Antithrombotic medication and endovascular interventions associated with short-term exposure to particulate air pollution: a nationwide case-crossover study.

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Abstract

Short-term exposure to air pollution has pro-thrombotic effects and triggers thrombo-embolic events such as myocardial infarction or stroke in adults. This study evaluates the association between short-term variation in air pollution and treatments for acute thrombo-embolic events among the whole Belgian population. In a bidirectional time-stratified case-crossover design, we included 227,861 events treated with endovascular intervention and 74,942 with antithrombotic enzymes that were reimbursed by the Belgian Social Security between January 1st 2009 and December 31st 2013. We compared the concentrations of particulate matter (PM) air pollution (PM_{10} and $PM_{2.5}$), as estimated at the municipality level on the day of the event (lag 0) and two days earlier (lag 1 and lag 2) with those of control days from the same month, matched by temperature and accounting for day of the week (weekend vs week days). We applied conditional logistic regression models to obtain odds ratios (OR) and their 95% CI for an increase of 10µg/m^3 (PM_{10}) or 5µg/m^3 ($PM_{2.5}$) in pollutant concentrations over three lag days (lag 0, 1 and 2). We observed significant associations of PM_{10} and $PM_{2.5}$ with treatment of acute thrombo-embolic events at the three lags. The strongest associations were observed for air pollution concentrations on the day of the event (lag0). Increases of 10 µg/m^3 PM_{10} and 5 µg/m^3 $PM_{2.5}$ on lag0 increased the odds of events treated with endovascular intervention by 2.7% (95%CI:2.3% to 3.2%) and 1.3% (95%CI:1% to 1.5%), respectively, and they increased the odds of events treated with antithrombotic enzymes by 1.9% (95%CI:1.1-2.7%) and 1.2% (95%CI:0.7% to 1.6%), respectively. The associations were generally stronger during autumn months and among children. Our nationwide study confirms that acute exposure to outdoor air pollutants such as PM_{10} or $PM_{2.5}$ increase the use of medication and interventions to treat thrombo-embolic events.

Keywords: PM_{10}; $PM_{2.5}$; thrombo-embolic diseases; antithrombotic enzymes; endovascular procedure; case-crossover.

Abbreviations: IMA-AIM:Intermutualistisch Agentschap – Agence Inter-Mutualiste; ATC: Anatomical Therapeutic Chemical; OR: Odds ratio; CI: Confidence interval.

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Competing interests: none

Introduction

Reviews of the World Health Organization conclude that short- term exposure to traffic-related air pollutants is a cause of cardiovascular mortality and morbidity (WHO 2013). One of the mechanisms involved in the associations between short-term exposure and cardiovascular events is an acute dysregulation of the coagulation system (Emmerechts and Hoylaerts 2012). Results from experimental studies suggest that exposure to traffic-related air pollutants leads to platelet activation, increase in haemostasis factors, histamine release, and heightened thrombus formation within one or few hours after exposure (Krishnan et al. 2013; Nemmar et al. 2002, 2003; Neri et al. 2016; Peters et al. 1997; Strak et al. 2013a, 2013b). Consistently, epidemiological studies show that short-term exposure to air pollution is a trigger of acute ischemic events such as myocardial infarction and stroke (Mustafić et al. 2012; Shah et al. 2013; Yu et al. 2014; Zhang et al. 2009). In addition, previous research has shown that air pollution may trigger hospital admission due to acute myocardial infarction among adults and elderly (Claeys et al. 2015; Collart et al. 2017).

Here, we present a comprehensive case-crossover study on the short term associations of air pollution on the use of antithrombotic medication or endovascular interventions, prescribed to treat thrombo-embolic events. We included more than 300,000 events that received antithrombotic enzymes or endovascular interventions between the first of January 2009 and the 31st of December 2013 in Belgium. In this study, we combined data of reimbursed antithrombotic medication and of endovascular interventions to treat thrombosis with daily air pollution information. We hypothesized that increases in the levels of air pollution result in increases in the number of antithrombotic treatments.

Material and methods

Antithrombotic medication and endovascular intervention reimbursement

In Belgium, 98% of the residing population (about 11 million in 2013) is enrolled in the social security system. Seven sickness funds reimburse health care expenditure including prescribed medication and surgical procedures of all individuals enrolled in the Belgian social security system. This information is centralized by the "Intermutualistisch Agentschap – Agence Inter-Mutualiste" (IMA-AIM). Thus, detailed records of reimbursed drugs and health care interventions (resource use) of almost all the population residing in Belgium (98%) are included in the IMA-AIM database.

The medication data are records of medication reimbursements 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 of the patient, and individual information (age, sex, and home address). The ATC classification system standardizes classifications of chemical substances to allow international comparisons. The active substances are divided into groups at 5 levels. The first level is according to the target organ/system, the second is according to their therapeutic properties, the 3rd and 4th levels classify the drugs according to pharmacological properties and the 5th level according to chemical properties. Thus, each substance is related to a unique ATC-code. In our study, we included all daily sales of prescribed antithrombotic medication in the group B01AD (Antithrombotic agents: enzymes) that were reimbursed, for residents in Belgium (all ages) registered in the Belgian social security during the study period (2009-2013). Such medication can only be administered in hospitals and, therefore, the date of purchase equals the date of use.

In addition to the medication data, the IMA-AIM database contains information on reimbursements of a wide spectrum of interventions (consultations, diagnostics procedures, surgical and non-surgical interventions, etc.). As for the medication data, each intervention's specific code is also linked to the date of its execution, the encoded national social security number of the patient, and individual information. Here, we considered all reimbursements of endovascular interventions for thrombotic events in Belgium for the same period as for medication. A list of the included medication and interventions is provided in Table S1 (online supplement). All data extractions and analyses were performed at IMA-AIM under supervision of the Chief Medical Officer. The other research partners received no personally identifiable information (including small cells) from IMA-AIM.

Outdoor air pollutants

In Belgium, a dense network of monitoring sites continuously measures the concentrations of various air pollutants (www.irceline.be). The temporal correlation of $PM_{2.5}$ measurements between monitoring stations located at 50km distance from each other is very high (r^2 above 0.9), and the correlation of $PM_{2.5}$ measurements between monitoring stations located at 300km distance from each other (maximum distance) is moderate (r^2 around 0.5). Data collected by the monitoring stations are combined with land use data from satellite images in a spatial-temporal interpolation model, that provides estimates for the measured pollutants on a 4x4 km grid (Janssen et al. 2008). To have a more accurate reflection of the population average exposure, the estimates obtained from the interpolation models were then weighted by the population living in the 4x4 km grids. In this study, we included the modelled daily average of particulate matter (PM) concentrations ($\mu g/m^3$) per municipality for the study period (2009 – 2013), focusing on PM_{10} and $PM_{2.5}$. We used the date of the event and the

municipality of residence to link the pollutant concentrations with the medication and intervention events.

Potential confounders and effect modifiers

Potential confounders considered in this study were day of the week and temperature. Because meteorological variables may increase coagulation (Wu et al. 2017), we used data on daily average temperature from the Belgian Royal Meteorological Institute (Uccle measurement station, Belgium). In addition, we considered season, age and sex as potential effect modifiers. Previous studies showed seasonal patterns in the effects of air pollution on mortality (Peng et al. 2005), in Belgium being stronger during summer (Nawrot et al. 2007). Seasons were defined as 4 groups of 3 full months (winter: December to February, spring: March to May, summer: June to August, and autumn: September to November). Furthermore, children and elderly may be considered susceptible populations for the health effects of air pollution (Sacks et al. 2011). Thus, we conducted subgroup analyses considering the following age groups: <18 years old (children), 18 to 30 years old (young adults), 30 to 65 years old (adults), >65 (elderly).

Statistical analyses

We used a bidirectional time-stratified case-crossover design (Janes et al. 2005). This design is a type of matched case–control design that includes features of the crossover design where each subject serves as his/her own control. Thus, time-invariant confounders are adjusted for by design.

We considered two types of event days separately: the days of the medication purchase and the days of the endovascular intervention. We matched event with control days based on four criteria. First, we took control days from the same month and year as the event days (i.e.

time-stratified), both before and after the event (i.e. bidirectional), therefore inherently controlling for possible seasonality and long-term trends (Janes et al. 2005). Second, event days had to be at least three days apart from control days to avoid short-term autocorrelation (Levy et al. 2001). Third, since thrombotic events and air pollution are both associated with temperature (Lian et al. 2015; Nawrot et al. 2007), we selected only control days with a daily average temperature within 2°C from that on the event day. Fourth, cases on weekends had controls also on weekends, and cases on weekdays had controls only during weekdays (Milojevic et al. 2014). This matching procedure rules out the possibility of potential confounding by seasonality, long-term trends, day of the week and temperature, with the advantage of avoiding the use of complex non-linear models that would be necessary to adjust for some potential confounders such as temperature. On average, the number of control days per event was 6.1 for endovascular interventions and 5.7 for antithrombotic enzymes events.

We used conditional logistic regression models to investigate the associations of medication and interventions for thrombo-embolic events with daily concentrations of air pollutants. We used separate models for each type of event, for each pollutant and for three single day lags: the day of the thrombo-embolic event (lag 0) and the two days before the event (lag1 and lag2). We calculated the odds ratios (OR) and their 95% confidence interval (CI) for an increase of 10 $\mu g/m^3$ in PM_{10} and of 5 $\mu g/m^3$ in $PM_{2.5}$. To assess potential effect modification by season, we stratified by warm (April to September) and cold (October to March) months. To investigate the associations in specific population subgroups we conducted stratified analyses by sex and age group (i.e. <18 years old, 18 to 30 years old, 30 to 65 years old, and 65 or older). In sensitivity analyses, we included only the first event of medication purchase or of intervention for each individual occurring during the study period. Statistical analyses were

performed with SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA). Statistical significance was set at a p-value<0.05.

Results

We included a total of 227,861 events treated with endovascular procedure and 74,942 events treated with antithrombotic enzymes and reimbursed in Belgium from January 1st 2009 to December 31st 2013. In both cases, events were evenly distributed among seasons. Among the included events, 67% (n=153,279) and 33% (n=25,019) were first events treated with endovascular procedure or with antithrombotic enzymes per patient, respectively. The mean age of individuals treated with antithrombotic enzymes was 68 (±17.4) years old, and that of individuals treated with endovascular intervention was 68 (±12.1) years old. Regarding sex, 49% of the events treated with endovascular procedure and 31% of those treated with enzymes were on females. Table 1 presents the distribution of the daily number of events and of air pollutant concentrations on event days, and the absolute differences in air pollutant concentrations between event and control days. The absolute difference shows the existence of sufficient variation around a non-zero mean value. The daily average concentrations of PM_{10} were strongly positively correlated with $PM_{2.5}$ concentrations (Spearman correlation coefficient = 0.954).

The ORs for increases of 10 $\mu g/m^3$ in PM_{10} or 5 $\mu g/m^3$ in $PM_{2.5}$ in lags 0, 1 and 2 for events treated with antithrombotic enzymes and those treated with endovascular intervention are shown on Table 2. For both treatments, events were significantly associated with ambient concentrations of air pollution. For both PM_{10} and $PM_{2.5}$, the strongest associations were observed on the day of the medication sale or endovascular intervention (lag 0). When comparing the day of the event with control days, a difference of 10 $\mu g/m^3$ in PM_{10} results in

a 2.7% (95% CI 2.3 to 3.2%) increased odds of endovascular intervention and 1.9% (95% CI 1.1 to 2.7%) of antithrombotic enzyme administration. For $PM_{2.5}$, a difference of 5 $\mu g/m^3$ on the day of the event is associated with 1.3% (95% CI 1.0 to 1.5%) increases in the odds of endovascular interventions and 1.2% (95% 0.7 to 1.6%) increases in the odds of antithrombotic enzymes. Similar results were obtained when considering only the first event (see Table S2 in the online supplement). Also, details on AICs of each models presented in tables 2 and S2 are provided in the online supplement (Table S3).

After stratifying by season, we observed generally stronger effects in autumn compared to other seasons (Table 3). Nevertheless, the strongest association estimates were observed during summer months, for the effects on endovascular interventions of PM10 and PM2.5 on the day of the event. The results of the subgroup analyses by age and sex are shown in the supplement (Table 4). The effects of both pollutants were generally stronger in children aged less than 18 years. Nevertheless, the association estimates were not always statistically significant. This may be due to the low number of events occurring in children. No differences were observed after stratifying by sex.

Discussion

Our case-crossover study including 227,861 thrombo-embolic events treated with antithrombotic enzymes and 74,942 events treated with endovascular procedure shows that acute exposure to ambient air pollution is associated with a higher odds of treatment for thrombo-embolic events. These associations were strongest during autumn and among children. To date, most epidemiological studies investigating the short-term associations of air pollution on cardiovascular outcomes have used data from hospital admissions, emergency rooms or mortality due to specific diseases like myocardial infarction, stroke or venous

thrombosis (Mustafić et al. 2012; Shah et al. 2013; Tang et al. 2016; Yu et al. 2014; Zhang et al. 2009). The latter conditions share common pro-thrombotic mechanisms explaining the triggering effects of air pollution (Emmerechts and Hoylaerts 2012).

In our study, we used information on the administration of antithrombotic enzymes and specific antithrombotic interventions. The use of data on treatments instead of recorded diagnoses has the advantage of including any thrombo-embolic event, regardless of the organ affected. Furthermore, it supports the findings reported in previous experimental studies on the mechanisms in the context of a large population based study (Lucking et al. 2008; Rudež et al. 2009). Experimental studies in animals and humans have demonstrated that short-term exposure to traffic-related air pollutants leads to platelet activation, independently of systemic inflammation. Enhanced platelet activity and thrombus formation occur already two hours after exposure and persist for 24 to 96 hours (Lucking et al. 2008; Rudež et al. 2009). In line with these results, we observed the strongest association estimates for pollutant exposure on the day of the event with a decrease in the magnitude of the association estimates for acute increments in pollution during the previous 24 and 48 hours.

In Belgium, a densely populated country (369 inhabitants/km^2 in 2013 (World Bank 2017)), the yearly means for PM_{10} and $PM_{2.5}$ concentrations showed a decreasing trend between 2009 and 2013 with all means being below the EU limits for annual means (i.e. 40µg/m^3 for PM_{10} and 25µg/m^3 for $PM_{2.5}$). During the study period, the median number of days with PM_{10} concentrations above 50µg/m^3 (i.e. the limit value set by the European Union for daily concentrations) ranged from 19 days (inter quartile range (IQR)=12) in 2013 to 32 days (IQR=21) in 2011. More detailed information on air quality in Belgium during the study period is available elsewhere (http://www.irceline.be/en). So far, the short term associations of air

pollution on thrombo-embolic events in Belgium have been investigated for acute myocardial infarction among adults and elderly (Claeys et al. 2015; Collart et al. 2017). These previous studies included one region or data only from hospitals with percutaneous coronary intervention units and concluded that air pollution has triggering effects on myocardial infarction. Our nationwide study confirms the results from the two previous smaller Belgian studies.

Previous research showed that in Belgium the associations between air pollution and mortality are stronger during the summer period (Nawrot et al. 2007). Here, we show the strongest effect estimates in autumn and summer. It is hypothesized that during warm periods exposure measurement error when using (modelled) measures of residential air pollution is less compared to colder periods because people spend more time outdoors. Also, seasonal variations in the composition of PM may contribute to explain the variations in the size of the effect (Peng et al. 2005). In addition, it is plausible that stronger effects are observed among children compared with adults. Children spend more time outdoors, where concentrations of air pollution are higher, they have higher baseline ventilation rates, are typically mouth-breathers and are more physically active than adults. These combination of factors results in higher doses of exposure to environmental air pollutants (Bateson and Schwartz 2008). Nevertheless, it is possible that such interventions/medication in young children are not provided for acute events but planned in children with chronic conditions. Therefore, caution is needed when interpreting the associations found in children.

A major strength of our study is its country-wide character and the coverage of the entire population. Our study is among the largest performed to date focusing on recent triggering associations of environmental pollution on thrombo-embolic events. It includes more than

300,000 treated thrombo-embolic events in Belgium during a period of 5 years. Such sample size allowed us to investigate associations in different age groups. Nevertheless, the number of events included among children aged less than 18 years was low and the confidence intervals wide, partly due to the low numbers resulting in low statistical power.

Further, some limitations have to be acknowledged. Issues to be considered when working with registry-based data are the availability of information on relevant confounders of the studied associations. However, the characteristics of the case-crossover design limit the potential confounders to variables that are time varying. In our study we selected control days within a month and matched them by temperature and by type of day (week or weekend). Therefore, our results were adjusted, by design, for seasonality, temperature and day of the week. Of somewhat more concern, the characteristics of the registry did not allow us to know whether the interventions were performed as a consequence of an acute event or were planned in advance, or if such interventions and medication were performed/administered at all. However, the studied interventions are mainly performed after an acute event and the inclusion of planned interventions in our study would only reduce our association estimates by introducing a bias towards the null. In addition, our study is based on reimbursement data about medication and interventions, and does not include any diagnosis. Therefore, all associations observed in our study cannot be directly attributed to diseases. Finally, we did not observe significant differences between the main analyses and analyses on first events. This may be due to the fact that we do not know if any events happened to the same person prior to the study period.

Another limitation to be considered in our study is the use of modelled air pollution measurements, which lacks precision regarding the actual personal exposure. Previous

research showed inconsistent results with over or under estimations of actual exposures depending on the area (Tayarani and Rowangould 2020). In Belgium, taking account mobility results in lower exposure estimates compared to residential exposure (Dhondt et al. 2012). Nevertheless, spatial variability in Belgium is small when compared with the temporal variability, which is mainly driven by meteorological conditions (Scheers et al. 2011), and we matched the case days with control days having similar temperature.

Compared with well-established risk factors of acute thrombo-embolic events such as cocaine, emotions, or alcohol consumption, the size of the associations observed in our study, as well as in previous studies (Mustafić et al. 2012; Shah et al. 2013; Tang et al. 2016; Yu et al. 2014; Zhang et al. 2009), is rather small. Nevertheless, the prevalence of exposure to air pollution is very high, thus reductions in air pollution levels would have significant impacts in public health relevance (Nawrot et al. 2011). Moreover, the costs for the health care system (and the society) should not be ignored. In Belgium, it has been estimated that a reduction of 10% in the weekly average of PM_{10} concentrations would result in a reduction of about 5 million € in the hospital costs of ischemic heart diseases (Devos et al. 2015). Our study, adds evidence of the impact of air pollution on the health care system showing increases in antithrombotic medication use and practice of endovascular interventions in days with higher levels of air pollution.

Conclusions

In this nationwide study, we focus on medication and interventions rather than diseases. We show a potential effect of air pollution on health care services that suggests higher health care expenses on days with high levels of air pollution. We found that recent elevations in the concentrations of PM_{10} or $PM_{2.5}$ are associated with treatment for thrombo-embolic events,

being the associations stronger during autumn months and in children. Our results on medication reimbursement are consistent with previous studies on the association between cardiovascular events and acute changes in air pollution (Mustafić et al. 2012; Shah et al. 2013; Tang et al. 2016; Yu et al. 2014; Zhang et al. 2009).

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TABLES

Table 1. Daily numbers of events, air pollution concentrations on event days, and absolute differences between the daily average concentrations of PM on event days and the average exposure on control days, Belgium 2009-2013.

	Mean	SD	min	p25	p50	IQR	max
Endovascular interventions							
Daily number of events	124.8	73.9	5	22	160	183	228
Exposure on event days							
PM_{10} ($\mu g/m^3$)	25.1	14.2	1.0	15.5	21.4	31.1	122.7
$PM_{2.5}$ ($\mu g/m^3$)	16.8	12.3	1.0	8.6	13.2	21.6	105.7
Exposure difference between event days and average of control days							
PM_{10} ($\mu g/m^3$)	8.9	9	0	2.7	6	12.1	80.3
$PM_{2.5}$ ($\mu g/m^3$)	7.4	7.9	0	2.2	4.9	9.9	78.8
Antithrombotic enzymes							
Daily number of events	41	17.5	3.0	32	44	53	91
Exposure on event days							
PM_{10} ($\mu g/m^3$)	24.7	13.9	1.0	15.3	21.1	30.4	130.6
$PM_{2.5}$ ($\mu g/m^3$)	16.4	12.2	1.0	8.1	12.8	21	126.5
Exposure difference between event days and average of control days							
PM_{10} ($\mu g/m^3$)	8.8	8.8	0	2.7	6	12.0	77.3
$PM_{2.5}$ ($\mu g/m^3$)	7.4	7.8	0	2.2	4.9	9.9	74.8

Table 2. Associations (OR and 95% confidence intervals) for 10 μg/m^3 increase in PM_{10} or 5 μg/m^3 increase in $PM_{2.5}$ in lags 0, 1 and 2 with events treated with endovascular interventions or antithrombotic enzymes.

	OR (95%CI) Endovascular intervention *(n events = 227,861)*	Antithrombotic enzymes *(n events = 74942)*
PM_{10} per 10μg/m^3		
lag 0	**1.027 (1.023-1.032)**	**1.019 (1.011-1.027)**
lag 1	**1.015 (1.010-1.019)**	1.007 (0.999-1.015)
lag 2	**1.005 (1.001-1.009)**	1.006 (0.998-1.014)
$PM_{2.5}$ per 5μg/m^3		
lag 0	**1.013 (1.010-1.015)**	**1.012 (1.007-1.016)**
lag 1	**1.007 (1.004-1.010)**	1.004 (0.999-1.009)
lag 2	1.002 (1.000-1.005)	**1.005 (1.000-1.010)**

Bold indicates p-value<0.05

Table 3. Associations (OR and 95% confidence intervals) for 10 µg/m^3 increase in PM_{10} or 5 µg/m^3 increase in $PM_{2.5}$ in lags 0, 1 and 2 with events treated with endovascular interventions and antithrombotic enzymes by season.

	Season			
	Winter	Spring	Summer	Autumn
Endovascular interventions	*n events = 55,837*	*n events =59,254*	*n events = 55,127*	*n events = 57,647*
PM10 per 10µg/m3				
lag 0	**1.027 (1.019-1.035)**	**1.014 (1.007-1.022)**	**1.059 (1.041-1.078)**	**1.044 (1.034-1.055)**
lag 1	**1.020 (1.013-1.028)**	1.001 (0.994-1.009)	1.012 (0.995-1.030)	**1.031 (1.021-1.041)**
lag 2	0.997 (0.990-1.004)	**1.007 (1.000-1.014)**	1.000 (0.983-1.017)	**1.018 (1.008-1.029)**
PM2.5 per 5µg/m3				
lag 0	**1.011 (1.007-1.016)**	1.004 (1.000-1.008)	**1.034 (1.024-1.045)**	**1.024 (1.018-1.031)**
lag 1	**1.009 (1.004-1.013)**	0.996 (0.992-1.001)	**1.016 (1.006-1.027)**	**1.021 (1.014-1.027)**
lag 2	0.997 (0.993-1.001)	1.001 (0.996-1.005)	**1.018 (1.007-1.028)**	**1.011 (1.005-1.017)**
Antithrombotic enzymes	*n events = 18,633*	*n events = 18,815*	*n events = 18,317*	*n events = 19,177*
PM10 per 10µg/m3				
lag 0	**1.006 (0.992-1.020)**	**1.030 (1.016-1.044)**	0.997 (0.967-1.029)	**1.028 (1.010-1.047)**
lag 1	0.994 (0.981-1.008)	1.000 (0.987-1.014)	1.029 (0.999-1.060)	**1.034 (1.015-1.052)**
lag 2	0.995 (0.982-1.008)	1.001 (0.988-1.014)	0.994 (0.964-1.024)	**1.043 (1.025-1.061)**
PM2.5 per 5µg/m3				
lag 0	1.002 (0.994-1.010)	**1.015 (1.007-1.023)**	1.014 (0.996-1.032)	**1.022 (1.011-1.033)**
lag 1	0.998 (0.991-1.006)	0.997 (0.989-1.006)	**1.024 (1.006-1.043)**	**1.019 (1.008-1.030)**
lag 2	0.999 (0.991-1.006)	0.998 (0.990-1.006)	1.015 (0.996-1.033)	**1.026 (1.015-1.036)**

Bold indicates p-value<0.05

Table 4. Associations (OR and 95% confidence intervals) for 10 μg/m^3 increase in PM_{10} or 5 μg/m^3 increase in $PM_{2.5}$ in lags 0, 1 and 2 with events treated with endovascular interventions and antithrombotic enzymes by sex and age group.

	Sex		Age group			
	Female	Male	<18 years old	18-30 years old	30-65 years old	>65 years old
Endovascular procedures	*n events = 70,727*	*n events = 157,134*	*n events = 205*	*n events = 403*	*n events = 83,771*	*n events = 143,482*
PM10 per 10μg/m3						
lag 0	**1.028 (1.020-1.036)**	**1.027 (1.022-1.033)**	1.043 (0.890-1.222)	1.083 (0.975-1.204)	**1.027 (1.019-1.034)**	**1.028 (1.022-1.034)**
lag 1	**1.014 (1.006-1.022)**	**1.015 (1.010-1.021)**	0.908 (0.782-1.055)	1.030 (0.926-1.146)	**1.011 (1.004-1.019)**	**1.017 (1.011-1.022)**
lag 2	1.004 (0.996-1.012)	**1.005 (1.000-1.011)**	0.926 (0.793-1.080)	0.972 (0.875-1.080)	1.007 (1.000-1.014)	1.004 (0.999-1.010)
PM2.5 per 5μg/m3						
lag 0	**1.012 (1.007-1.017)**	**1.013 (1.010-1.016)**	1.021 (0.928-1.124)	1.017 (0.955-1.084)	**1.014 (1.009-1.018)**	**1.012 (1.009-1.015)**
lag 1	**1.005 (1.000-1.010)**	**1.008 (1.005-1.011)**	0.954 (0.872-1.043)	1.011 (0.948-1.078)	**1.007 (1.002-1.011)**	**1.007 (1.004-1.011)**
lag 2	1.001 (0.996-1.006)	**1.003 (1.000-1.006)**	0.973 (0.889-1.065)	0.980 (0.920-1.043)	1.004 (1.000-1.009)	1.001 (0.998-1.005)
Antithrombotic enzymes	*n events = 36,697*	*n events = 38,245*	*n events = 1,973*	*n events = 990*	*n events = 23,043*	*n events = 48,936*
PM10 per 10μg/m3						
lag 0	**1.013 (1.002-1.025)**	**1.024 (1.012-1.036)**	**1.056 (1.006-1.108)**	1.015 (0.946-1.089)	**1.022 (1.007-1.037)**	**1.016 (1.006-1.026)**
lag 1	1.003 (0.992-1.015)	**1.011 (1.000-1.023)**	**1.072 (1.012-1.137)**	1.005 (0.924-1.093)	**1.027 (1.010-1.045)**	**1.019 (1.008-1.032)**
lag 2	1.001 (0.990-1.012)	**1.011 (1.000-1.023)**	1.046 (0.997-1.097)	1.039 (0.969-1.115)	0.998 (0.984-1.013)	1.009 (0.999-1.019)
PM2.5 per 5μg/m3						
lag 0	**1.008 (1.001-1.015)**	**1.015 (1.008-1.021)**	**1.038 (1.009-1.069)**	1.016 (0.975-1.059)	1.001 (0.992-1.009)	1.004 (0.998-1.010)
lag 1	1.001 (0.994-1.008)	**1.007 (1.000-1.014)**	1.007 (0.985-1.031)	1.032 (0.997-1.068)	1.001 (0.994-1.008)	1.003 (0.998-1.008)
lag 2	1.002 (0.996-1.009)	**1.007 (1.001-1.014)**	1.016 (0.988-1.044)	1.027 (0.985-1.070)	1.004 (0.996-1.013)	1.004 (0.998-1.010)

Bold indicates p-value<0.05

SUPPLEMENTARY MATERIAL

Table S1. List of specific medication and interventions included in the study.

	ATC code
Antithrombotic enzymes	
streptokinase	B01AD01
alteplase	B01AD02
anistreplase	B01AD03
urokinase	B01AD04
fibrinolysin	B01AD05
brinase	B01AD06
reteplase	B01AD07
saruplase	B01AD08
ancrod	B01AD09
drotrecogin alfa (activated)	B01AD10
tenecteplase	B01AD11
protein C	B01AD12
Endovascular interventions	
Arterial embolectomy or thrombectomy	N/A
Percutaneous endovascular dilatation of the coronary arteries	N/A
Percutaneous endovascular dilatation of other arteries	N/A
Percutaneous endovascular dilatation of arteries other than the coronary arteries during a surgical intervention.	N/A
Percutaneous insertion of endovascular catheters in the coronary vessels	N/A
Percutaneous insertion of endovascular catheters other vessels	N/A

N/A: not applicable

Table S2. Associations (OR and 95% confidence intervals) for 10 µg/m^3 increase in PM_{10} or 5 µg/m^3 increase in $PM_{2.5}$ in lags 0, 1 and 2 with first ischemic events treated with medication or endovascular interventions.

	OR (95%CI) Endovascular intervention (n events = 153,279)	Antithrombotic enzymes (n events = 25,019)
PM_{10} per 10µg/m^3		
lag 0	**1.024 (1.018-1.029)**	**1.030 (1.015-1.044)**
lag 1	**1.010 (1.004-1.015)**	1.013 (0.999-1.027)
lag 2	1.004 (0.999-1.010)	1.012 (0.999-1.026)
$PM_{2.5}$ per 5µg/m^3		
lag 0	**1.011 (1.008-1.015)**	**1.015 (1.007-1.024)**
lag 1	**1.005 (1.002-1.008)**	**1.008 (1.000-1.017)**
lag 2	1.002 (0.999-1.006)	1.008 (1.000-1.016)

Bold indicates p-value<0.05

Table S3. AIC of the conditional logistic regression models for all events and for first events.

	Endovascular intervention	Antithrombotic enzymes
All events		
lag 0	253645	806762
lag 1	254123	806957
lag 2	254616	807544
First event		
lag 0	84308	543486
lag 1	84589	543228
lag 2	84318	543152