Published in final edited form as:

Environ Res. 2015 January ; 136: 491–499. doi:10.1016/j.envres.2014.09.007.

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

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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 (PM₁₀) 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 PM₁₀ 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 PM₁₀ on respiratory admissions in subjects treated with theophylline (Odds Ratio (OR) of treatment for an increment of 10 µg/m³ in PM₁₀

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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 PM₁₀ 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.

Keywords

particulate matter; pharmacological treatments; effect modification; case-only analysis

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; Ruckerl 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).

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 µm in aerodynamic diameter (PM₁₀) (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 PM₁₀ 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 PM₁₀ 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 codes 491); asthma (ICD-9-CM codes 493); lung abscess (ICD-9-CM codes 513.0); other diseases of lung (ICD-9-CM codes 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 PM₁₀, temperature and relative humidity, measured from all the stations located within 10 km from the city-center. Since the number of PM₁₀ monitoring stations that fulfill 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 PM₁₀ monitoring stations in Appendix A (Figure 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).

2.3 Statistical analyses

We used a case-only approach, originally applied in the investigation of gene-environment interactions, in order to evaluate the potential modification due to medical treatment of the effect of PM₁₀ exposure on hospital admissions for cardiovascular or respiratory diseases. Several investigators (Armstrong 2003; Medina-Ramon and Schwartz 2008; Medina-Ramon et al. 2006a; Schwartz 2005) pointed out that this approach was suitable to analyze how the effect of a time-varying exposure (e.g. PM₁₀ concentration) is modified by some individual characteristics that do not vary over time (e.g. sex, age and medical treatment, when considering two months of observation). It consists in modeling the relationship between the conditional probability of observing the hypothesized modifier given that the subject is a case as a function of the time-varying exposure of interest and the possible confounders. In order to allow a more flexible control for confounding through splines, we decided to use a logistic generalized additive model, rather than the usually employed logistic generalized linear model. Though this approach provides greater statistical power to examine interactions, the number of events was still limited enough that we decided to analyze the area as a whole, rather than stratifying on city.

We performed the analyses for the whole study period, as well as stratifying on cold (October to March) and warm period (April to September), and we carried out separate analyses for hospital admissions due to respiratory and cardiovascular diseases: for the former, we evaluated only the effect modification due to respiratory drugs, while for the latter we focused on cardiovascular treatments. We fitted separate models using each

category of drugs as the dependent variable. Long and short term confounding was considered, and we included in the model a linear predictor for the date and a categorical variable for the day of the week; potential heterogeneity between cities was controlled with a categorical predictor indicative of the city of residence of the hospitalized patient. Since many subjects received more than one treatment at a time, we included in the model dummy variables indicating whether the patient took other cardiovascular or respiratory medications in addition to the analyzed one, in order to capture the modification due to the single drug. Moreover, we adjusted for sex and age, respectively through a binary variable and a penalized cubic regression spline with 3 or 4 knots, depending on the outcome being analyzed. Furthermore we accounted for patients' pathologic conditions at hospitalization through Charlson Comorbidity Index (Charlson et al. 1987; Quan et al. 2005), as computed on the six diagnoses reported in the HD. This index is a score defining patient's complexity and it is computed by identifying which comorbidities within a wide set, ranging from MI to AIDS/HIV (see Quan et al. 2005 for the complete list), affect the patient, and subsequently summing them up with specific weights. We included this Index in the model either in a linear form or as a penalized cubic regression spline with 3 knots, depending on which model fitted better according to the Akaike Information Criterion (AIC). In addition, we evaluated the performance of various models to control for the potential confounding due to temperature: we included temperature or apparent temperature at different lags (up to 6 days) in either a linear or a spline form. Finally, we built different models introducing a linear term of PM_{10} concentration at different lags (up to 6 days). Based on the AIC we chose to include a linear term of the apparent temperature of the day of hospitalization and the average of PM_{10} concentrations on the day of admission and on the previous day.

In case we observed a significant effect modification, we stratified the analysis first by sex and then by age, to investigate if there are potential susceptible subpopulations. Age was categorized into three groups for respiratory admissions: age 0–19, age 20–64, age 65+, and two categories for cardiovascular admissions: age 0–64 and age 65+.

Seasonal differences in the distribution of demographic characteristics and treatments were tested through Chi-square test of association or Wilcoxon test, whichever was more appropriate. The differences between the estimated Odds Ratio of prescription for warm and cold period and for the stratified analyses were tested for relative effect modification, as described in literature (Faustini et al. 2012).

3. Results

In Table 1 we report mean and standard deviation (SD) of daily mean concentration of PM_{10} together with the number of residents and of cardiorespiratory admissions in the selected cities during 2005. The study population included 471,868 resident individuals. We selected 2,821 hospital admissions with a respiratory diagnosis and 5,831 hospital admissions with a cardiovascular diagnosis. As far as the exposure is concerned, the average daily concentration in the study area was $47\mu g/m^3$ (SD 29.52) and it was significantly (p-value Wilcoxon test, < 0.0001) higher during the cold season as compared with the warm one.

Among the 2,821 hospital admissions for respiratory causes 1,558 occurred during the warm season (Table 2). Females constituted 42.96% of the admission, and most of the hospitalizations (64.06%) affected subjects aged more than 64 years. Furthermore, 17.44% of the hospitalizations regarded subjects younger than 20 years. The most commonly used respiratory treatments were adrenergic inhalants (12.73%), followed by systemic (11.63%) and inhaled (10.67%) glucocorticoids. The 5,831 examined hospital discharges with a cardiovascular cause were divided into 3,465 during the warm and 2,366 during the cold season (Table 2). Females contributed 42.94% of the hospitalizations and a substantial proportion of admissions (77.86%) occurred in people aged more than 64 years. 37.04% of the admissions regarded people who had a pre-hospitalization treatment with cardiac therapy. Subjects received a pre-hospitalization treatment with lipid modifying agents in 22.26% of the admissions, and other cardiovascular drugs in 65.80%.

The results of the case-only analyses to evaluate the potential modification of the effect of PM₁₀ exposure on hospital admissions for cardiorespiratory diseases due to respiratory and cardiovascular drugs are shown in Table 3 in terms of Odds Ratio (OR) related to an increase of 10 µg/m³ in pollution. A significant modification of the effect of PM₁₀ on respiratory hospitalizations emerged only for theophylline, for which we observed a significant and positive effect (OR=1.119, 95% CI, 1.013 – 1.237), which persisted during the cold season (OR=1.178, CI 95% 1.027 – 1.351). Furthermore, systemic and inhaled glucocorticoids showed a protective, though not statistically significant, effect against PM₁₀, especially during the warm season.

For effect modification due to cardiovascular treatments before cardiovascular admissions and considering the overall analysis, a significant effect modification emerged for cardiac therapy (OR=0.967, 95% CI, 0.940 – 0.995) and lipid modifying agents (OR=0.962, 95% CI, 0.931 – 0.995). The trend observed for the whole year was confirmed both in the warm and in the cold season, though only the estimates for the warm season statistically differed from unity: the estimated OR was 0.922 (95% CI 0.866 – 0.982) for cardiac therapy and 0.923 (95% CI 0.859 – 0.992) for lipid modifying agents.

The results of the analyses stratified by gender (Figure 1) confirm a significant protective effect modification due to the use of cardiac therapy and lipid modifying agents respectively on males and females, during the warm season. The age stratification confirms the trend observed in the general population for both age classes, but the effect modification emerges as statistically significant only in people older than 64 years.

4. Discussion

We carried out a study on a subarea of Lombardy with a population of approximately 470,000 people. Importantly, our analysis included the whole population of that area, avoiding some selection bias. Using a case-only analysis, we showed that pre-hospitalization cardiovascular and respiratory pharmacological treatments are potential modifiers of the association between PM₁₀ concentration and cardiovascular or respiratory hospitalizations. The observed modification was particularly strong for theophylline, which increased the risk of PM associated respiratory admissions, and for lipid modifying agents, which reduced the

risk of PM-associated cardiovascular admissions. Another interesting finding was that cardiac therapy drugs appear to play a similar protective role, which to our knowledge has never been detected previously.

In our analysis of the effect of consumption of respiratory drugs on the relationship between PM₁₀ and respiratory admissions, a protective pattern was noticed for glucocorticoids. Other authors support our findings: Silverman (Silverman et al. 1992) analyzed a sample of asthmatic subjects and suggested that the therapy with xanthines, oral and inhaled glucocorticoids or adrenergic medications could ameliorate the potential adverse effect of the exposure to the pollutant during winter. Delfino (Delfino et al. 1998) investigated a panel of asthmatic children and concluded that the probability of developing respiratory symptoms related to PM₁₀ is lower in subjects treated with inhaled corticosteroids. Our study adds to these by examining the entire population of seven cities, rather than sensitive subgroups, and by looking at more serious outcomes – hospital admissions.

As far as the increased effect of PM₁₀ observed in those subjects who use theophylline, it should be noted that this drug has a modest anti-inflammatory potential at low doses and, at higher doses, it acts as bronchodilator; it is commercialized in sustained-release formulations, for chronic therapy of asthma and COPD, and in short-acting formulation, for disease exacerbation. 2005 guidelines on asthma and COPD did not recommend the use of short-acting theophylline (slower onset of action and higher risk of side effects), and limited the use of slow-release theophylline to those patients who did not achieve control on inhaled glucocorticosteroids alone, and anyways as second line, after the association of glucocorticoids and long-acting inhaled β_2 -agonists (Global Initiative for Asthma (GINA) 2005; Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2005). Our interpretation is that the hospitalized patients with prior theophylline treatment are those who do not tolerate or respond to first-line treatment, often with a more compromised health condition.

Our analysis showed an overall protective pattern for cardiovascular medications, reaching statistical significance for both cardiac therapy and lipid modifying agents.

To our knowledge, no epidemiological studies have analyzed the interaction between exposure to PM₁₀, cardiovascular disturbances and intake of cardiac therapy, a broad class of pharmacological treatments including drugs used to manage congestive heart failure, hypertension and arrhythmia. However, it should be considered that epidemiological studies (Anderson et al. 2010; Peters et al. 2000; Rich et al. 2004; Vedal et al. 2004) confirmed the relationship between exposure to PM₁₀ and arrhythmia and some toxicological findings (Brown et al. 2007; Rhoden et al. 2005) suggested possible interaction between antiarrhythmic drugs and exposure to PM₁₀. Human studies showed that the exposure to atmospheric particulate is related with episodes of cardiac arrhythmia and, from a therapeutic point of view, with the activation of implantable cardioverter defibrillators. In particular, Peters (Peters et al. 2000) followed a group of 100 patients with implantable cardioverter defibrillator for 2 years and concluded that high concentrations of particulate matter could lead to potentially fatal arrhythmias; similar results were obtained by Vedal (Vedal et al. 2004) and Rich (Rich et al. 2004). Anderson (Anderson et al. 2010) identified a

positive association between episodes of activation of the defibrillator and the concentration of pollutants. A toxicological study was carried out by Brown (Brown et al. 2007); he analyzed the mouse macrophage cell line J774 and showed that synthetic oxidants, like tBHP, induced TNF-alpha production via calcium signaling; Verapamil, an antiarrhythmic drug targeted on calcium channels, was observed to inhibit calcium signaling, thus reducing the effect of exposure. Furthermore he explored possible interactions between PM₁₀-treated macrophages and lung epithelial cells in a conditioned medium derived from activated monocytes: the release of TNF-alpha and IL-8 was shown to be increased and the expression of ICAM-1 on epithelial cells was also enhanced; all the effects were prevented by pre-treatment with Verapamil. Another *in vivo* study (Rhoden et al. 2005) showed that the increments in heart chemiluminescence and wet/dry ratio, a measure of the water content of an organ that can indicate the presence of edema, induced by urban ambient particles and concentrated ambient particles could be prevented by pre-treating the experimental subjects with atenolol, a betablocking agent.

As far as the observed protective effect of lipid modifying agents intake is concerned, in Lombardy the most commonly prescribed agents are statins and Schwartz (Schwartz et al. 2005) highlighted that in certain population subgroups the use of statins seems to counteract some of the adverse effects of PM_{2.5}. Similarly, a study carried out on a panel of diabetic patients (O'Neill et al. 2007) pointed out that the use of statins seems to reduce the inflammatory and endothelial response to PM exposure. Furthermore, a multi-city European study (Ruckerl et al. 2007) investigated the effect of PM on blood markers of inflammation among MI survivors, most of whom were treated with statins. Results highlighted an increase in interleukin-6, but no variation in C-reactive protein blood levels, suggesting a protective effect of the drug.

Sakamoto (Sakamoto et al. 2009) looked at the effects of statins on PM₁₀-induced cytokine production in human bronchial epithelial cells and alveolar macrophages, to confirm the presumed anti-inflammatory effect of the drug itself. His results suggested that atorvastatin could interfere with the production of PM-induced cytokine by alveolar macrophages, but not by bronchial epithelial cells; the medication seemed to modulate the production of mediators, thus influencing the inflammatory response to PM₁₀, which is believed to play a role in the cardiovascular diseases. Similar conclusions were shown by two *in vivo* studies (Miyata et al. 2012; Miyata et al. 2013), which demonstrated that lovastatin intake can attenuate the PM₁₀-induced inflammation by reducing the release of pro-inflammatory mediators and polymorphonuclear leukocytes and by enhancing the activity of alveolar macrophages thereby promoting the clearance of particles from the lung.

Some limitations in our analysis should be noted. The major limitation in any observational study examining therapeutic drug use as a modifier of an exposure is confounding by indication (Psaty et al. 1999), that occurs when a certain treatment is actually a proxy for some patients' characteristics and therefore the estimated interaction between exposure and treatment is actually an interaction between the exposure and these characteristics. This issue clearly emerged in the analysis of the effect modification due to theophylline: it is plausible that the intake of this drug is a proxy for the patients' compromised health condition, that in turn makes them more susceptible to the effect of PM. If the same

conclusions should apply to cardiac therapy and lipid modifying agents, we should expect these treatments to be proxies for some individual condition that reduce susceptibility to air pollution: it might be argued that subjects who are treated are those who receive better medical attention, but under this assumption we would expect to observe similar results when analyzing all the other cardiovascular drugs, while we didn't. We therefore conclude that the risk reduction we estimated plausibly identifies a real protective effect of cardiac therapy and lipid modifying agents against PM.

A further limitation, as this was a pilot study, is that the selected population was relatively small and the observational time was short (just one year), therefore the resulting number of events proved to be too small to build an analysis based on a generalized additive model. This limitation was overcome thanks to the use of the case-only approach, but because of the limited number of cases no analysis stratified by diagnosis could be carried out. We were therefore forced not to make any distinction between different subgroups of respiratory or cardiovascular discharges. Pathologies affected by PM₁₀ through different pathways (e.g. asthma and COPD) had to be grouped together.

Another possible limitation is our definition of pre-treated subjects. Indeed, the observational time was too short to distinguish between chronic and acute treatments; furthermore we assume that the subject is really taking the medication and that the active agent is still effective as the hospitalization occurs, because DENALI doesn't gather information on the actual compliance. This might have led to a certain amount of misclassification. However, it should be noted that misclassification should be stronger for acute treatments which can be suspended after a short period of time, while lipid modifying agents and cardiac therapy are mainly chronic. Furthermore, thanks to DENALI we know when the medications were purchased; this should more likely indicate that they were actually taken.

Due to the use of the case-only approach, the results were expressed as relative odds. This means that it was impossible to ascertain whether the negative association between pre-hospitalization treatments and PM₁₀ concentration represented a decrease in risk in days with a higher concentration of PM₁₀ or a less pronounced increase as compared with subjects who were not treated.

Furthermore there is an intrinsic limitation regarding the exposure measurement, because it was impossible to establish whether the measured PM₁₀ concentration coincided with the real exposure of the subject for different reasons: we didn't have data about indoor air pollution; we used outdoor measurements from monitoring stations, that might poorly represent personal exposure; each subject was assigned the average exposure of his city, as DENALI didn't include information on residents' addresses and daily movements.

Finally, we analyzed multiple outcomes and potential modifiers: specifically 2 outcomes (respiratory and cardiovascular hospitalizations), with respectively 5 (systemic glucocorticoids, adrenergic inhalants, glucocorticoid inhalants, anticholinergics inhalants, theophylline) and 3 (cardiac therapy, lipid modifying agents, all other cv drugs) modifiers.

We believe that this set is limited enough to reasonably infer that our results might not be given by chance, but more work is needed to confirm our findings.

In spite of all the limitations, this study shows the advantage of using administrative databases, which contain information about the whole population of the study area. Thanks to DENALI, we reconstructed each subject's medical history by linking different databases, and we could analyze hospitalizations together with medical prescriptions on every single subject living in the selected cities. We were therefore able to develop one of the first studies to investigate the pharmacological treatment as an effect modifier of PM pollution in real-world settings. Though on a small sample of individuals, we analyzed a more variegated and wide population as compared with previous studies, which were forced to select only a small cohort of patients and to follow them up in order to establish which medical treatment they used.

5. Conclusions

The findings of our study provide a better insight of the interaction between pharmacological treatments and PM₁₀ on health outcomes. Although this is a pilot study, it gives some interesting indication of cardiac therapy and lipid modifying agents having a protective effect against the negative consequences of exposure to PM₁₀. Moreover, it detects a synergy between PM₁₀ and theophylline, which is likely due to confounding by indication, and suggests that treated subjects are more complex and therefore more susceptible to the pollutant's effect. It is desirable to widen the study, expanding the temporal period or the geographical area of interest.

Acknowledgments

This study was supported by Cariplo Foundation (TOSCA project). The funding source was not involved in any stage of the research process.

This publication was made possible by USEPA grant (RD-83479801). Its contents are solely the responsibility of the grantee and do not necessarily represent the official views of the USEPA. Further, USEPA does not endorse the purchase of any commercial products or services mentioned in the publication.

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Appendix A

Figure A.1 Location of the cities involved in the study and of the selected PM₁₀ monitoring stations.

Highlights

- We carried out a pilot study in Northern Italy using administrative databases.
- We retrieved data on cardiorespiratory hospitalizations and drug prescriptions.
- We evaluated how pre-hospitalization treatments modify the effect of PM₁₀.
- Cardiac therapy and lipid modifying agents might mitigate the effect of PM₁₀.
- Subjects treated with theophylline seem more susceptible to the effect of PM₁₀.

Figure 1.

Association between PM₁₀ and prescription of cardiac therapy and lipid modifying agents among cases hospitalized for cardiovascular causes. Results stratified by season, sex and age classes. Vertical lines represent 95% Confidence Intervals.

^a Odds Ratio of prescription for an increment of 10 µg/m³ in PM₁₀ concentration.

Descriptive statistics of PM₁₀ concentration, resident population and number of hospital admissions in the selected cities during the year 2005.

Table 1

City of residence	PM ₁₀ (µg/m ³) - Mean (SD)			Population	N admissions		
	Warm season ^a	Cold season ^b	Overall		Respiratory	Cardiovascular	
Total	30 (15.08)	64 (30.93)	47 (29.52)	471,868	2,821	5,831	
Saronno	28 (18.18)	64 (36.03)	46 (33.65)	37,465	341	549	
Sondrio	26 (16.17)	56 (26.06)	41 (26.41)	21,839	132	295	
Monza	29 (11.33)	59 (27.63)	44 (25.94)	122,112	558	1,207	
Sesto San Giovanni	33 (14.79)	72 (33.45)	52 (32.28)	83,486	594	1,082	
Bergamo	29 (13.50)	60 (28.66)	45 (27.05)	116,354	524	1,378	
Mantova	34 (14.11)	60 (26.36)	47 (24.98)	47,887	355	747	
Lodi	31 (15.28)	74 (33.00)	52 (33.29)	42,725	317	573	

^a April – September

^b October – March

Table 2

Demographic characteristics and treatments at hospitalization.

Characteristic	Respiratory hospitalizations			Cardiovascular hospitalizations		
	Warm Season (n=1,558)	Cold Season (n=1,263)	Total (N=2,821)	Warm Season (n=3,465)	Cold Season (n=2,366)	Total (N=5,831)
Demographic characteristics						
Female - N(%)	662 (42.5)	550 (43.5)	1,212 (43.0)	1,484 (42.8)	1,020 (43.1)	2,504 (42.9)
Age at hospitalization						
Mean (SD)	62 (27.3) ^c	58 (31.6)	60 (29.4)	72 (12.6)	72 (12.7)	72 (12.6)
Median (Q1 ^a - Q3 ^b)	72.5 (56 - 81)	71 (36 - 81)	72 (48 - 81)	74 (66 - 8)	74 (66 - 8)	74 (66 - 81)
Ageclass at hospitalization - N(%)						
0-19	219 (14.0)	273 (21.6)	492 (17.4)	10 (0.3)	9 (0.9)	19 (0.3)
20-64	305 (19.6) ^d	217 (17.2)	522 (18.5)	753 (21.7)	519 (21.9)	1,272 (21.8)
65	1,034 (66.4) ^d	773 (61.2)	1,807 (64.1)	2,702 (78.0)	1,838 (77.7)	4,540 (77.9)
Charlson Index						
Mean (SD)	1.29 (1.6) ^c	1.17 (1.5)	1.24 (1.6)	1.11 (1.3)	1.16 (1.3)	1.13 (1.3)
Median (Q1 ^a - Q3 ^b)	1 (0 - 2)	1 (0 - 2)	1 (0 - 2)	1 (0 - 2)	1 (0 - 2)	1 (0 - 2)
Previous respiratory treatments - N(%)						
Systemic glucocorticoids	184 (11.8)	144 (11.4)	328 (11.6)	132 (3.8)	78 (3.3)	210 (3.6)
Adrenergic inhalants	187 (12.0)	172 (13.6)	359 (12.7)	94 (2.7)	68 (2.9)	162 (2.8)
Glucocorticoid inhalants	158 (10.1)	143 (11.3)	301 (10.7)	93 (2.7)	83 (3.5)	176 (3.0)
Anticholinergic inhalants	120 (7.7)	94 (7.4)	214 (7.6)	62 (1.8)	39 (1.6)	101 (1.7)
Theophylline	43 (2.8)	35 (2.8)	78 (2.8)	18 (0.5)	21 (0.9)	39 (0.7)
Previous cardiovascular treatments - N(%)						
Cardiac therapy	291 (18.7)	250 (19.8)	541 (19.2)	1,327 (38.3) ^e	833 (35.2)	2,160 (37.0)
Lipid modifying agents	116 (7.4)	75 (5.9)	191 (6.8)	784 (22.6)	514 (21.7)	1,298 (22.3)
All other cv drugs	679 (43.6)	508 (40.2)	1,187 (42.1)	2,285 (65.95)	1,552 (65.6)	3,837 (65.8)

^a 1st quartile^b 3rd quartile

p-value of Chi-square test <0.05 vs Cold season

p-value of Chi-square test <0.05 vs Cold season, pairwise comparison with age 0–19

p-value of Wilcoxon test >0.05 vs Cold season

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Table 3

Association between exposure to PM₁₀ and drug prescription among hospitalized subjects.

Modifier	Total		Warm season		Cold season	
	OR ^a	CI 95% ^b	OR ^a	CI 95% ^b	OR ^a	CI 95% ^b
Respiratory treatments						
Systemic glucocorticoids	0.940	0.823 – 1.075	0.984	0.907 – 1.067	0.960	0.903 – 1.020
Adrenergic inhalants	1.034	0.905 – 1.181	0.991	0.920 – 1.067	1.006	0.951 – 1.065
Glucocorticoids inhalants	0.887	0.759 – 1.036	0.991	0.915 – 1.074	0.988	0.929 – 1.052
Anticholinergic inhalants	1.014	0.858 – 1.198	0.987	0.892 – 1.092	0.991	0.919 – 1.068
Theophylline	1.131	0.880 – 1.453	1.178 ^c	1.027 – 1.351	1.119 ^c	1.013 – 1.237
Cardiovascular treatments						
Cardiac Therapy	0.922 ^c	0.866 – 0.982	0.982	0.945 – 1.021	0.967 ^c	0.940 – 0.995
Lipid modifying agents	0.923 ^c	0.859 – 0.992	0.971	0.928 – 1.017	0.962 ^c	0.931 – 0.995
All others cv drugs	0.958	0.900 – 1.021	1.006	0.966 – 1.048	0.997	0.968 – 1.027

^a Relative odds of prescription for an increment of 10 µg/m³ of PM₁₀

^b 95% Confidence Interval

^c p-value < 0.05