

ORIGINAL ARTICLE

Effects of airborne fine particles (PM_{2.5}) on deep vein thrombosis admissions in the northeastern United States

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Summary. *Background:* Literature relating air pollution exposure to deep vein thrombosis (DVT) and pulmonary embolism (PE), despite biological plausibility, is sparse. No comprehensive study examining associations between both short- and long-term exposure to particulate matter (PM)_{2.5} and DVT or PE has been published. Using a novel PM_{2.5} prediction model, we study whether long- and short-term PM_{2.5} exposure is associated with DVT and PE admissions among elderly across the northeastern United States. *Methods:* We estimated daily exposure of PM_{2.5} in each ZIP code. We investigated the long- and short-term effects of PM_{2.5} on DVT and PE hospital admissions. There were 453 413 DVT and 151 829 PE admissions in the study. For short-term exposure, we performed a case crossover analysis matching month and year and defined the hazard period as lag 01 (exposure of day of admission and previous day). For the long-term association, we used a Poisson regression. *Results:* A 10– $\mu\text{g m}^{-3}$ increase in short-term exposure was associated with a 0.63% increase in DVT admissions (95% confidence interval [CI] = 0.03% to 1.25%) and a 6.98% (95% CI = 5.65% to 8.33%) increase in long-term exposure admissions. For PE, the associated risks were 0.38% (95% CI = –0.68% to 1.25%) and 2.67% (95% CI = 5.65% to 8.33%). These results persisted when analyses were restricted to location-periods meeting the current Environmental Protection Agency annual standard of 12 $\mu\text{g m}^{-3}$. *Conclusions:* Our findings showed that PM_{2.5} exposure was associated with DVT and PE hospi-

tal admissions and that current standards are not protective of this result.

Keywords: air pollution; deep vein thrombosis; environment; epidemiology; public health; venous thrombosis.

Introduction

A strong body of evidence published in recent years has consistently shown that fine particulate matter (PM)_{2.5} particles with an aerodynamic diameter $\leq 2.5 \mu\text{m}$ is associated with increased hospital admissions throughout the United States and the world [1–6]. Exposure to PM_{2.5} can increase hospital admissions for multiple causes [3,7], including *inter alia* admissions for all respiratory causes [2,8], chronic obstructive pulmonary disease [4,9,10], cardiovascular disease [11,12], stroke [5], myocardial infarction [6], and diabetes [3].

Epidemiology research on cardiovascular effects of PM exposure has mostly focused on the effects of both short- and long-term PM exposure on arterial disease, such as triggering of myocardial infarction or stroke or the development of atherosclerosis and related ischemic disease in the heart and the brain [13]. A large body of evidence related to this research has linked short- and long-term PM exposure with changes in a variety of subclinical physiological end points that are part of the etiology of venous thromboembolism (VTE), including enhanced systemic inflammation and increased blood coagulation [14,15]. Yet, the literature relating air pollution exposure to DVT is sparse. DVT is a manifestation of VTE. Although most DVT is occult and resolves spontaneously without complication, death from DVT-associated massive pulmonary embolism (PE) causes as many as 300 000 deaths annually in the United States [16]. To the best of our knowledge, no comprehensive study looking at associations between exposure to both short-term (acute) and long-term (chronic) exposure to PM_{2.5} and DVT or PE has been published to date.

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Two key studies conducted in recent years by Baccarelli and colleagues have related long-term exposure to air pollution with increased risk of DVT [17,18]. In the first study [17], they examined the association of exposure to PM_{10} with DVT risk. They found that every 10-mg m^{-3} increase in inhalable PM was associated with a 70% (95% confidence interval [CI] = 30–123%) increased risk of DVT. A second study by the same group [18] was based on an expansion of the previous analysis. The study found that DVT risk was significantly greater for those living closer to major traffic roads. In a more recent study, Dales *et al.* [19] looked at air pollution and hospitalization for VTE in Chile. They used a time-series approach to test the association between daily air pollution and VTE hospitalizations in Santiago. They found a 1.05 increased relative risk (95% CI = 1.03–1.06) for a $20.02\text{-}\mu\text{g m}^{-3}$ increase in $PM_{2.5}$.

There have been two studies that looked at the association between DVT and air pollution and did not find an association. Kan *et al.* [20] examined the association between long-term traffic exposure and incident VTE in a population-based prospective cohort study (ARIC Study). Shia *et al.* [21] looked at ambient particulate matter air pollution and VTE in the women's health initiative hormone therapy trials. They found no evidence of an association between short-term or long-term PM exposure and VTE, or clinically important modification by randomized exposure to exogenous estrogens among postmenopausal women.

We recently presented a new method of assessing spatiotemporal resolved $PM_{2.5}$ exposures for epidemiological studies [22,23] and applied it in various epidemiology studies [3,24,25]. As opposed to many commonly used exposure models, our model makes use of satellite aerosol optical depth (AOD) measurements, which allowed us to estimate spatially resolved $PM_{2.5}$ on a daily basis across the northeastern United States. In addition, previous studies of DVT were limited to populations living close to monitoring stations and thus did not include individuals living in suburban and rural areas where no monitoring stations were available. In contrast, our model allows the use of the entire population in the study area, resulting in more generalizable results.

In this work, we use our $PM_{2.5}$ prediction model to study whether long- and short-term $PM_{2.5}$ exposure is associated with DVT admissions among elderly persons (aged 65 and older) across the entire population in the northeastern United States. We also look at PE as a secondary analysis.

Methods

Study domain

For this study, we considered a spatial domain that included the entire northeast region of the United States

comprising Washington, DC, Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont, Delaware, Maryland, New Jersey, Pennsylvania, Virginia, New York, and West Virginia (Fig. 1). The data cover an area of $681\,945\text{ km}^2$ for a population of $71\,748\,181$ [26].

Exposure data

$PM_{2.5}$ exposures for 2000–2008 were assessed by using our spatiotemporal resolved prediction models [22,23] that incorporate satellite AOD data. The exposure dataset encompasses daily $PM_{2.5}$ predictions at a $10 \times 10\text{-km}$ spatial resolution across the study area (Fig. 1) during the entire study period.

This spatiotemporal model incorporates classic land use regression (elevation, distance to major roads, percent of open space, point emissions, and area emissions), meteorological variables (temperature, wind speed, relative humidity, and visibility), and satellite-based AOD data. The model is run in stages where in stage 1, we calibrate the $10 \times 10\text{-km}$ AOD grid-level observations to the $PM_{2.5}$ monitoring data collected within 10 km of each AOD reading. The model consists of a mixed model for observed $PM_{2.5}$ monitoring data that contains both fixed and day-specific random effects for the intercept and the AOD and temperature slopes. In the following stage of the model, we estimate $PM_{2.5}$ concentrations in grid cells without monitors but with available AOD measurements by using the stage 1 fit. Finally, in stage 3 of the model, we estimated daily $PM_{2.5}$ concentration levels for all grid cells in the study domain for days when AOD data were unavailable. The model is fit with a smooth function of latitude and longitude and a random intercept for each cell (similar to universal kriging) that takes advantage of associations between grid cell AOD values and $PM_{2.5}$ data from monitors located elsewhere and associations with available AOD values in neighboring grid cells. The model performance was excellent with a mean 10-fold cross-validation “out-of-sample” $R^2 = 0.82$. These $PM_{2.5}$ daily predictions were matched to ZIP codes by using ArcGIS (ESRI, Redlands, CA, USA) and SAS (SAS Institute, Cary, NC, USA) based on spatial location and date. For more detailed information on the prediction model, please refer to Kloog *et al.* [22,23].

DVT hospital admission data

Individual DVT and PE hospital admittance records were obtained from Medicare. Medicare is a national social insurance program, administered by the US federal government since 1966, that guarantees access to health insurance for Americans aged 65 and older. The dataset includes DVT and PE hospitalization for all residents of age 65 and older, for all available years (2000–2008). We defined cases as those with a DVT and PE admission and

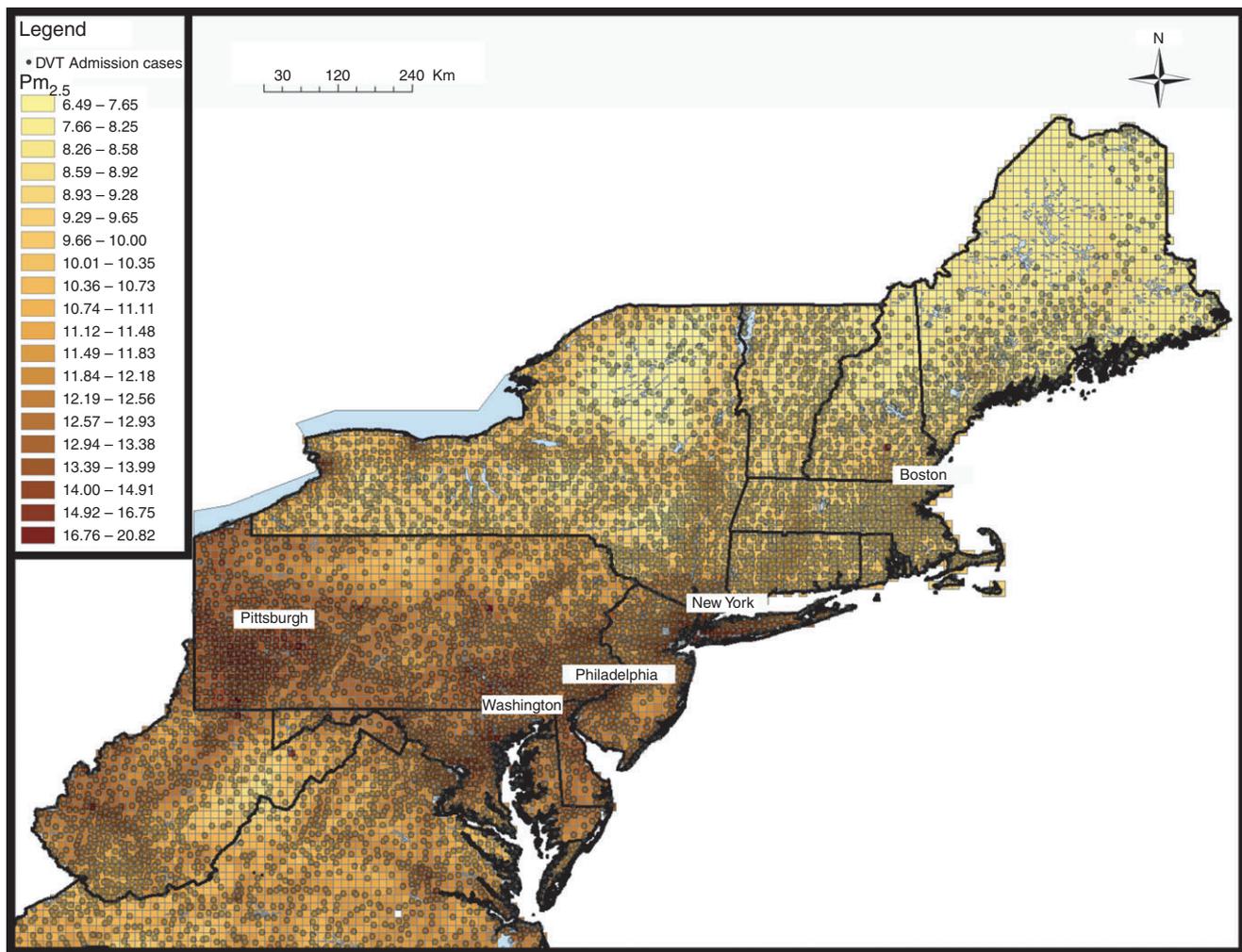


Fig. 1. Map of the study area showing the residential location of admission cases juxtaposed over a sample $\text{PM}_{2.5}$ 10×10 -km pollution grid for January 8, 2001.

a primary discharge diagnosis using the *International Classification of Diseases, Ninth Revision* for DVT- and PE-related admissions. These records included information such as age, sex, date of admission, race/ethnicity, and ZIP code of residence. The US Medicare data are previously collected administrative data and do not require individual patient consent.

Covariates

Temperature data were obtained through the National Climatic Data Center (NCDC) [27]. Only continuous operating stations with daily data running from 2000 to 2008 were used. For meteorological variables, ZIP codes were matched to the closest weather station. All socioeconomic variables were obtained through the US Census Bureau from the 2000 social, economic, and housing characteristics datasets [28]. Socioeconomic variables used included the following ZIP code-level information: percentage of minorities (defined as non-white), age,

education (people with no high school education), and median income.

Statistical methods

ZIP code-specific DVT admissions were matched with our exposure estimates for each 10×10 -km grid cell. We used a case-crossover analysis approach for the acute effects. We used a Poisson proportionate hazard survival analysis based on the approach of Laird and Oliver [29], with a baseline hazard that varies for each follow-up interval to estimate the long-term effects. The resulting model specifies that each follow-up interval has a separate intercept and an offset representing person-time at risk. Because the entire available Medicare population is being analyzed and DVT admission cases are rare events, the person-time at risk varies slowly and smoothly across time. In the limit as the time interval gets small, the time-period specific intercept also approaches a smooth function of time, and hence both can be replaced with the

smooth function of time, λ(t). λ(t) will be estimated with a natural cubic spline with 5degrees of freedom per year. Specifically:

$$\log(\lambda_{it}) = \lambda_i + \lambda(t) + \text{temporal covariates}$$

where

$$\lambda_i = \delta + \gamma_1 PM_{2.5i} + \text{spatial covariates} + \text{zipcode} + e_i$$

Where λ_i is the long-term admission rate in grid cell *i*, λ(t) is a smooth function of time, temporal covariates are temperature and day of the week, PM_{2.5i} is the long-term yearly moving average PM_{2.5} concentrations in cell *i*, spatial covariates are the socioeconomic factors defined at the ZIP code level (percentage minority, median income, percentage with less than high school education), and *e_i* is the remaining unexplained difference in admission rate between cell *i* and other cells, which is treated as a mean zero normal random effect with variance estimated from the data. This approach has previously been used to estimate long-term air pollution effects [3].

The case-crossover design was developed as a variant of the case-control design to study the effects of transient exposures on acute events [30]. This design samples only cases and compares each subject’s exposure experience in a time period just before a case-defining event with that subject’s exposure at other times. Because there is perfect matching on all measured or unmeasured subject characteristics that do not vary over time, there can be no confounding by those characteristics. If, in addition, the control days are chosen to be close to the event day, slowly varying subject characteristics are also controlled by matching. Bateson and Schwartz [31,32] demonstrated that by choosing control days close to event days, even very strong confounding by seasonal patterns could be controlled by using this design. Levy *et al.* [33] showed that a time-stratified approach to choosing controls, such as sampling control days from the same month of the same year, avoided some subtle selection bias issues and resulted in a proper conditional logistic likelihood. Schwartz *et al.* [34] demonstrated via simulation that this approach gave unbiased effect estimates and coverage probabilities even in the presence of strong seasonal confounders. We used this time-stratified approach in our analysis and defined the base hazard period as the same day and the day before the hospital admission: The case window was defined as the “at risk” period preceding the event (i.e., PM_{2.5} exposure at the same day and the day before the hospital admission). The control windows are periods of the same length as, and not overlapping with, the case window that provides an estimate of the expected frequency of exposure for each case (i.e., 2-day average PM_{2.5} exposure every third day in the same month not overlapping with the case window). The case window and the control windows derive from the same person at different times; that is, the case-crossover design is based on

subject-matched sampling. It should be noted that concordant pairs in the case crossover analysis are dropped out.

The data were analyzed using conditional logistic regression (PROC PHREG, release 8.2; SAS Institute). Temperature with the same moving average as PM_{2.5} was included in the model as a potential confounder. To investigate the robustness of our results, various sensitivity analyses were run. Specifically, we analyzed other averaging periods: we examined PM_{2.5} exposure 3 days prior to admission: lag02 (a moving average of day of admittance exposure and 2 days of previous exposure) and PM_{2.5} exposure on day of admission-lag0 (day of admittance exposure) vs. lag01 (a moving average of day of admittance exposure and previous day exposure). We also looked at the differences between the sexes.

Finally, we also looked at the long-term association when we restricted the analysis to periods below the EPA current annual standard of 12 µg m⁻³ to determine whether associations persist at low concentrations.

Results

Table 1 gives the characteristics of the admitted people included in our analyses, which included 453 413 DVT admissions (and 151 829 PE admissions). Of these DVT admissions, the majority were males (62.69%) and white (85.27%), with an average age of 79 years. Table 2 contains a summary of the predicted exposures for both the short-term PM exposure (lag 1—which denotes a 2-day moving average from day of admission) and long-term exposure (1-year moving average from day of admission), as well as temperature across all grid cells in the analysis. Table 3 presents the estimated percentage increase for DVT and PE, and associated 95% CIs, in hospital admissions for a 10-µg m⁻³ increase in PM_{2.5} for both the short- and long-term exposures. Our results indicated that short-term exposure was associated with a 0.63% increase in DVT admissions (95% CI = 0.03–1.25%), while long-term exposure was associated with a 6.98% increase in DVT admissions (95% CI = 5.65–8.33%). In addition, we

Table 1 Descriptive statistics for deep vein thrombosis hospital admissions (mean [SD] age, 79.04 [7.84] years) across the northeastern United States for 2000–2008

Variable	No. (%)	Short-term PM _{2.5} exposure, mean (SD)	Long-term PM _{2.5} exposure, mean (SD)
Sex			
Male	170 067 (37.51)	12.48 (6.74)	12.69 (2.20)
Female	283 346 (62.49)	12.69 (6.84)	12.86 (2.19)
Race			
White	386 606 (85.27)	12.44 (6.72)	12.63 (2.17)
Black	54 842 (12.10)	13.67 (7.16)	13.86 (1.95)
Other	11 965 (2.64)	13.31 (7.19)	13.55 (2.29)

Table 2 Descriptive statistics for short-term PM_{2.5} exposure and temperature across the northeastern United States for 2000–2009

Covariate	Mean	Min	Max	Median	SD	Range	IQR	Q1	Q3	Days of data available
Acute (2-day moving average) PM _{2.5} ($\mu\text{g m}^{-3}$)	12.6	0.0	96.0	11.1	6.8	100.7	8.3	7.7	15.9	453 413
Chronic (1-y exposure) PM _{2.5} ($\mu\text{g m}^{-3}$)	12.8	0.0	29.0	12.9	2.2	24.5	3.0	11.3	14.3	453 413
Temperature (F°)	48.0	12.2	60.6	50.5	5.5	48.4	9.8	42.2	52.1	453 413

Q1 and Q3 are quartiles.

Table 3 Estimated percentage increase in DVT hospital admissions for a 10- $\mu\text{g m}^{-3}$ increase in short- and long-term PM_{2.5}

Type	DVT % increase	PE % increase
Short term (lag1)	0.64 (0.03 to 1.25)	0.38 (−0.68 to 1.44)
Long term	6.98 (5.65 to 8.33)	2.67 (1.66 to 3.75)
Sensitivity analysis		
Short term (lag0)	0.59 (0.07–1.11)	0.68 (−0.02 to 1.38)
Short term (lag2)	0.68 (−0.02 to 1.38)	0.59 (0.07 to 1.11)

DVT, deep vein thrombosis; PE, pulmonary embolism.

found that short-term exposure was associated with a 0.38% increase (albeit not significant) in PE admissions (95% CI = −0.68% to 1.25%), while long-term exposure was associated with a 2.67% increase in PE admissions (95% CI = 5.65–8.33%).

The results from the sensitivity analysis are presented in Table 3 as well. In general, the results of the sensitivity analysis were consistent with the primary analysis, albeit the 2-day lag results were non-significant (marginally): lag0 exposure was associated with a 0.59% increase in DVT admissions (95% CI = 0.07–1.1%), while lag2 exposure was associated with a 0.68% increase in DVT admissions (95% CI = −0.02% to 1.38%). Lag0 exposure was associated with a 0.68% increase in PE admissions (95% CI = −0.02% to 1.38%), while lag2 exposure was associated with a 0.59% increase in PE admissions (95% CI = 0.07–1.11%).

We found differences (albeit not significant based on the *P* value of the interaction term) in the PM_{2.5} associations with DVT between the sexes. Males showed a 0.83% increase in DVT admissions (95% CI = 0.50–1.17%), while females showed a 0.73% increase in DVT admissions (95% CI = 0.42–1.04%). The low exposure analysis found that long-term exposure was still significantly associated with a 4.27% increase in DVT admissions (95% CI = 2.32–6.25%) and a 1.91% increase in PE admissions (95% CI = 0.06–3.80%) when restricted to observations below the Environmental Protection Agency national ambient air quality standard of 12 $\mu\text{g m}^{-3}$.

Discussion

We examine associations between PM_{2.5} exposure estimates generated by a new spatiotemporal resolved prediction model and increased DVT and PE hospital

admissions in an elderly population (aged 65 and older) across the northeastern United States. We found that the associations with DVT for both short- and long-term exposures were significantly positive. In addition, we found positive associations with PE, albeit only the long-term association was statistically significant. Notably, this study includes more events than previous studies of DVT and incorporates the entire 65 years and older population in the study area, not just the more urban population located near monitors such as was used in the two reports by Baccarelli and colleagues [17,18], in which because some area residents had no local monitoring stations around them and thus were removed from the analysis. In addition, the association with long-term exposure persists at exposure levels below the Environmental Protection Agency annual standard of 12 $\mu\text{g m}^{-3}$.

Although DVT symptoms often go unnoticed for days (the lag between symptom initiation and diagnosis can last as long as 30 days [17]), we still saw associations with short-term exposure. One explanation is that air pollution peaks might worsen the symptoms, such as by increasing the size of an already existing clot that can lead to hospitalization. It should be noted that there is a possibility that these findings could be mediated through these other disease states. We plan to look into such meditations in future studies.

Recent studies have associated exposure to air pollution with activation of inflammatory pathways, production of reactive oxygen species, endothelial injury and dysfunction, arterial vasoconstriction, and alterations in blood coagulation factors [35–37]. Venous thromboembolism is the third most common cardiovascular disease, after acute coronary syndromes and stroke [38]. Determinants of arterial thromboembolism and VTE have been considered as distinctly different conditions. Recent studies showed that there are pathophysiological links between arterial thromboembolism and VTE and that they share common risk factors such as age, obesity, diabetes mellitus, hypertension, hyperlipemia, and potential exposure to air pollution [39]. The current evidence, albeit limited, suggests that exposure to air pollution can contribute to pulmonary and systemic inflammation and blood coagulation; therefore, an epidemiological link between air pollution and both arterial thromboembolism and VTE is plausible [40].

There are a few limitations in the present study. The spatial resolutions for the Medicare data (ZIP codes) are

not individual addresses, but those are not available because of privacy concerns. In addition, long-term PM_{2.5} exposure may be associated with other confounders that can potentially increase DVT risk. Although the analysis was adjusted for available risk factors for DVT, we cannot exclude that other unmeasured confounders might have influenced our results. These confounders (e.g., smoking, lifestyle, physical activities conducted, or other exposures that are difficult to measure) were unavailable during this study and thus were not used. This confounding is not an issue in the case crossover design, which eliminates confounding by stable individual characteristics.

Selection bias is always a concern in such studies. In the United States, all people older than 65 are entitled to free Medicare insurance, so we expect the population studied to be representative of the overall population (older than 65 years). Another limitation of this study is that we do not have information on other risk factors such as body mass index, medication use, or existing comorbidities. This may potentially lead to some potential residual confounding if they are also associated with pollution. In addition, the association of PM_{2.5} with DVT could be a downstream consequence of its association with cancer. Finally, misclassification of the outcome can be expected as a result of diagnostic or coding errors. However, these errors are likely unrelated to PM levels and are expected to reduce the precision of our estimates and potentially bias the relative risk toward the null.

The use of 10 × 10 km for the satellite data could also be improved as higher-resolution satellite data become available. As satellite remote sensing evolves and progresses, higher spatial resolution data (such as 1 × 1 km) are expected to be released and will further reduce exposure error [41]. Such finer resolution should enable us to assess more precise estimated daily individual exposure as they relate to different locations such as residence, workplace, and so on, for datasets where individual addresses are available.

Our findings showed that PM_{2.5} exposure was associated with DVT hospital admissions. In addition, we demonstrate that our AOD-based exposure models can be successfully applied to epidemiological studies.

Addendum

I. Kloog designed and performed research, collected data, and contributed to discussion and wrote the manuscript. A. Zanobetti performed research and collected, analyzed, and interpreted the data. F. Nordio collected data and helped design the research. B. A. Coull contributed to discussion and statistical analysis and edited the manuscript. A. A. Baccarelli designed research, interpreted data, contributed to discussion, and edited the manuscript. J. Schwartz designed research, interpreted data, contributed to discussion, and co-wrote the manuscript.

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Disclosure of Conflict of Interest

The authors state that they have no conflict of interest.

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