter-Mutualiste” (IMA-AIM). The IMA-AIM database contains detailed records of sales of prescribed drugs that are reimbursed for every person covered by the social security. It consists of records of medication purchase in pharmacies (i.e. one record per box of drugs) linked to the product code, the ATC (Anatomical Therapeutic Chemical) code (WHO Collaborating Center for Drug Statistics Methodology, 2013), the date of purchase, the encoded national social security number, and individual information (age, sex, and home address).

The ATC classification system (WHO Collaborating Center for Drug Statistics Methodology, 2013) aims at standardizing chemical substance classifications to allow international comparisons. The active substances are divided into groups at 5 levels according to the target organ/system (1st level) and their therapeutic (2nd), pharmacological (3rd and 4th) and chemical properties (5th). Thus, each medication is related to a unique ATC-code. Due to the similarities in the physiology and symptomatology of asthma and COPD, the medication prescribed for both disorders is the same. Nevertheless, COPD is unlikely to affect people below 40 years old, so medication sales below this age are most likely to be taken by asthmatics. In our study, we included daily sales of prescribed asthma and COPD medication (R03) that were reimbursed, for residents of the Brussels-Capital Region during the study period (2005–2011), those were daily sales of boxes of drugs that we consider as indicators of medication consumption. We also separately considered the short-acting medications. A list of the included medication is provided in Table S1 in the online supplement. Cough and cold medications (R05) were also considered, but the findings relative to these drugs with unproven efficacy are only shown in the online supplement. The use of the reimbursement data was authorized by the Sectorial Committee of Social Security and Health in the Commission for the Protection of Privacy.

### 2.4. Potential confounders

Daily meteorological conditions (temperature and relative humidity (RH)) and weekly influenza-like infections during the study period were considered. We obtained daily minimum temperatures (°C) and daily averages of RH (%) from the Belgian Royal Meteorological Institute. Information on influenza-like infections is available from a national reporting system, based on weekly reports by general practitioners, with a binary indicator for influenza epidemics being defined by an epidemic threshold of 140 visits per 100,000 inhabitants per week during two consecutive weeks (Van Casteren et al., 2010).

### 2.5. Statistical analyses

For each pollutant, we constructed a single daily exposure variable for the entire region: we weighted the 4x4km$^2$ grid cells for which the daily exposure concentrations are given, by the total population per cell, to account for the proportion of exposed individuals in each cell. In Belgium, pharmacies are open Monday to Friday. We excluded from the main analyses medication sales performed on Saturdays, Sundays and official holidays, when pharmacies open only until noon (Saturdays) or take turns in providing drugs. From the sales records, we excluded individual purchases of more than five eligible products on a single day. Such atypical events (0.15% of the sales) were likely due to registration errors or inappropriate sales. Data were aggregated into ecological time series and dates were used to link the environmental data with the health data.

We used over-dispersed Poisson Generalized Linear Model (GLM) and adjusted for time using cubic splines with seven degrees of freedom per year, for daily minimum temperature using natural cubic splines with six degrees of freedom, for average relative humidity using natural cubic splines with three degrees of freedom, for day of the week, and for influenza epidemics. We opted for single pollutant models because of the large correlation among pollutants. For each pollutant, we fitted unrestricted models with various lags from zero up until 21 days before the sale event. We estimated relative risks (RR) for an increase of the interquartile ranges (IQR) of the pollutant concentrations. The RR were calculated for specific lags (lag 0 to lag 21) and cumulative lags (lag 0 to 1, 0 to2, 0 to7, 0 to14, and 0 to 21) among the entire population as well as for the seven previously described age groups.

In sensitivity analyses, we ran the same models including medications sold on Saturdays. Moreover, because influenza infections may (partly) mediate the association between the pollutants and medication sales (Xu et al., 2013), we also ran our models without adjusting for influenza epidemics.

We used the *R*3.1.0 statistical package for all the statistical analyses (R, Development Core team, 2014).

## 3. Results

The population covered by the social security system in the study region ranged from an average of 964,500 individuals in 2005 to 1,050,000 individuals in 2011. On average, the population was composed of 23.0% children and adolescents (≤18 y), 61.5%, adults and 15.5% elderly (≥65 y). The daily concentrations of $PM_{10}$ and $NO_2$, the average RH and the minimum temperature in Brussels-Capital Region during the study period are described in Table 1. The median concentrations of $PM_{10}$ and $NO_2$ were 25 μg/m$^3$ (IQR = 17.1 μg/m$^3$) and 38 μg/m$^3$ (IQR = 20.5 μg/m$^3$), respectively. The time-series plots of $PM_{10}$ and $NO_2$ concentrations (Fig. 1) show that the concentrations were higher during winter, and the highest concentrations of both pollutants were achieved during the winter of 2008. The seasonal variability observed in the Figures is consistent with the negative correlation between minimum temperature and both pollutants (Table S2 in the online supplement). The correlation between $PM_{10}$ and $NO_2$ concentrations during the study period was strong and positive (correlation coefficient = 0.7). The median $SO_2$ concentrations during the study period were largely below the thresholds proposed by the WHO and the EC (median $SO_2$ concentrations: 2.5 μg/m$^3$; IQR = 2.3 μg/m$^3$) and they were also

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