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The short-term effect of particulate matter on cardiorespiratory drug prescription, as a proxy of mild adverse events

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ABSTRACT

Introduction and aims: The association between particulate matter < 10 μm in aerodynamic diameter (PM_{10}) and mild disease episodes, not leading to hospitalization or death, has been rarely investigated.

We studied the short-term effect of PM_{10} on purchases of specific cardiorespiratory medications, as proxies of mild episodes, in 7 small- and medium-sized cities of Northern Italy, during 2005–2006.

Materials and methods: We extracted information on purchased prescriptions from healthcare administrative databases, and we obtained daily PM_{10} concentrations from fixed monitoring stations. We applied a time-stratified case-crossover design, using the time-series of antidiabetic drugs purchases to control for confounding due to irregularities in daily purchase frequencies.

Results: During the warm season, we estimated a delayed (lags 2–6) increased risk of buying glucocorticoid (4.53%, 95% Confidence Interval (CI): 2.62, 6.48) and adrenergic inhalants (1.66%, 95% CI: 0.10, 3.24), following an increment (10 $\mu g/m^3$) in PM_{10} concentration. During the cold season, we observed an immediate (lags 0–1) increased risk of purchasing antiarrhythmics (0.76%; 95% CI: 0.16, 1.36) and vasodilators (0.72%; 95% CI: 0.30, 1.13), followed by a risk reduction (lags 2–6), probably due to harvesting.

Conclusions: Focusing on drug purchases, we reached sufficient statistical power to study PM_{10} effect outside large urban areas and conclude that short-term increments in PM_{10} concentrations might cause mild cardiorespiratory disease episodes.

1. Introduction

A wide variety of epidemiological and toxicological studies have investigated the short-term association between exposure to particulate matter (PM) and human health (Rückerl et al., 2011). Epidemiological studies provide evidence of a positive association between PM and outcomes such as daily rates of hospital admission, emergency room visit and mortality for respiratory and cardiovascular diseases (Brook et al., 2010; Rückerl et al., 2011), while toxicological studies identify oxidative stress and inflammatory response as drivers of such association (Brook et al., 2010; Hogg and van Eeden, 2009). Several studies have focused on the fraction of PM < 10 μm in aerodynamic diameter (PM_{10}), and found positive associations between its daily concentration and exacerbations of chronic obstructive pulmonary disease (COPD) (Zhu et al., 2013), asthma (Guarnieri and Balmes, 2014), arrhythmic episodes (Link and Dockery, 2010) and acute myocardial infarctions (AMI) (Mustafic et al., 2012) among other causes.

Though literature is rich in studies addressing the short-term relationship between PM_{10} and hospital admissions or mortality, these outcomes might be good markers for acute effects of the pollutant within a restricted fraction of population, whose health condition is already compromised (Vegni et al., 2005). In the attempt to extend the investigation to mild PM-related events potentially affecting a wider population, few studies have investigated alternative outcomes such as respiratory symptoms (Tramuto et al., 2011), emergency room visits (Santus et al., 2012), outpatient clinic visits (Chardon et al., 2007), and the prescription or sale of specific medications (Carlsen et al., 2012; Chimonas and Gessner, 2007; Dusseldorp et al., 1995; Menichini and Mudu, 2010; Peters et al., 1997; Rabinovitch et al., 2006; Roemer et al., 1993; Vegni et al., 2005). The few studies that have focused on this last

Abbreviations: AIC, Akaike's information criterion; AMI, acute myocardial infarction; CHF, congestive heart failure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DB, database; df, degrees of freedom; DL, distributed lag; IR, increase in risk; PM, particulate matter; PM_{10}, fraction of Particulate matter < 10 μm in aerodynamic diameter; SD, standard deviation

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outcome have proved it to be a sensitive indicator of respiratory symptoms typical of COPD and asthma (Carlsen et al., 2012; Menichini and Mudu, 2010), but to our knowledge no investigation has been carried out on medications that are used to contrast arrhythmia or angina, conditions that might precede acute cardiovascular events (e.g. AMI).

Furthermore, it is worth noting that the major studies linking PM to hospitalizations or mortality have involved large cities (Atkinson et al., 2001; Dominici et al., 2005; Katsouyanni et al., 2009). However, the composition and concentration of PM, and consequently its effect, might be different outside those cities; therefore, further investigation in smaller cities or rural areas is desirable. Nevertheless, in such small areas, where the resident population is less numerous, the number of observed hospitalizations and deaths could be too small to guarantee a sufficient statistical power to detect the small expected effect of PM (Zeghnoun et al., 1999). The focus on medical prescriptions purchases, a much more frequent outcome, might help overcoming this problem.

In order to address these two issues, we carried out a pilot study to investigate the short-term effect of PM_{10} exposure on the purchase of specific medications used in the treatment of COPD, asthma, arrhythmia, angina and congestive heart failure (CHF). We focused on 7 small and medium-sized cities located throughout Lombardy, a highly industrialized and densely populated region in Northern Italy, where air pollution effects deserve investigation: this area is characterized by frequent episodes of thermal inversion, that facilitate air pollutants stagnation (Baccini et al., 2011), and by one of the highest annual average PM_{10} concentration in Europe.

2. Materials and methods

2.1. Study area

Lombardy encloses a vast area of the Po Valley including Milan, the second largest Italian city, together with hills and highlands. This diversity of geographic and correlated meteorological conditions impacts PM_{10} concentrations, which vary greatly within the region (Baccini et al., 2011).

National and international studies addressing the health effects of air pollution in Italy have frequently involved Milan (Atkinson et al., 2001; Biggeri et al., 2004, 2001; Colais et al., 2009; Scarinzi et al., 2013; Stafoggia et al., 2013). Only a few studies extended the analyses to other areas of Lombardy (Baccini et al., 2015; Carugno et al., 2016).

Therefore, since the urban area of Lombardy has been extensively analyzed in literature, we selected 7 small and medium-sized cities (from 22,000 to 122,000 residents) located in different geographic areas of the region (Bergamo, Lodi, Mantova, Monza, Sesto San Giovanni, Saronno and Sondrio) accounting overall for around 500,000 residents. A map of the study area is provided in Fig. S1 of the Supplementary material.

2.2. Health data

Italian Healthcare System provides universal coverage; therefore it includes most of the residents' inpatient, outpatient and pharmacological expenses, that are recorded on a regional basis in administrative databases (DB), together with some clinical and demographic information.

In Lombardy, we built the data warehouse DENALI, that links several health DB on services delivered to all residents (e.g. DB of hospital discharges, DB of drug prescriptions), and merges them with each resident's vital status and demographic information. Probabilistic record linkage is used to determine matches between records belonging to the same person, but hosted in different DB (Fornari et al., 2008).

Based on the Anatomical Therapeutic Chemical Classification System code, we extracted from DENALI all drug prescriptions for some specific cardiovascular and respiratory treatments (Table 1) that were purchased during the years 2005–2006 by the residents of the 7 selected cities, and we used them as proxies of mild episodes of COPD, asthma, arrhythmia, angina and CHF. Respiratory treatments included systemic and topical medications for asthma and COPD: systemic glucocorticoids; adrenergic, glucocorticoid and anticholinergic inhalants, and theophylline. Cardiovascular treatments included class I and III antiarrhythmics, typically employed in the treatment of arrhythmia, and vasodilators used in cardiac diseases, prescribed for the management of angina and CHF. Since one disease episode might require multiple prescriptions of the same treatment over a few days, we excluded all prescriptions of the same treatment purchased within 7 days (blanking period) from a first one, as we assumed them to be related to the same episode.

Furthermore, we extracted all prescriptions of intermediate- and long-acting drugs used in diabetes, and lipid modifying agents (Table 1), with the aim of developing a method for the control of confounding due to short-term fluctuations in the daily frequency of drug prescription. For lipid modifying agents we applied again a 7-days blanking period, while for drugs used in diabetes we joined into a single event only prescriptions occurred on the same day, as these prescriptions were selected to describe the overall frequency of drug purchase and not to identify disease episodes.

2.3. Environmental data

The Regional Environmental Protection Agency of Lombardy manages a network of fixed monitoring stations (data available at http://www.arpalombardia.it). For each city, we obtained daily measurements of mean PM_{10} concentration, from all stations within the city limits and all background stations within 10 km from them, and temperature, from all stations within 10 km, for the years 2005 and 2006. We then excluded all monitors with more than 25% missing daily measurements (see Fig. S1 of the Supplementary material). We then followed a standard methodology (Biggeri et al., 2001) to impute the remaining missing values of the included monitors, and we computed city-specific daily concentrations by averaging the monitor concentrations.

2.4. Statistical methods

We investigated the short-term relationship between exposure to PM_{10} and drug purchases using a time-stratified case-crossover design, with control days matched by year, month and day of the week (Mittleman et al., 1995); thus we adjusted for long-term trend, seasonality and day of the week by design. Previous Italian case-crossover studies have analyzed hospitalizations (Chiusolo et al., 2011; Stafoggia et al., 2009) adjusting for temperature, influenza epidemics, and irregularities due to holidays and summer population decrease. However, since drug purchases are influenced by opening and closure days of pharmacies, their irregularities might differ from those observed for hospitalizations: for instance, they should reach a minimum during holidays and summer vacation, and spike on Sunday extra openings (Zeghnoun et al., 1999). Therefore, we first aimed at identifying a variable that could adjust for confounding due to such irregularities.

To do this, we built city-specific daily time-series of purchase of intermediate- and long-acting antidiabetics, these are chronic treatments and should reflect the main trends in drug consumption, without being affected by temperature, PM_{10} exposure and influenza epidemics. We then eliminated long-term and weekly trends by fitting city-specific generalized additive models for location, scale and shape (Stasinopoulos and Rigby, 2007), in which we assumed that the daily frequency of sale followed a finite mixture distribution of 2, 3 or 4 negative binomial distributions, depending on the city (see Supplementary material). We extracted the standardized residuals, thus obtaining a variable representing the fluctuation of the daily frequency of purchases around the mean. Thereafter, we tested if this variable