Environmental Research 136 (2015) 491–499

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Cardiorespiratory treatments as modifiers of the relationship between particulate matter and health: A case-only analysis on hospitalized patients in Italy

Sara Conti[a,*], Alessandra Lafranconi[b], Antonella Zanobetti[c], Carla Fornari[a], Fabiana Madotto[a], Joel Schwartz[c], Giancarlo Cesana[a]

[a] Research Centre on Public Health. Department of Statistics and Quantitative Methods. University of Milano – Bicocca. Via Cadore 48, I-20052 Monza, (MB), Italy
[b] School of Hygiene and Preventive Medicine. Department of Health Sciences. University of Milano – Bicocca. Via Cadore, 48, I-20052 Monza, (MB), Italy
[c] Department of Environmental Health, Harvard School of Public Health, P.O. Box 15698, Landmark Center-415-K, Boston, MA 02215, USA

ARTICLE INFO

Article history:
Received 29 May 2014
Received in revised form
8 August 2014
Accepted 5 September 2014

Keywords:
Particulate matter
Pharmacological treatments
Effect modification
Case-only analysis

ABSTRACT

Background: A few panel and toxicological studies suggest that health effects of particulate matter (PM) might be modified by medication intake, but whether this modification is confirmed in the general population or for more serious outcomes is still unknown.
Objectives: We carried out a population-based pilot study in order to assess how pre-hospitalization medical treatments modify the relationship between PM < 10 μm in aerodynamic diameter (PM_{10}) and the risk of cardiorespiratory admission.
Methods: We gathered information on hospitalizations for cardiorespiratory causes, together with pre-admission pharmacological treatments, that occurred during 2005 in seven cities located in Lombardy (Northern Italy). City-specific PM_{10} concentrations were measured at fixed monitoring stations. Each treatment of interest was analyzed separately through a case-only approach, using generalized additive models accounting for sex, age, comorbidities, temperature and simultaneous intake of other drugs. Analyses were stratified by season and, if useful, by age and sex.
Results: Our results showed a higher effect size for PM_{10} on respiratory admissions in subjects treated with theophylline (Odds Ratio (OR) of treatment for an increment of 10 $\mu g/m^3$ in PM_{10} concentration: 1.119; 95% Confidence Interval (CI): 1.013–1.237), while for cardiovascular admissions treatment with cardiac therapy (OR: 0.967, 95% CI: 0.940–0.995) and lipid modifying agents (OR: 0.962, 95% CI: 0.931–0.995) emerged as a protective factor, especially during the warm season. Evidence of a protective effect against the pollutant was found for glucocorticoids and respiratory admissions.
Conclusions: Our study showed that the treatment with cardiac therapy and lipid modifying agents might mitigate the effect of PM_{10} on cardiovascular health, while the use of theophylline seems to enhance the effect of the pollutant, possibly due to confounding by indication. It is desirable to extend the analyses to a larger population.

1. Introduction

The scientific literature from the last 20 years consistently related ambient particulate matter (PM) exposure with an increased risk of hospital admission for broadly defined respiratory or cardiovascular causes (Brook et al., 2010; Rückerl et al., 2011). PM exposure has been associated with short-term increases in hospital admissions for many health outcomes, such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infections (mainly pneumonia), cerebrovascular diseases, ischemic heart diseases (especially myocardial infarction (MI)), heart failure and arrhythmia. All the studies support the hypothesis that high levels of PM are associated with short-term increase in hospital admissions for exacerbation of the disease in a susceptible population (Dominici et al., 2006; Gold and Samet, 2013; Medina-Ramon et al., 2006b; Peters et al., 2000; Rich et al., 2004; Vedal et al., 2004; Wellenius et al., 2006; Zanobetti and Schwartz, 2005; Zanobetti and Schwartz 2006; Zanobetti et al., 2000).

* Corresponding author. Fax: +39 0264488169.
E-mail addresses: sara.conti@unimib.it (S. Conti), lafranconi.ale@gmail.com (A. Lafranconi), azanobet@hsph.harvard.edu (A. Zanobetti), carla.fornari@unimib.it (C. Fornari), fabiana.madotto@unimib.it (F. Madotto), joel@hsph.harvard.edu (J. Schwartz), giancarlo.cesana@unimib.it (G. Cesana).

http://dx.doi.org/10.1016/j.envres.2014.09.007
0013-9351/

Ambient PM is therefore widely recognized as an important and modifiable determinant of respiratory and cardiovascular diseases (Bernstein et al., 2004; Brunekreef and Holgate, 2002). Exposure to PM has been shown to induce the activation of alveolar macrophages (Bouthillier et al., 1998; Driscoll et al., 1995), mediated by reactive oxygen species (ROS) (MacNee and Donaldson, 2003) and calcium (Brown et al., 2004), to diminish the clearance of activated macrophages (Brown et al., 2002), and to cause damage of the respiratory epithelium (Gualtieri et al., 2009). These in turn are linked to asthma exacerbation, especially in children, worsening of COPD and pneumonia (Delfino et al., 2004; Donaldson et al., 2000). The systemic inflammatory response and the production of ROS have been related also to atherogenesis, plaque destabilization and rupture, which causes acute cardiovascular and cerebrovascular events, such as MI and stroke (Bai et al., 2007; Dockery, 2001; Donaldson et al., 2001; Frampton, 2001; Mills et al., 2009; Zanobetti and Schwartz, 2005). Mediators of the same process have been identified responsible of vessel and cardiac remodeling (Baccarelli et al., 2008; Ying et al., 2009). Finally exposure to PM has been associated with disorders of autonomic function of the vessels, like acute vasoconstriction and arterial blood pressure changes, and of the heart, including increased heart rate, decreased heart variability, increased electrical instability and increased cardiac arrhythmias (Bartoli et al., 2009; Brook et al., 2002; Chan et al., 2004; Ren et al., 2010; Zanobetti et al., 2009).

Over the last decade, some researchers have examined the relationship between environmental pollution and drug consumption, for instance analyzing the increased use of asthma medication in association with ambient fine and ultrafine particles (von Klot et al., 2002), or looking at how atorvastatin modulates cytokine production by human alveolar macrophages and bronchial epithelial cells, following the exposure to $PM < 10\ \mu m$ in aerodynamic diameter (PM_{10}) (Sakamoto et al., 2009). A study has explored the effect of statins on the PM-induced inflammatory response and has shown that outcomes related to PM exposure, like heart rate variability, are modified by the use of statins in certain subgroups of the population (Schwartz et al., 2005). Although these studies have produced evidence of a potential interaction between PM_{10} and medical treatments, the analyses of such an interaction remain sporadic and focus on selected pathologies and active agents, probably due to the difficulties of obtaining pharmacologic data concerning a wide sample of individuals.

In the present pilot study we investigated the effect of PM_{10} on respiratory and cardiovascular hospital admissions in a sample of the resident population of Lombardy, a region of Northern Italy, during the year 2005. Our aim was to explore a potential modification of the pollutant effects due to pre-hospitalization medical treatment.

2. Materials and methods

2.1. Health data

The Lombardy Health System provided data on hospital admissions and medical prescriptions that occurred during year 2005 to the residents in the cities of Sesto San Giovanni, Monza, Bergamo, Lodi, Mantova, Sondrio and Saronno. These seven cities were chosen because they are located in areas that differ both for morphology and degree of urbanization and therefore provide a range of PM exposures. Data were extracted from the data warehouse (DWH) DENALI, which incorporates various administrative healthcare databases, including those of hospital discharges (HD) and medical prescriptions. One of the distinguishing features of DENALI is the probabilistic reconstruction of links (probabilistic record linkage (Fellegi and Sunter, 1969)) among databases without a unique identifier and with missing, defective or incorrect records. In short, probabilistic record linkage uses available individual information (e.g. demographic characteristics) to compute a matching probability that is proportional to the concordance among information of interest. Two records are assigned to the same person if the probability is higher than a pre-specified threshold, overcoming the issue of non optimal data quality (Fornari et al., 2008; Madotto et al., 2013).

In detail, we followed-up each resident of the seven cities from January 1st 2005, or the date of immigration, up to December 31st 2005 or the day of emigration or death, whichever came first. For each subject we extracted from the DWH all HDs occurring in 2005 and reporting one of the following cardiovascular or respiratory diagnoses in at least one of the first two causes of discharge: acute respiratory infections [International Classification of Diseases, Clinical Modification 9th Revision (ICD-9-CM) codes 460–466]; pneumonia and influenza (ICD-9-CM codes 480–487); chronic bronchitis (ICD-9-CM code 491); asthma (ICD-9-CM code 493); lung abscess (ICD-9-CM code 513.0); other diseases of lung (ICD-9-CM code 518.8); ischemic heart disease (ICD-9-CM codes 410–414); diseases of pulmonary circulation (ICD-9-CM codes 415–417) and other forms of heart disease (ICD-9-CM codes 420–429). HDs also included information on patients' sex and age. Subsequent hospitalizations related to the same patient were considered as the same event.

Furthermore, using the Anatomical Therapeutic Chemical (ATC) Classification System, we identified all the medical prescriptions for a selection of respiratory and cardiovascular drugs that were actually purchased during 2005 by the study population. With regards to respiratory prescriptions, we included systemic and topical drugs routinely used to treat asthma, COPD and pneumonia, as there is evidence that they could modify the effects of PM on the respiratory system (Delfino et al., 1998; Silverman et al., 1992; von Klot et al., 2002). Through their molecular structures and exposure routes, we identified five different classes: systemic glucocorticoids (ATC code H02AB01, H02AB04, H02AB07), adrenergic inhalants (ATC code R03AC02, R03AC12, R03AC13, R03AK04, R03AK06, R03AK07), glucocorticoid inhalants (ATC code R03BA01, R03BA02, R03BA03, R03BA05), anticholinergic inhalants (ATC code R03BB01, R03BB02, R03BB04) and theophylline (ATC code R03DA04). As for the cardiovascular prescriptions, we included the whole category of drugs for the cardiovascular system (ATC code starting with C). Since some toxicological studies suggested that antiarrhythmics (Brown et al., 2007; Rhoden et al., 2005) and statins (Miyata et al., 2012; Miyata et al., 2013; Sakamoto et al., 2009) could modify the effect of PM on the cardiovascular system, we divided the cardiovascular prescriptions into three branches: cardiac therapy (first 3 characters of the ATC code C01), including antiarrhythmics; lipid modifying agents (first 3 characters of the ATC code C10), including statins; all other cardiovascular treatments (first 3 characters of the ATC code C02 C03 C04 C05 C07 C08 C09).

We finally restricted the analyses to cases who underwent at least one of the selected hospitalizations, and built dummy variables indicating which treatments every subject was undergoing prior to hospitalization. We considered a patient treated with systemic glucocorticoids, cardiac therapy, lipid modifying agents or other cardiovascular treatments if he had purchased at least one of these drugs during the two months preceding the hospitalization. Similarly, a patient was considered treated with adrenergic inhalants, glucocorticoid inhalants, anticholinergic inhalants or theophylline if we observed at least one purchase of these drugs during the month preceding the hospitalization. The length of the pre-hospitalization observational time was dictated by the fact that Italian law (Legge n. 388 23 dicembre, 2000; Legge n. 405 16 novembre, 2001) establishes that a maximum of two blister packs of the same therapy can be dispensed with a single prescription, and that we observed that two blister packs of the selected therapies can last a maximum of either one or 2 months, depending on the treatment. In order to avoid misclassification arising from different pre-hospitalization follow-up durations, we excluded all admissions preceded by less than two months of observation, thereby eliminating all hospitalizations occurred in January and February 2005.

2.2. Environmental data

The Regional Agency for Environmental Protection (ARPA, Italian acronym) of Lombardy collects data about weather conditions and pollutant concentrations by means of monitoring stations located all over the region. For each of the examined cities, ARPA provided time-series of the year 2005 of daily average concentration of PM_{10}, temperature and relative humidity, measured from all the stations located within 10 km from the city-center. Since the number of PM_{10} monitoring stations that fulfilled this criterion was low, we gave priority to the background stations, but we included also traffic or industrial monitors if the correlation between their measurements and those from the background stations was sufficiently high (Pearson and Lin's correlation coefficient ≥ 0.8 (Lin, 1989)) or if such sites were located within the city of interest in areas with high population density. We provide a map of the study area, together with the locations of the selected PM_{10} monitoring stations in Appendix A (Fig. A.1).

We considered eligible for the analyses all the time-series with less than 25% missing data and separately for each city we imputed the missing values following the methodology adopted in the MISA study (Biggeri et al., 2001). We subsequently averaged the obtained daily time-series for each city, thus assessing the city-specific daily exposure to air pollution concentration and climatic conditions.

Finally, we computed the time-series of apparent temperature basing on the averaged time-series of temperature and relative humidity (Berti et al., 2009).