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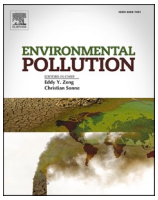

Long-term ambient air pollution and venous thromboembolism in a population-based Swedish cohort☆

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ABSTRACT

Air pollution is a major contributor to the global burden of disease and has been linked to several diseases and conditions, including cardiovascular disease. The biological mechanisms are related to inflammation and increased coagulability, factors that play an important role in the pathogenesis of venous thromboembolism (VTE, i.e., deep vein thrombosis or pulmonary embolism). This study investigates if long-term exposure to air pollution is associated with increased VTE incidence. The study followed 29 408 participants from the Malmö Diet and Cancer (MDC) cohort, which consists of adults aged 44–74 recruited in Malmö, Sweden between 1991 and 1996. For each participant, annual mean residential exposures to particulate matter <2.5 μg ($PM_{2.5}$) and <10 μg (PM_{10}), nitrogen oxides (NO_x) and black carbon (BC) from 1990 up to 2016 were calculated. Associations with VTE were analysed using Cox proportional hazard models for air pollution in the year of the VTE event (lag0) and the mean of the prior 1–10 years (lag1-10). Annual air pollution exposures for the full follow-up period had the following means: 10.8 μg/m^3 for $PM_{2.5}$, 15.8 μg/m^3 for PM_{10}, 27.7 μg/m^3 for NO_x, and 0.96 μg/m^3 for BC. The mean follow-up period was 19.5 years, with 1418 incident VTE events recorded during this period. Exposure to lag1-10 $PM_{2.5}$ was associated with an increased risk of VTE (HR 1.17 (95%CI 1.01–1.37)) per interquartile range (IQR) of 1.2 μg/m^3 increase in $PM_{2.5}$ exposure. No significant associations were found between other pollutants or lag0 $PM_{2.5}$ and incident VTE. When VTE was divided into specific diagnoses, associations with lag1-10 $PM_{2.5}$ exposure were similarly positive for deep vein thrombosis but not for pulmonary embolism. Results persisted in sensitivity analyses and in multi-pollutant models. Long-term exposure to moderate concentrations of ambient $PM_{2.5}$ was associated with increased risks of VTE in the general population in Sweden.

1. Introduction

Air pollution exposure has been linked to several diseases and conditions (Brook et al., 2010; Kampa & Castanas, 2008). Globally, ambient air pollution has been estimated to cause 4.2 million excess deaths annually (World Health Organization, 2021). The aerodynamic properties of air pollution particles are important to their effects, because smaller particles can to a larger extent reach the lower respiratory system and the alveoli (Hofmann, 2011) where they can trigger pulmonary inflammation. Smaller particles can also pass into the blood stream and contribute to vascular and systemic inflammation (Brook et al., 2010; Pope et al., 2016). Particulate matter with an aerodynamic diameter <2.5 μm ($PM_{2.5}$) has been more clearly associated with increased disease burden compared to larger PM and other air pollutants (Brook

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et al., 2010; World Health Organization, 2021). However, it is difficult to clearly disentangle the separate health effects of different air pollutants in epidemiological studies as they are largely concurrent. Associations with both cardiovascular diseases and mortality have also been observed for larger particles (particulate matter with an aerodynamic diameter <10 μm (PM_{10})), Black Carbon (BC)), and nitrogen oxides (NO_x) (Huang et al., 2021; World Health Organization, 2012).

Venous thromboembolism (VTE) is the umbrella term for deep vein thrombosis (DVT) and pulmonary embolism (PE). DVT usually occurs and develops in veins of the lower legs to pelvis area whereas PE occurs in the arteries of the lungs. The conditions are highly linked as the main source of PE are considered to be embolisms from DVT, with one study finding that 44 out of 99 patients with symptomatic PE had a simultaneous DVT (van Langevelde et al., 2013). VTE is associated with increased mortality rates (Heit, 2015). Globally, there is an incidence of 10 million cases of VTE per year. The annual incidence of VTE within the general Caucasian population ranges from 103 to 183 per 100 000 (Di Nisio et al., 2016; Heit, 2015).

Risk factors of VTE lead to increased thrombosis risk by influencing coagulability, blood flow and/or endovascular wall function, i.e., Virchow's triad (Di Nisio et al., 2016; Rosendaal, 1999; Zöller et al., 2020). Older age, cancer, pregnancy, high BMI, previous VTE, surgery, immobilization, long travel, Hormone Replacement Therapy (HRT), oral contraceptive use and paresis are examples of risk factors for VTE occurrence (Barsoum et al., 2010; Heit, 2015). Individuals that are in nursing homes or are hospitalized account for 60% of VTE diagnoses, and around 20% of VTE cases are cancer related (Di Nisio et al., 2016; Heit, 2015).

The underlying biological mechanisms linking air pollution exposure and health effects are widely studied. Systemic inflammation (seen through increased cytokine levels, activated immune cells, and increased platelet count), endothelium and vascular dysfunction, and autonomic nervous system imbalance are the known mechanisms (Brook et al., 2004; Brook et al., 2010), all of which can increase blood coagulability, an important contributor to the pathogenesis of VTE (Furie & Furie, 2005; Rosendaal, 1999; Turetz et al., 2018). Therefore, air pollution could be a contributing factor to VTE (A. Baccarelli et al., 2008; Brook et al., 2010; Tang et al., 2016).

Previous studies investigating the association between air pollution exposure and VTE mainly focused on relatively short exposure periods (e.g., days or months before the event) and have yielded inconsistent results (Franchini et al., 2016; Tang et al., 2016). To our knowledge, there was only one study focusing on longer term exposure (> one year), which found an increased risk of VTE (Gwon et al., 2022). Thus, more studies, especially those focusing on longer term exposure, are warranted. Overall, the current epidemiological evidence on air pollution and VTE is still limited, especially regarding longer term exposure. The aim of the present study was to investigate if long-term exposure to moderate concentrations of particulate air pollution was associated with increased VTE incidence in a large population-based cohort.

2. Materials and method

2.1. Study population

The Malmö Diet and Cancer (MDC) cohort is a prospective population-based cohort that was originally created to study the association between diet and cancer. Malmö residents were invited to an initial screening between 1991 and 1996; men born 1923–1945 and women born 1923–1950 were eligible to participate. A total of 30 446 participated and answered a questionnaire about medical history and lifestyle factors such as smoking habits, alcohol intake, dietary habits, education and occupation at enrolment. Furthermore, they underwent a clinical examination, including measurements of weight, height and blood pressure, and blood sampling. All participants have since been followed through the National Patient Register (NPR).

In this study, participants with a previous VTE diagnosis at enrolment (n = 326, diagnosis codes listed below) or with a malignancy diagnosis 0–5 years before enrolment (n = 723) were excluded, resulting in 29 408 participants in the main analyses. VTE events occurring within five years after a malignancy diagnosis or one year before were not used in the analysis (n = 548). The observation period was set from the date of enrolment to the end of follow-up on December 31, 2016. The individuals were censored after event, death or emigration from Sweden.

All participants provided written consent. The study was approved by the Regional Ethics Committee at the University of Lund (dnr 2016/4).

2.2. VTE endpoint

VTE event data, defined as either DVT of the legs or PE, were collected from the NPR using International Classification of Diseases (ICD) 8–10. The following ICD-8 codes were used for events occurring before 1979: 451.00 (DVT), 450.01 (PE), and 450.09 (PE). These ICD-9 codes were used for events occurring between 1979 and 1996: 415B (PE) and 451B (DVT lower limbs). And these ICD-10 codes were used for 1997 and after: I26 (PE) and I80 (excluding I80.0 – superficial vein thrombosis (SVT) lower limbs). In a review of patient records from 118 patients with VTE in the MDC cohort, the diagnosis was correct in 106 patients, i.e., 90% (Manderstedt et al., 2022). Almost all VTE diagnoses within the city of Malmö were based on at least one objective method, such as phlebography, CT (computer tomography) scan or ultrasound (Isma et al., 2009).

2.3. Air pollution modelling

The air pollution exposure modelling has been described in several previous publications on other health effects of air pollution in the MDC cohort (Azzouz et al., 2022; Carlsen et al., 2022; Xu et al., 2022). In brief, the Environmental Department of the City of Malmö used a Gaussian dispersion model (AERMOD) and emission databases for the region to model air pollution concentrations with a resolution of 50 × 50 m^2 for the Malmö urban area with the EnviMan (Opsis AB, Sweden) software. Annual mean concentrations were modelled approximately every ten years during the study period (1992, 2000 and 2011). Concentrations for intervening years were interpolated, and for 2012–16 extrapolated, adjusted annually for meteorological variables. Concentrations for 1990–91 were estimated linearly without meteorology. Traffic-related air pollutants were estimated using version 3.3 of the Handbook Emission Factors for Road Transport (HBEFA) (Mario Keller and Philipp, 2017).

Locally emitted concentrations for each pollutant were calculated by summing road traffic (exhaust from vehicles and traffic wear), household emissions including heating, and emissions from shipping and industries. Long-range transport (LRT) concentration was estimated by subtracting modelled concentrations from all local sources at the official urban background monitoring station (Rådhuset) from those measured there. This LRT concentration was then added to the local concentrations for the entire study area to estimate total concentrations. The current study used modelled total concentrations of $PM_{2.5}$, PM_{10}, NO_x and BC, and supplementary analysis was done with locally emitted concentrations of $PM_{2.5}$, PM_{10}, NO_x and BC. All measurement data are available at https://datavardluft.smhi.se/portal/concentrations-in-air. The following instruments were in use at the end of the study: nitrogen oxides were monitored using chemiluminescence (CLD700AL, Echophysics, Swizerland), $PM_{2.5}$ and PM_{10} were measured using tapered element oscillation microbalance (FDMS 8500, Rupprecht & Patashnick, NY, USA). The use of different instruments in earlier years does not substantially influence the data collected. No measurement of black carbon was done at Rådhuset, but instead the concentration was estimated from other available official monitoring sites (such as Vavihill monitoring station) in the region (filter sampling with 24-h resolution).

Participants were geocoded by the entrance to their residential building, using annually updated addresses collected from Statistics Sweden. Geocoding was manually checked and corrected for inconsistencies. Version 3.10.3 of QGIS was used to assign participants air pollution exposure based on their residential entrance (QGIS development team, 2020).

In this study, two exposure time windows to reflect long-term air pollution exposure were used. Lag0 was defined as the mean exposure for the concurrent year and lag1-10 was defined as the moving average for the preceding 1–10 years (e.g., a lag1-10 exposure for the year 2000 was the annual mean level from 1990 to 1999) to reflect historical exposure. Lag 1–10 was calculated only for individuals with at least 80% complete exposure data in the time window, that is, data for at least 8 of the 10 years.

2.4. Covariates

All covariates were collected at enrolment. Systolic and diastolic blood pressures (in mmHg), height and weight were measured at the screening centre. BMI (height in meters divided by squared weight in kg) was categorized into high BMI (>25) and low BMI (≤25). Apolipoprotein A1 (Apo-A1) and apolipoprotein B (Apo-B) were analysed in fasting blood samples (in g/L) that were frozen in −80 °C from recruitment to analysis, and the Apo-A1/Apo-B ratio was calculated.

Lifestyle and demographic factors were collected from the questionnaire. Educational attainment was categorized as low (1–9 years), intermediate (10–12 years), or high (>12 years). Occupational class was categorized into three groups (blue-collar/white-collar/self-employed, farmers, others) based on the Swedish socioeconomic classification (Statistics Sweden, 1982). Self-reported smoking status was categorized as regular smoker, occasional smoker, previous smoker, and never smoker), with the number of cigarettes per day also obtained for regular and occasional smokers. Birth country was categorized into Sweden or outside of Sweden. Cohabitation with a partner (yes/no) was used rather than marital status since unmarried partnerships are common in the population. Alcohol consumption was estimated as grams of alcohol per day. Data on leisure-time physical activity were collected using a modified version of the Minnesota leisure-time physical activity questionnaire composed of 18 questions about physical activity during the four seasons (Berglund et al., 1993). An aggregate physical activity score was created from the results taking both intensity and time into account, and participants were divided into quartiles based on the score.

Self-reported disease history (prevalent diabetes, CVD, malignancy) and use of medications (non-steroidal anti-inflammatory drugs (NSAIDS), anticoagulants, statins, and HRT) were gathered from the questionnaire and further complemented through information from the NPR. Incident malignancies (not including in situ cervical cancer and non-melanoma skin cancer) during the study period were further collected from the NPR.

In addition to the covariates at the individual level, an area-level covariate indicating neighbourhood mean income (i.e., Small Areas for Marketing Statistics, SAMS) for the year 1994 was obtained through Statistics Sweden.

2.5. Statistical analysis

In the descriptive analysis, the population was divided into quartiles based on the mean residential $PM_{2.5}$ exposure (i.e., the mean level $PM_{2.5}$ the year of enrolment and four years back). For those enrolled 1991–1993 the baseline exposure was calculated as the mean of the available years from 1990, the earliest exposure modelling year to the year of enrolment.

To estimate the associations between air pollution and risk of VTE, a Cox proportional hazard model was adopted with age as the time axis and lag1-10 and lag0 air pollution as time-varying exposures. A directed acyclic graph (DAG) using a priori assumptions of causal relationships was adopted to select possible confounding variables (Supplementary Fig. 1). Finally three covariate models were chosen. Model 0 (M0) was adjusted for sex and calendar year. Model 1 (M1) was further adjusted for educational attainment, occupational class, cohabitation, and physical activity, as suggested by the DAG as a minimally sufficient adjustment set with a lowest Akaike information criterion (AIC) score. M1 was considered the main model in this study. Model 2 (M2) was further adjusted for BMI, systolic blood pressure, Apo-B/Apo-A1 ratio, smoking status, number of cigarettes per day, mean area income, alcohol consumption, birth country, disease history (prevalent diabetes, CVD and AF), and use of medications (NSAIDs, statins, and HRT). These were considered risk factors of VTE, or possible mediators or confounders not suggested by the DAG in the minimally sufficient adjustment set. There was a loss of participants between the models due to missing values in the covariates, which led to approximately 7.9% fewer participants in M1 than M0 and 4.6% fewer in M2 than M1.

Several stratified analyses and sensitivity analyses were performed using M1 for lag0 $PM_{2.5}$ and lag 1–10 $PM_{2.5}$ exposure. Stratified analyses were performed in people 68 or older and under 68 (the median age of the study population), men and women, never- and ever-smokers, people with prevalent VTE at enrolment (excluded in the main analysis) and without, people with a BMI ≤25 and > 25, and by calendar period (1991–2005 and 2006–2016). For each stratified analysis, a joint model to investigate the effect modification of age, sex, smoking, previous VTE, BMI and calendar period was done by introducing interaction terms. Three sensitivity analyses were performed: 1) including VTE events close to malignancy; 2) including participants with a previous VTE before enrolment; 3) using a broader definition of VTE, including SVT. The ICD-9 codes 415, 451, 452 and 453, and the ICD-10 codes I26, I63.6, I67.6, I80, I81.9, I82.0 – I82.3, I82.8 and I82.9 (2910 VTE events) were used for the broader definition. We also performed multipollutant models (NO_x together with $PM_{2.5}$ in the same model and NO_x, PM_{10} in the same model) when correlations between air pollutants were low enough ($r < 0.5$). All analyses used an alpha level of 0.05 and were done using STATA 16.1 (StataCorp, Texas, TX, USA).

3. Results

3.1. Population characteristics

Descriptive statistics of study population demographics are presented in Table 1, and descriptive statistics for excluded participants (those with previous VTE and malignancy diagnosis close to enrolment) are presented in Supplementary Table 1. The study included 29 408 participants (60% women) and in total 575 326 person-years. The mean follow-up period was 19.5 years and 1418 VTE events occurred. The mean age at enrolment was 58 and the mean BMI was 26 kg/m^2. The follow-up period was longer in the higher exposure quartiles, with the recruitment age slightly lower. Few participants used statin-, anticoagulant-, or NSAID medication at enrolment, while slightly more used HRT. In the highest quartile of $PM_{2.5}$ exposure at baseline, the mean area income was slightly lower, a low education level more common, and living alone less common compared to the other exposure quartiles. Smoking habits were roughly consistent across exposure quartiles. Approximately half of the study population were white-collar workers, and 87% were born in Sweden.

Total air pollution exposure concentrations during the study period are presented in Fig. 1 and concentrations from local emissions are presented in Supplementary Fig. 2. The correlations between air pollutants were generally high, with Spearman's correlation coefficients above 0.5 for all except between NO_x and $PM_{2.5}/PM_{10}$ (Supplementary Table 2).

Table 1
Characteristics of the study population.

	All n = 29 408	$PM_{2.5}$ Quartiles (n = 29 394)				
		Q1 (7.9–9.7) n = 7349	Q2 (9.7–10.0) n = 7348	Q3 (10.0–10.4) n = 7349	Q4 (10.4–12.2) n = 7348	Missing (n)
Follow-up period (mean, range)	19.5 (0.01–25.8)	18.5 (0.01–25.8)	18.8 (0.04–25.8)	19.9 (0.01–25.8)	20.4 (0.15–25.8)	
Age at enrolment, years (mean, p_5 – p_{95})	58 (47–71)	58 (46–72)	59 (47–72)	58 (48–68)	57 (48–66)	0
Sex (n (%))						0
Male	11 681 (40%)	2575 (35%)	2834 (39%)	3246 (44%)	3021 (41%)	0
Female	17 727 (60%)	4774 (65%)	4514 (61%)	4103 (56%)	4327 (59%)	
BP, mmHg (mean, p_5 – p_{95})	141 (112–178)	141 (110–180)	142 (112–180)	141 (112–176)	140 (112–176)	47
ApoB/apoA1 ratio (mean, p_5 – p_{95})	0.7 (0.4–1.1)	0.7 (0.4–1.1)	0.7 (0.4–1.1)	0.7 (0.4–1.1)	0.7 (0.4–1.1)	2571
Statin use (n (%))	142 (0%)	36 (0%)	40 (1%)	40 (1%)	26 (0%)	0
Anticoagulant use (n (%))	449 (2%)	112 (2%)	135 (2%)	109 (1%)	93 (1%)	0
NSAID use (n (%))	277 (1%)	73 (1%)	70 (1%)	58 (1%)	76 (1%)	0
HRT use (n (%))	2891 (10%)	813 (11%)	656 (9%)	668 (9%)	754 (10%)	0
Diabetes (n (%))	1347 (5%)	296 (4%)	352 (5%)	339 (5%)	359 (5%)	0
Prevalent CVD (n (%))	904 (3%)	234 (3%)	238 (3%)	226 (3%)	206 (3%)	0
Prevalent atrial fibrillation (n (%))	282 (1%)	73 (1%)	71 (1%)	72 (1%)	66 (1%)	0
Prevalent malignancy[a] (n (%))	995 (3%)	264 (4%)	280 (4%)	242 (3%)	209 (3%)	0
BMI (mean, p_5 – p_{95})	26 (20–33)	26 (20–33)	26 (20–33)	26 (20–33)	26 (20–33)	48
Area Income, 1000SEK (mean, p_5 – p_{95})	148 (100–208)	161 (112–215)	147 (98–208)	148 (98–215)	137 (97–178)	157
Education (n (%))						1865
Low (1–9 years)	11 521 (42%)	2614 (37%)	2884 (42%)	2938 (43%)	3081 (45%)	
Medium (9–12 years)	9657 (35%)	2549 (37%)	2394 (35%)	2377 (35%)	2333 (34%)	
High (>12 years)	6365 (23%)	1812 (26%)	1583 (23%)	1511 (22%)	1455 (21%)	
Occupational class[b] (n (%))						2.020
Blue collar	10 230 (37%)	2368 (34%)	2630 (39%)	2550 (38%)	2679 (39%)	
White collar	14 007 (51%)	3685 (53%)	3445 (50%)	3448 (51%)	3422 (50%)	
Self-employed/Farmer/others	3151 (12%)	887 (13%)	753 (11%)	781 (12%)	728 (11%)	
Alcohol consumption, g/day (mean, p_5 – p_{95})	11 (0–34)	11 (0–32)	11 (0–34)	11 (0–35)	11 (0–36)	2114
Smoking status (n (%))						1807
Regular smoker	6602 (24%)	1547 (22%)	1639 (24%)	1639 (24%)	1776 (26%)	
Occasional smoker	1244 (5%)	261 (4%)	309 (4%)	348 (5%)	326 (5%)	
Previous smoker	9287 (34%)	2395 (34%)	2314 (34%)	2314 (34%)	2257 (33%)	
Never smoker	10 468 (38%)	2793 (40%)	2617 (38%)	2536 (37%)	2518 (37%)	
No. of cigarettes per day (#)	13 (0–28)	12 (0–25)	13 (0–25)	12 (0–30)	13 (0–30)	0[c]
Physical activity (n (%))						2058
Low	6814 (25%)	1728 (25%)	1722 (25%)	1730 (26%)	1630 (24%)	
Low-moderate	6857 (25%)	1704 (24%)	1737 (25%)	1701 (25%)	1713 (25%)	
Moderate-high	6836 (25%)	1805 (26%)	1680 (25%)	1628 (24%)	1719 (25%)	
High	6843 (25%)	1721 (25%)	1687 (25%)	1691 (25%)	1743 (26%)	
Living alone vs with partner (n (%))						1818
Live alone	6775 (25%)	1257 (18%)	1779 (26%)	1663 (24%)	2074 (30%)	
With partner	20 815 (75%)	5736 (82%)	5100 (74%)	5171 (76%)	4798 (70%)	
Born in Sweden (n (%))						1805
Sweden	24 134 (87%)	6296 (90%)	5996 (87%)	5920 (87%)	5912 (86%)	
Outside of Sweden	3469 (13%)	700 (10%)	881 (13%)	919 (13%)	967 (14%)	
VTE cases during the study period (n (%))	1418 (5%)	346 (5%)	352 (5%)	319 (4%)	400 (5%)	0
DVT cases during the study period (n (%))	857 (3%)	204 (3%)	222 (3%)	188 (3%)	242 (3%)	0
PE cases during the study period (n (%))	720 (2%)	177 (2%)	169 (2%)	176 (2%)	198 (3%)	0

[a] After exclusion of those with a malignancy diagnosis 0–5 years before enrolment.
[b] Categorized according to the Swedish socioeconomic classification.
[c] Only collected for regular and occasional smokers (set as 0 for previous and never smokers).

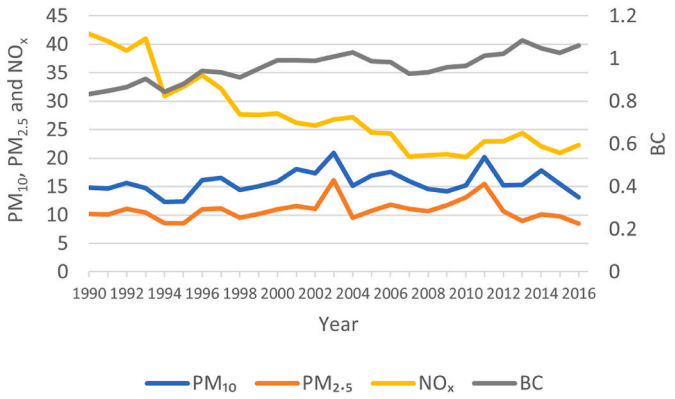

Fig. 1. Annual average total concentrations (local + long range transport) of air pollutants (μg/m^3) in the cohort during 1990–2016.

3.2. Associations between air pollutants and VTE

Hazard Ratios (HRs) for the associations between air pollutants and VTE incidence are presented in Table 2. Exposure to lag1-10 $PM_{2.5}$ was associated with increased risk of VTE (HR 1.17, 95% CI 1.01–1.37, per IQR of 1.2 μg/m^3) after adjusting for potential confounders (model M1). For DVT the associations were significant also after further adjustment for additional risk factors in model M2 ($p = 0.05$). The HRs in all models were also slightly higher for only DVT compared to all VTE. For other air pollutants, no statistically significant associations were found for lag 1–10 exposure for either VTE or DVT in any models. Moreover, there was no significant association between any air pollutants and PE in any model.

There were no significant associations between air pollutants and outcomes for lag0 exposure using any model, except for PM_{10} in M0 before adjustment for confounders. HRs between air pollution from local sources and baseline exposure and VTE were generally weaker than for total air pollution concentrations and were non-significant (Supplementary Table 3).

3.3. Sensitivity- and stratified analysis

The results from the sensitivity analysis are presented in Supplementary Table 4. The associations between lag1-10 $PM_{2.5}$ exposure and VTE were essentially unchanged and significantly positive when including those with previous VTE before enrolment or VTE cases close to a malignancy diagnosis, and when using a broader definition of VTE (including SVT and other vein thromboses). Lag0 $PM_{2.5}$ exposure was associated with VTE when using a broader definition of VTE. Using multipollutant models including both $PM_{2.5}$ and NO_x or PM_{10} and NO_x produced significant associations for lag1-10 $PM_{2.5}$ and lag1-10 PM_{10}, with somewhat stronger associations than in the single-pollutant models. No significant association was found for NO_x or the lag0 exposures.

Results from stratified analyses are presented in Figs. 2 and 3, and in greater depth (including results from interaction analysis) in Supplementary Table 5. Associations between lag1-10 $PM_{2.5}$ and VTE were stronger in ever-smokers compared to never-smokers, in those aged >68 years compared to the younger age group, and in the later calendar period compared to the earlier. The only p value for interaction below 0.05 was for BMI; however, the association between lag1-10 $PM_{2.5}$ and VTE was stronger for those with a low BMI. Participants without a previous VTE diagnosis had an elevated risk for an incident VTE at lag 1–10 $PM_{2.5}$ exposure, but the confidence intervals were very wide for the analysis for those with previous VTE diagnosis due to small sample size. Both men and women showed an increased risk of VTE associated with lag 1–10 $PM_{2.5}$ exposure.

Table 2
Hazard ratios for incident VTE, DVT and PE per IQR increase in total air pollution exposure.

Exposure			VTE		DVT		PE	
	IQR		Hazard ratio (95% CI)	P value*	Hazard ratio (95% CI)	P value*	Hazard Ratio (95% CI)	P value*
Lag0								
$PM_{2.5}$	1.5	M0	1.04 (1.00–1.09)	0.06	1.05 (0.99–1.11)	0.053	1.02 (0.96–1.08)	0.57
		M1	1.03 (0.98–1.08)	0.20	1.05 (0.99–1.11)	0.13	1.00 (0.94–1.07)	0.94
		M2	1.03 (0.98–1.07)	0.26	1.05 (0.99–1.11)	0.11	0.99 (0.93–1.06)	0.86
PM_{10}	2.7	M0	**1.07 (1.00–1.15)**	**0.04**	1.05 (0.97–1.15)	0.23	1.09 (1.00–1.20)	0.06
		M1	1.05 (0.98–1.13)	0.17	1.04 (0.95–1.14)	0.35	1.06 (0.96–1.17)	0.29
		M2	1.03 (0.96–1.11)	0.40	1.04 (0.95–1.14)	0.39	1.02 (0.92–1.13)	0.70
NO_x	12	M0	1.00 (0.89–1.11)	0.96	0.95 (0.82–1.09)	0.46	1.05 (0.90–1.23)	0.52
		M1	0.99 (0.88–1.11)	0.85	0.93 (0.80–1.08)	0.35	1.06 (0.90–1.24)	0.52
		M2	0.94 (0.83–1.07)	0.34	0.92 (0.78–1.08)	0.30	0.98 (0.82–1.17)	0.80
BC	0.16	M0	1.02 (0.93–1.11)	0.71	0.97 (0.87–1.09)	0.65	1.05 (0.93–1.19)	0.42
		M1	1.01 (0.92–1.11)	0.80	0.97 (0.86–1.10)	0.66	1.05 (0.92–1.19)	0.49
		M2	0.97 (0.87–1.07)	0.49	0.96 (0.85–1.09)	0.56	0.97 (0.85–1.12)	0.70
Lag1-10								
$PM_{2.5}$	1.2	M0	**1.18 (1.02–1.37)**	**0.02**	**1.24 (1.03–1.50)**	**0.03**	1.07 (0.87–1.31)	0.53
		M1	**1.17 (1.01–1.37)**	**0.04**	**1.23 (1.01–1.50)**	**0.04**	1.05 (0.85–1.30)	0.63
		M2	1.13 (0.96–1.32)	0.14	**1.23 (1.00–1.51)**	**0.05**	0.99 (0.79–1.23)	0.91
PM_{10}	1.7	M0	1.08 (0.98–1.19)	0.13	1.09 (0.96–1.24)	0.17	1.02 (0.89–1.17)	0.80
		M1	1.07 (0.96–1.19)	0.20	1.09 (0.95–1.25)	0.21	1.01 (0.87–1.17)	0.91
		M2	1.03 (0.92–1.15)	0.66	1.08 (0.94–1.25)	0.27	0.93 (0.79–1.09)	0.36
NO_x	10.8	M0	0.99 (0.90–1.08)	0.76	0.97 (0.86–1.09)	0.61	0.99 (0.87–1.13)	0.90
		M1	0.99 (0.90–1.09)	0.81	0.98 (0.86–1.11)	0.7	1.00 (0.87–1.15)	0.97
		M2	0.93 (0.83–1.04)	0.18	0.96 (0.84–1.10)	0.55	0.90 (0.77–1.05)	0.17
BC	0.13	M0	1.04 (0.95–1.13)	0.41	1.03 (0.92–1.15)	0.61	1.03 (0.91–1.16)	0.65
		M1	1.03 (0.94–1.13)	0.50	1.03 (0.92–1.15)	0.62	1.02 (0.90–1.16)	0.75
		M2	0.98 (0.89–1.08)	0.68	1.02 (0.90–1.15)	0.74	0.93 (0.81–1.07)	0.30

Model 0 (M0) was adjusted for sex and calendar year. Model 1 (M1) was further adjusted for educational attainment, occupational class, cohabitation, and physical activity. Model 2 (M2) was further adjusted for BMI, systolic blood pressure, Apo-B/Apo-A1 ratio, smoking status, number of cigarettes per day, mean area income, alcohol consumption, birth country, disease history (prevalent diabetes, CVD and AF), and use of medications (NSAIDs, statins, and HRT). *Significant associations ($p < 0.05$) are marked in bold.

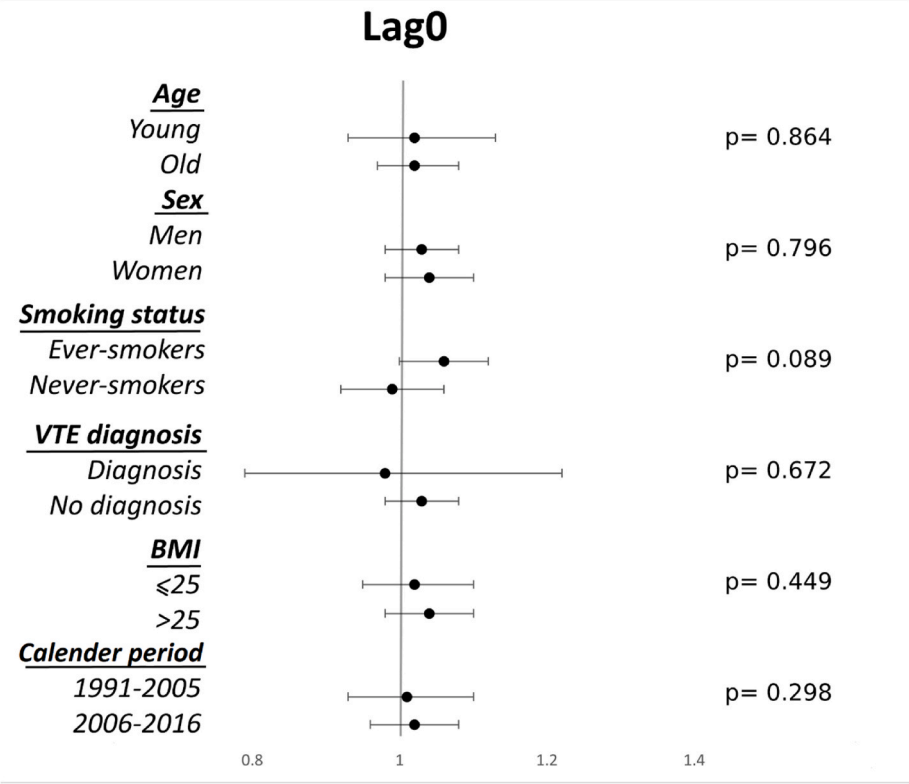

Fig. 2. Forest plot of associations between VTE and lag0 $PM_{2.5}$ exposure from stratified analyses with interaction terms. Effect estimates with 95% confidence intervals. Presented p values are from the interaction terms introduced in the joint model.

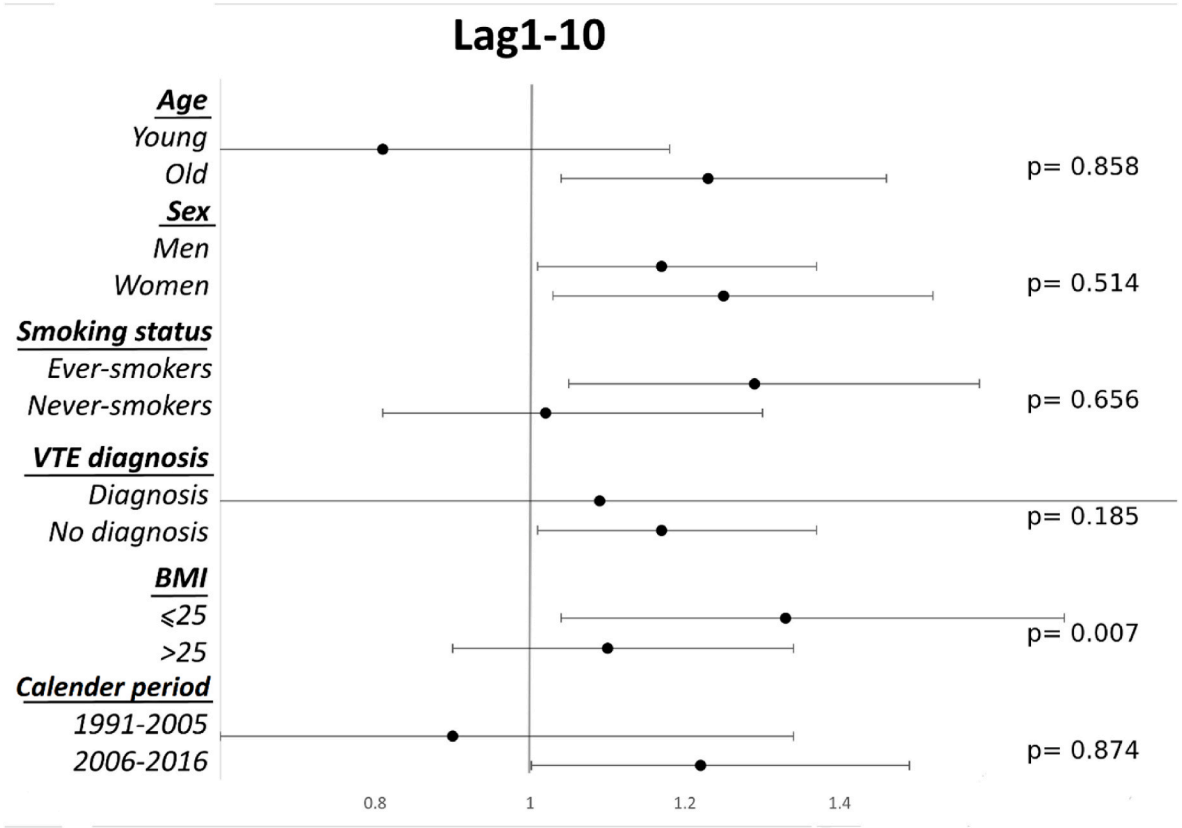

Fig. 3. Forest plot of associations between VTE and lag1-10 $PM_{2.5}$ exposure from stratified analyses with interaction terms. Effect estimates with 95% confidence intervals. Presented p values are from the interaction terms introduced in the joint model.

4. Discussion

In this large population-based cohort study of moderate exposure concentrations, long-term mean exposure to ambient $PM_{2.5}$ in the prior decade (lag 1–10) was associated with increased incidence of VTE in Malmö, Sweden. The mean $PM_{2.5}$ exposure during the year of the event was only significantly associated with VTE when using a broader definition of VTE (including SVT and other vein thromboses). When VTE was divided into DVT and PE the associations were significantly positive only for DVT. If the association is causal, the potential health effects are not negligible at a population level, with an increased hazard of 17% for VTE and 23% for DVT per 1.2 $\mu g/m^3$ (IQR) increase in lag1-10 $PM_{2.5}$ concentrations. No significant associations were found between PM_{10}, NO_x or BC exposure and VTE incidence. Previous research on multiple years of air pollution exposure has mainly focused on cancer or diseases connected to the arteries, such as cardio- and cerebrovascular disease (Rajagopalan et al., 2018), while most studies on VTE has included less than one year of exposure. Our results suggest that health effects of chronic exposure to fine particles further back than one year extends to the venous system.

Our results persisted in sensitivity analyses that included VTE events close to a malignancy, and when using a broader definition of VTE that included SVT. We found no significant association for those with previous VTE, however, even though that is one of the strongest risk factors for VTE (Raskob et al., 2014). A possible explanation is the small sample size for this group. We observed somewhat stronger associations in those at higher risk for VTE events, i.e., older participants, smokers, women, and VTE cases close to a malignancy diagnosis. The association between $PM_{2.5}$ and VTE was also stronger in the latter study period, but since age in the cohort increased with calendar year, we cannot disentangle these factors. For malignancy cases, it is also a possibility that air pollution exposure led to increased risk of malignancy, which in turn increased the risk of VTE (Heit, 2015; Turner et al., 2020). However, for these analyses the differences in effect size were generally small and remained consistent with the effect for the whole population. The reason for a stronger association in those with a lower BMI is unclear. One could speculate that other risk factors in overweight participants will outweigh an association with air pollution. A chance finding is also possible as we ran multiple analyses. When we used a broader definition of VTE that included SVT and other vein thromboses there was a significant association also for lag0 $PM_{2.5}$, presumably because of the increased power as the HR did not change much. In our main analysis, the HRs were slightly attenuated in the more adjusted models, and the associations between lag1-10 $PM_{2.5}$ and VTE below the limit of statistical significance in M2, the model that included all risk factors and possible mediators. Such attenuation may be due to inclusion of mediatory covariates (such as prevalent diabetes and atrial fibrillation) in M2, or due to the loss of study participants across models.

A recent meta-analysis did not find an association between VTE and air pollution, either short term (days before event) or long term (months to one year before event) exposure (Tang et al. (2016). This study performed multiple pooled analyses regarding short-/long-term exposure and air pollutants. However, it analysed only long-term exposure to PM_{10}, with exposure time windows no longer than one year. Although the studies were of high quality, the meta-analysis found only eight, which were further heterogenous regarding air pollutants and time windows. The meta-analysis noted the need for more studies with similar designs. In comparison, a systematic review by Franchini et al. (2016) concluded that there *was* a relationship between air pollution exposure and VTE. They included 11 studies, with eight showing a positive association. Six of the studies assessed long-term exposure (Baccarelli et al., 2009; Baccarelli et al., 2008; Chiu & Whittaker, 2013; Kan et al., 2011; Kloog et al., 2015; Shih et al., 2011). Like Tang et al. (2016) the authors also noted that more studies with comparable designs are needed. Again, the time windows for studies using long-term exposure in this review ranged between months and one year before the event, with no instances of exposure further back in time or for longer time periods. The $PM_{2.5}$ concentrations within these studies varied but were in general higher than in the current study, which might explain positive findings in contrast with the null associations for exposure in the year of event in our study.

One recent retrospective cohort study investigated the association between long-term PM_{10} exposure and VTE using exposure further back than one year, namely average air pollution concentrations from 2002 to 2015 (Gwon et al. (2022). The authors found a HR of 1.064 (95% CI 1.05–1.07) per 1 $\mu g/m^3$ increase in PM_{10} exposure. Our study did not find a significant association lag1-10 PM_{10} in the single-pollutant model after adjusting for confounders (HR 1.07 (95% CI 0.96–1.19) per 1.7 $\mu g/m^3$ increase). However, we did find a significant association in a multi-pollutant model when adjusting also for NO_x (HR 1.19 (95%CI 1.02–1.40) per 1.7 $\mu g/m^3$ increase). The study by Gwon et al. had a very large sample size of 338 616 participants and thus higher statistical power to detect associations. However, Gwon et al. did not account for important confounders such as malignancies. Our findings, in combination with those of Gwon et al. (2022), suggest that the increased risk of VTE is associated more with longer term particulate concentrations and slow biological processes than with concurrent exposure.

Our results indicate stronger associations with $PM_{2.5}$ than with PM_{10} or NO_x. Previous epidemiological and experimental research has also noted a stronger association between $PM_{2.5}$ and adverse health effects such as mortality and CVD (Brook et al., 2010; World Health Organization, 2021). Particles smaller than approximately 4 μm aerodynamic diameter, but not larger, can reach the lower respiratory system and the alveoli (Hofmann, 2011), and to some extent also pass into the bloodstream where their presence can trigger inflammation (Brook et al., 2010). There particles can contribute to vascular and systemic inflammation with increased cytokine levels, activated immune cells and increased platelet count as a result (Brook et al., 2010; Rajagopalan et al., 2018). Vascular and systemic inflammation increase blood coagulability, which plays an important role in the pathogenesis of VTE (Furie & Furie, 2005; Rosendaal, 1999; Turetz et al., 2018). We did not find any significant associations between locally emitted air pollutants and VTE nor between NO_x and VTE, indicating that the total $PM_{2.5}$ concentrations people are exposed to are more important than specific emissions from traffic or other local sources. Thus, to reduce the risk of VTE, interventions to reduce the level of air pollution need to address the total exposure to fine particles, and be done not only at the local level. The relatively low concentrations of local exposures compared with LRT could also be an explanation for the lack of positive findings.

There are several limitations to this study. 1) This study was not designed to study daily variations in exposure, but rather two different time windows of chronic exposure, namely lag0 for concurrent long-term exposure and lag1-10 for long-term historical exposure. Our results suggest that it is primarily the historical chronic exposure to $PM_{2.5}$ that affects VTE incidence. 2) Air pollution concentrations during the whole year of the event were assigned to participants; consequently the assigned lag0 exposure includes exposure also after the date of the VTE event, which could partly explain the null results between lag0 $PM_{2.5}$ exposure and VTE. 3) As with other large epidemiological studies on air pollution exposure, we used residential air pollution exposure based on each participant's address and not personal exposure, which will cause misclassification of the total air pollution exposure. This misclassification should be non-differential and bias the estimate towards null, meaning that the associations might be underestimated. 4) The population in the cohort was overall representative of the middle-aged and older urban population in Sweden, but caution should be taken when generalizing to other geographical settings, or to rural or younger populations. 5) Geographical differences in undiagnosed VTE within our population could affect our results. VTE has historically been underdiagnosed, but sensitivity has improved in later years with the clinical implementation of, for example, CT-imaging. Undiagnosed VTE in our population would probably represent a non-differential misclassification

and therefore attenuate a true association, but geographical differences cannot be excluded. However, all diagnoses of VTE in Malmö used at least one objective method such as CT-imaging or ultrasound and validity for the registers used is high, with an accuracy of 95% (Ludvigsson et al., 2011). 6) The air pollution exposure concentrations in this study were moderate, somewhat above the recent 2021 WHO guidelines of 5 $\mu g/m^3$ for one-year mean $PM_{2.5}$, but lower than in most other regions of the world (World Health Organization, 2021).

One strength of this study is that the air pollution modelling had a high resolution of 50 × 50 m^2 and included several types of air pollutants from multiple sources. Another strength of this study is that it examines the association between VTE incidence and air pollution exposure further back than one year while controlling for important confounders such as malignancy which, to our knowledge, has not previously been done.

5. Conclusion

Long-term historical exposure to moderate concentrations of ambient $PM_{2.5}$ air pollution was associated with increased risks of VTE, in particular DVT, in a cohort representative of the general middle-aged population in Sweden. New evidence of associations between long-term air pollution exposure and additional diseases such as VTE increases the estimated burden of disease due to air pollution, and positive findings at these moderate exposure levels support implementing the new, stricter WHO 2021 air quality guidelines.

Consistent with previous research, we observed clearer association to $PM_{2.5}$ compared to other pollutants. However, we also found statistically significant associations to PM_{10} in a multi-pollutant model. Our findings suggest that the association for VTE may be related to total long-term PM exposure, as opposed to emissions from traffic or other local sources.

We found clearer associations to mean $PM_{2.5}$ exposure 1–10 years before the event compared to mean $PM_{2.5}$ exposure the year of the event. Both of these time windows reflect chronic exposure, but the stronger lag1-10 historical exposure association argues for slow rather than acute physiological effects on the venous system. However, when we used a broader definition of VTE, including SVT and other vein thromboses, we found statistically significant associations with mean $PM_{2.5}$ exposure the year of the event. Previous research on exposure to air pollution further back than one year and the venous system is limited. Our results suggest that more research is needed on whether longer-term exposure to PM is associated with VTE and other diseases of the venous system.

Authors statement

Mehjar Azzouz: Conceptualization, Methodology, Formal analysis, Writing - Original Draft, Visualization. **Yiyi Xu**: Writing - Review & Editing, Methodology. **Lars Barregard**: Writing - Review & Editing, Supervision, Methodology. **Bengt Zöller**: Writing - Review & Editing, Methodology. **Peter Molnar**: Writing - Review & Editing, Data Curation **Anna Oudin**: Writing - Review & Editing. **Mårten Spanne**: Writing - Review & Editing, Data Curation, Resources. **Gunnar Engström**: Writing - Review & Editing, Methodology. **Leo Stockfelt**: Writing - Review & Editing, Funding acquisition, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2023.121841.

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