European Journal of Internal Medicine 27 (2016) 10–13

Contents lists available at ScienceDirect

European Journal of Internal Medicine

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

Review Article

Association between particulate air pollution and venous thromboembolism: A systematic literature review

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ARTICLE INFO

Article history:
Received 16 July 2015
Received in revised form 26 October 2015
Accepted 11 November 2015
Available online 27 November 2015

Keywords:
Air pollution
Particulate matter
PM
Venous thromboembolism
Deep vein thrombosis
Pulmonary embolism
Systematic review

ABSTRACT

Air pollution is a leading global problem for public health. A number of ambient pollutants have been involved, including carbon monoxide (CO), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), ozone (O_3) and particulate matter (PM). Although exposure to PM has been linked to a wide array of cardiovascular and respiratory disorders, its effect on venous thrombotic disorders is still uncertain. To elucidate this issue, we have performed a systematic review on the existing literature on the association between PM and venous thromboembolism (VTE), using MEDLINE, EMBASE and Cochrane electronic databases. Of the 158 reviewed studies, 11 of them (3 case-crossover studies, 2 time-series studies, 2 case–control studies, 2 prospective cohort studies, 2 retrospective studies) involving more than 500,000 events fulfilled the inclusion criteria and results are presented here. Because there was substantial heterogeneity in study design, duration of follow-up, statistical measure of effects, clinical outcomes and threshold, we refrained to perform a quantitative analysis of the available data and carried out only a systematic review. Overall, the literature data suggest a link between PM and VTE, but further trials on larger populations of patients with homogeneous study designs and outcomes are warranted.

1. Introduction

It has been increasingly recognized that air pollution has wide-ranging and deleterious effects on human health and is a major issue for the global community [1,2]. It is caused by a number of ambient pollutants including carbon monoxide (CO), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), ozone (O_3) and particulate matter (PM). A number of experimental and epidemiological data support the association between both gaseous and PM pollutants and all-cause mortality and morbidity [3–5]. In particular, short-term and long-term exposure to PM_{10} (with aerodynamic diameter less than 10 μm, further classified in coarse [$PM_{10–2.5}$ with aerodynamic diameter between 2.5 and 10 μm] and fine [$PM_{2.5}$ with aerodynamic diameter less than 2.5 μm]) has been consistently associated with an increased risk of cardiovascular disease [6–10]. Several PM-related mechanisms have been suggested to play a role in the pathways leading to cardiovascular diseases. One of the most plausible is hypercoagulability, resulting from increased plasma levels of coagulation proteins (including factor VIII, von Willebrand factor, fibrinogen and a shortened prothrombin time) and platelet activation [11–13]. From a clinical point of view, while a close link between PM air pollution and arterial thrombosis (i.e., myocardial infarction and ischemic stroke) has been consistently documented, less is known pertaining to the association with venous thromboembolism (VTE) (including deep vein thrombosis [DVT] and pulmonary embolism [PE]) owing to the presence of contrasting data in the few published studies [10]. Besides biological plausibility indirect clinical evidence corroborates the possible existence of such an association: for instance, a recent systematic review and meta-analysis concluded that VTE had a significantly higher incidence in winter, a finding that matched the parallel seasonal increase in PM occurring in the same geographical areas where the studies were conducted [14]. Thus, in order to elucidate the possible association of exposure to PM air pollution on VTE development, we chose to perform a pooled analysis of the existing studies that had investigated this topic.

2. Methods

A protocol was first developed, detailing the specific objectives, criteria for study selection, risk of bias assessment, outcomes and statistical methods.

2.1. Objectives

The goal of this systematic review was to collect studies concerning the relationship between particulate air pollution and VTE. The short-

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http://dx.doi.org/10.1016/j.ejim.2015.11.012
0953-6205/

and long-term effects of PM_{10} and $PM_{2.5}$ on VTE risk were evaluated. Short-term studies have linked VTE-related morbidity and/or mortality to day-to-day variations in air pollution, whereas long-term studies on large cohorts of exposed individuals have evaluated the adverse effects of continuous exposure.

2.2. Search strategy

We tried to identify all published studies which evaluated the influence of outdoor air pollution on VTE development, using the MEDLINE (1980 to May week 1, 2015) and EMBASE (1980 to May week 1, 2015) and The Cochrane Central Register of Controlled Trials (CENTRAL) electronic databases. The search strategy was developed with no language restriction and used the following keywords and subject headings: air pollution, particulate matter, PM, venous thromboembolism, venous thrombosis, pulmonary embolism, deep vein thrombosis, cause-specific mortality, cardiopulmonary, cardiovascular, admission, short-term, long-term. Our search was supplemented by manually reviewing abstracts from the main meetings on the topic plus the reference lists of all included studies and recent review articles in order to identify additional eligible studies.

2.3. Study selection and data extraction

All type of studies (randomized or observational) in humans were considered eligible for the purposes of this review. We excluded animal studies, *ex vivo* and toxicological studies, commentaries and editorials, case reports and studies with no original data. Study selection was performed independently by two reviewers (MF and MC), with disagreements resolved through discussion and on the basis of the opinion of a third reviewer (CB) if necessary.

2.4. Study quality assessment

We evaluated both the quality of reporting and the methodological quality of the studies included in the analysis. For this purpose we adopted the Newcastle–Ottawa checklist, using an adapted reading grid [15]. The Newcastle–Ottawa Scale (NOS) is a nine-point scale that assigns points on the basis of the process of selection of the cohorts or of cases/controls (0–4 points), the comparability of the cohorts or of cases/controls (0–2 points), and the identification of the exposure and the outcomes of study participants (0–3 points). The NOS was developed in order to assess the quality of nonrandomized studies for the purpose of incorporating quality assessments in the interpretation of meta-analytic results. This scale is recommended by the Cochrane Non-Randomized Studies Methods Working Group available at the electronic address (http://www.ohri.ca/programs/clinicalepidemiology/oxford.htm).

3. Results

Our initial search yielded 427 references. After the exclusion of 269 references following title and abstract screening, we identified 158 potentially relevant studies (Fig. 1). After the exclusion of 116 additional references, 42 were retrieved for more detailed evaluation and finally 11 **(3** case-crossover studies, 2 time-series studies, 2 case–control studies, 2 prospective cohort studies, 2 retrospective studies) met the inclusion criteria and were considered for this systematic review [16–26]. The characteristics of the included studies are reported in Table 1.

The NOS checklist for case–control is presented in the Appendix (Table 1, Online Supplementary Material). The quality of case–control studies, as assessed by the NOS, was high: all the studies met quality criteria for patient selection; three studies included community controls [16,17,26] and three hospital controls [18,24,25]. There were three case-crossover analyses [18,25,26]. Control for thrombophilia was not stated in two studies [18,25]. Ascertainment for exposure was adequate in all

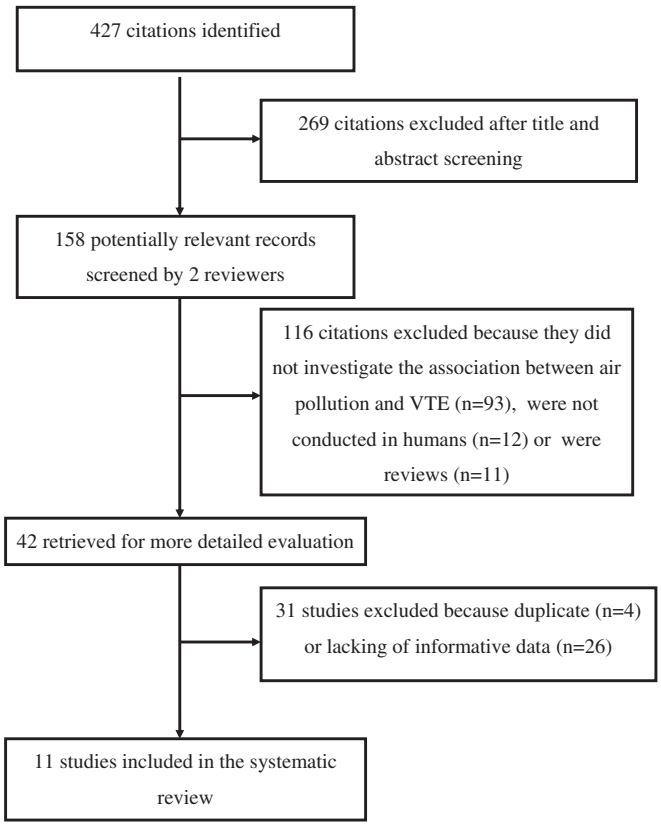

Fig. 1. Flow chart of the inclusion of studies.

studies. The quality of the cohort studies is summarized in the Appendix (Table 2, Online Supplementary material). All the analyzed studies reported the scientific background, described the setting and locations and provided a clear description of the inclusion criteria. Almost all studies gave a clear definition of outcomes and follow-up. Regarding the only randomized study included in the systematic review [21], it did evaluate a subset of patients enrolled in two previous double-blind, randomized controlled trials. However, inclusion criteria were not specified and follow-up was not available for all the included patients.

Overall, 552,296 venous thrombotic patients/events were recorded within the 11 studies included in the systematic review, with the number of cases per study ranging between 105 and 453,413. The study population was predominantly the general population, with the exception of one study that focused on post-menopausal women [21]. Five studies assessed PM-related short-term effects [18,19,22,24,25], four studies long-term effects [16,17,20,23] and two studies [21,26] both. Five studies assessed VTE [19–23], two [16,17] and three [18,24,25] studies only DVT and PE, respectively, and one study [26] both. Besides the study design and clinical outcomes, studies differed also for the threshold of PM increase considered: 10 $\mu g/m^3$ [16,18,20,21,26], 20–37 $\mu g/m^3$ [19] or 19 $\mu g/m^3$ [22]. Eight studies [16,17,19,22–26] reported a significant association with the different risks (odds ratio [OR], relative risk [RR] and hazard ratio [HR]) ranging from 1.05 to 5.24, while the remaining three studies [18,20,21] observed no association. The supplementary Table 3 and the related comments provide an analysis of the literature data from a meta-analytical pooling approach. No sufficient data were retrieved to perform a meta-analysis.

4. Discussion

While there is currently a large body of evidence on a close link between PM and morbidity/mortality related with arterial occlusive