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IN FOCUS

Effects of inhalable particulate matter on blood coagulation

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Summary. *Background:* Particulate matter (PM) exposure has been linked to increased risk of cardiovascular disease, possibly resulting from hypercoagulability and thrombosis. Lung and systemic inflammation resulting from PM inhalation may activate blood coagulation, but mechanisms for PM-related hypercoagulability are still largely unknown. *Objectives:* To identify coagulation mechanisms activated by PM in a population with well-characterized exposure. *Methods:* We measured prothrombin time (PT), activated partial thromboplastin time, endogenous thrombin potentials (ETPs) with/without exogenous triggers and with/without soluble thrombomodulin, tissue-type plasminogen activator (t-PA) antigen, D-dimer and C-reactive protein (CRP) in 37 workers in a steel production plant with well-characterized exposure to PM with aerodynamic diameter of < 1 μm (PM_1) and coarse PM ($PM_{10} - PM_1$). Blood samples were collected from each subject on the first (baseline) and last (postexposure) day of a 4-day work week. We analyzed differences between baseline and postexposure levels using a paired Student's *t*-test. We fitted multivariate mixed-regression models to estimate the associations of interquartile range PM_1 and coarse PM exposure with parameter levels. *Results:* None of the parameters showed any significant changes from baseline in postexposure samples. However, exposure levels were associated with shorter PT ($\beta[PM_1] = -0.33$ s, $P = 0.08$; $\beta[PM_{coarse}] = -0.33$ s, $P = 0.01$), and higher ETP without exogenous triggers and with thrombomodulin ($\beta[PM_1] = +99$ nM min, $P = 0.02$; $\beta[PM_{coarse}] = +66$ nM min, $P = 0.05$), t-PA ($\beta[PM_1] = +0.72$ ng mL^{-1}, $P = 0.01$; $\beta[PM_{coarse}] = +0.88$ ng mL^{-1}, $P = 0.04$), and CRP ($\beta[PM_1] = +0.59$ mg L^{-1}, $P = 0.03$; $\beta[PM_{coarse}] = +0.48$ mg L^{-1}, $P = 0.01$). *Conclusions:* PM exposure did not show any short-term effect within the week of the study. The association of PM exposure with PT, ETP and CRP provides some evidence of long-term effects on inflammation and coagulation.

Keywords: coagulation, endogenous thrombin potential, environmental risk factors, occupational health, particulate matter.

Introduction

Epidemiologic studies have linked exposure to particulate matter (PM) in urban environments with increased morbidity and mortality from cardiovascular disease [1–4]. PM metal components have been shown to play important roles in determining PM-related cardiovascular effects [5]. The underlying mechanisms linking the inhalation of ambient air particles to cardiovascular diseases are not completely understood [3], but inflammation and hypercoagulability have been indicated as primary mediators [6].

Seaton *et al.* [7] first hypothesized that inhalation of PM into the lungs would lead to local alveolar and systemic inflammation, followed by hypercoagulability and increased risk of thrombotic events. Previous investigations have demonstrated that levels of coagulation factors such as factor VIII and fibrinogen, which form part of the acute-phase responses mediated by cytokines released during inflammatory reactions, increase in association with PM exposure in humans [8–10]. In a study conducted in Italy, we recently showed that PM ambient levels were associated with shortened prothrombin time (PT) in healthy subjects [11] and patients with deep vein thrombosis [2], a finding that is substantiated by evidence from animal models of PM exposure [12]. However, the finding of a PM-related shortening of PT has not yet been evaluated in subsequent human

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studies, and other epidemiologic investigations measuring individual coagulation factors failed to produce consistent results [13–16].

During inflammatory conditions, reactive oxygen species and inflammatory mediators, including C-reactive protein (CRP), stimulate the production of tissue factor [17], a primary initiator of *in vivo* coagulation [17,18]. The thrombin generation test is a global functional assay that describes overall coagulability and represents the time course of formation and decay of thrombin, the key enzyme in clot formation [19,20], in response to triggering by tissue factor. Thrombin generation decreases in patient with anticoagulant treatment [21], increases in patients with thrombophilia [22], and has been recently been correlated with higher risk of thromboembolism [23].

Previous studies on PM effects have usually investigated blood coagulation in heterogeneous study groups in relation to exposure levels that have often been estimated using outdoor measurements from monitoring stations located at variable distances from the residence of the study participants. Variations of exposure due to daily activities, including work-related activities, have not usually been considered in these analyses. Work conditions may cause exposure to indoor PM levels that are considerably higher than outdoor concentrations. In industrial settings, workers are usually assigned to specific job tasks that tend to be repeated regularly over time. Differences in work routines may thus determine wide and stable gradients of individual exposure to particles, even among workers in the same work facility. Steel workers are exposed to high levels of metal-rich air particles, and are at higher risk for cardiovascular disease [24]. In the present study, we investigated a group of steel workers exposed to a wide range of PM levels, in order to identify inflammation-dependent alterations in blood coagulation using functional global tests, as well as measures of individual hemostatic and inflammatory components.

Materials and methods

Study subjects

We recruited, in a steel production plant in Brescia, northern Italy, two complete teams of shift workers free of cancer and cardiopulmonary disease, giving a total of 37 male subjects. All participants had been working in the current job position for at least 1 year. All of them had a rotating weekly schedule based on four consecutive working days of 8 h each, followed by 2 days of rest. In order to discriminate short-term and long-term effects of PM, we obtained blood samples for coagulation and other biomarkers at two different times: (i) the time 1 sample was collected on the morning of the first day of a working week (following 2 days off work) before the beginning of any work activity; and (ii) the time 2 sample was collected at the same hour on the fourth day of work, following three consecutive days of work.

A self-administered questionnaire was used to collect detailed information on lifestyle, drug use, medical conditions, body mass index (BMI), education, and residential history. Records from the factory administrative files were used to obtain information on occupational history. Individual written informed consent and approval from the local Institutional Review Board were obtained before the study.

Exposure assessment

Measures of PM with aerodynamic diameters of < 10 μm (PM_{10}) and < 1 μm (PM_1), obtained in each of the 11 work areas of the steel production plant, were used to estimate individual exposures. PM_{10} and PM_1 were measured during the days between time 1 and time 2, using a GRIMM 1100 light-scattering dust analyzer (Grimm Technologies, Douglasville, GA, USA). The fractions considered for this study were PM_1 and coarse particles, defined as the difference between PM_{10} and PM_1 [25]. During the three working days between time 1 and time 2, each of the study subjects recorded the time spent in each of the work areas in a personal log. Individual exposure was calculated as the average of area-specific PM levels weighted by the time spent in each area. PM levels in each of the work areas have shown very little variability over time, as measures repeated over 1 year showed very high correlation ($r^2 > 0.90$). Because all of the study subjects reported in the questionnaire that they had performed their standard work routine during the 3 days of the study, the time-weighted PM_1 and coarse PM concentrations also represented a measure of their usual exposure.

Laboratory methods

Blood for coagulation testing was drawn into vacuum tubes (Becton Dickinson, Meylan, France) containing 0.109 M trisodium citrate at a ratio of 9 : 1 (blood/anticoagulant).

PT was measured with human relipidated recombinant thromboplastin (Recombiplastin, Instrumentation Laboratory, Orangeburg, NY, USA) in combination with a fully automated photo-optical coagulometer (ACL; Instrumentation Laboratory, Lexington, MA, USA). The activated partial thromboplastin time (APTT) was measured with "Automated-APTT" (bioMerieux, Durham, NC, USA), using an ACL coagulometer (Instrumentation Laboratory). PT and APTT were expressed as clotting times in seconds.

Tissue-type plasminogen activator (t-PA), D-dimer and C-reactive protein (CRP) were determined using commercially available enzyme-linked immunosorbent assay (ELISA) assays (ELISA-Zymutest; HYPHEN BioMed, Neuville-Sur-Oise, France). Thrombin generation was assessed according to Hemker *et al.* [20], as described by Chantarankgkul *et al.* [26]. The test was based on the activation of coagulation in platelet-poor plasma with calcium chloride, with or without tissue factor and phospholipids as exogenous triggers of blood coagulation. The composition of the phospholipid mixture was as follows: 1,2-dioleoyl-sn-glycero-3-phosphoserine, 1,2-diol-

eoyl-sn-glycero-3-phosphoethanolamine, and 1,2-dioleoyl-sn-glycero-3-phosphocholine (Avanti Polar Lipids Inc., Alabaster, AL, USA), in a molar ratio of 20 : 20 : 60. The tissue factor (Recombiplastin; Instrumention Laboratory) and phospholipid concentrations, when they were included in the test system, were 1 pM and 1 μM, respectively. Testing was also performed in the presence of soluble rabbit thrombomodulin (ICN Biomedicals, Aurora, OH, USA) as activator of protein C, added to the reaction mixture at a final concentration of 4 nM. Continuous registration of the generated thrombin was achieved with a fluorogenic synthetic substrate (Z-Gly-Gly-Arg-AMC-HCl; Bachem, AG, Bubendorf, Switzerland) added to the test system at a final concentration of 417 μM. The procedure was carried out with an automated fluorometer (Fluoroskan Ascent; ThermoLabsystem, Helsinki, Finland). Readings from the fluorometer were automatically recorded and analyzed with dedicated software (THROMBINOSCOPE; Thrombinoscope BV, Maastricht, The Netherlands), which displays thrombin generation curves [nM thrombin vs. time (min)] and calculates the area under the curve, defined as endogenous thrombin potential (ETP) and expressed as nM thrombin × minutes (nM min). Thrombin generation is measured as function of an internal calibrator for thrombin (Thrombin Calibrator; Thrombinoscope BV). ETP represents the plasma balance between the action of procoagulants and that of anticoagulants.

Statistical analysis

We investigated the relationship of PM exposure to inflammation and coagulation markers to identify transient and permanent effects. Transient effects were evaluated by means of paired Student's *t*-tests that compared inflammation and coagulation markers (outcome measures) measured on the first day of a working week (time 1, following 2 days off work) with those those measured after three consecutive working days (time 2) of the same week. In this analysis, we aimed at identifying rapid changes associated with the 3-day exposure occurring between time 1 and time 2. We also used multivariate regression models that included as the dependent variable the difference in individual outcome measures between the two time points (time 2 – time 1), and as independent variables PM_1 or coarse PM levels, as well as covariates for potential confounders, including age (continuous), education (primary, secondary, or college), BMI (continuous), current smoking (yes/no), and use of non-steroidal anti-inflammatory drugs (NSAIDs) in the 7 days before the examination (yes/no).

We also evaluated, for each of the outcome measures investigated, the effect of particle exposure levels regardless of whether the outcome measures were measured at time 1 or time 2. This set of analyses was performed using multivariate mixed-effect models to account for within-subject correlation in repeated measures, and was based on the following assumptions, as previously described [27]: (i) the exposure measured during the study reflected a gradient of exposure among the workers examined that did not have major variations over time; and (ii) the effects of particles identified in these analyses were 'permanent', that is, had equal associations with the outcomes at time 1 and time 2. The two assumptions were considered to be valid on the basis of the following findings: (i) high correlation of particle levels that were repeatedly measured in each of the 11 work areas during a 1-year period, as described above; (ii) no variation of the job tasks assigned to each of the study participants in the year before the study; and (iii) for those exposures that showed significant associations in the mixed-model analysis, the associations with outcomes at time 1 and time 2 were similar ($P > 0.05$ for interaction term between exposure and time).

In mixed-regression models, we included the same covariates as in the analysis of transient effects, that is, age, education, BMI, current smoking, and NSAID use in the last 7 days. To allow for comparison of the size of effects of PM_1 and coarse PM, we report all model results as regression coefficients (β) estimating the change in the outcome measure due to an increment in exposure equal to the difference between the 75th and 25th centiles (interquartile range). A two-sided *P*-value of < 0.05 was considered to be statistically significant. Data were analyzed using STATA (Version 10.0; Stata Corp., College Station, TX, USA).

Results

The general characteristics of the study participants are shown in Table 1. Study subjects were found to be exposed to average PM levels up to five times higher than the levels of action used for the general population (50 μg m^{-3} for PM_{10}, EU directive 50/2008), with a wide gradient of exposures (Table 2). As expected, individual exposures to PM_1 and coarse PM were highly correlated with each other (Pearson's coefficient $r = 0.94$, $P < 0.001$).

Inflammation, blood coagulation and fibrinolysis markers measured at time 1 and time 2 are shown in Table 3. No significant differences were found between the two time points in PT, APTT, t-PA, D-dimer, ETP, CRP, and white blood cell (WBC) count. Neither PM_1 nor coarse PM levels showed associations with the difference between time 1 and time 2 in PT, APTT, t-PA, D-dimer, ETP, CRP, or WBC count (data not shown).

Table 1 Characteristics of the study population ($n = 37$)

Variable	
Age [years (SD)]	42 (7)
Body mass index [kg m^{-2} (SD)]	266 (27)
Education categories, *n* (%)	
Primary	10 (27)
Secondary	22 (59)
College	5 (14)
Current smokers, *n* (%)	18 (49)
Current cigarettes, *n* (SD)	12 (6)
Use of NSAIDs, *n* (%)	6 (16)

NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation.

Table 2 Individual exposure to PM_{10}, PM_1 and coarse PM ($PM_{10} - PM_1$) ($n = 37$)

Particle concentration	Mean (SD)	Median	IQR	Minimum	Maximum
PM_{10} ($\mu g\ m^{-3}$)	262 (272)	159	110–306	74	1220
PM_1 ($\mu g\ m^{-3}$)	8.0 (7.7)	3.6	2.9–11	1.7	30.5
Coarse PM ($\mu g\ m^{-3}$)*	254 (265)	162	106–293	71	1190

IQR, interquartile range; PM, particulate matter; SD, standard deviation. *Coarse PM was calculated by subtracting PM_1 from PM_{10} exposure levels.

Table 3 Blood coagulation and inflammation-related markers measured in male foundry workers ($n = 37$) on the first working day (time 1) and the last working day (time 2, after three consecutive days of work) of a 4-day working week

Outcomes	Mean (SD)		
	First day (time 1)	Last day (time 2)	*P*-value (paired *t*-test)
PT (s)	11.2 (0.8)	11.2 (0.9)	0.25
APTT (s)	29.0 (2.4)	29.2 (2.5)	0.28
t-PA antigen (ng mL^{-1})	7.3 (4.2)	7.5 (4.4)	0.52
D-dimer (ng dL^{-1})	150 (63)	149 (70)	0.89
ETP TM+ (nM min)*	474 (283)	451 (332)	0.62
ETP TM− (nM min)*	791 (444)	780 (442)	0.87
ETP TM+ (nM min)†	782 (315)	796 (316)	0.68
ETP TM− (nM min)†	1486 (290)	1496 (293)	0.79
CRP (mg L^{-1})	1.5 (1.6)	1.4 (1.4)	0.41
WBCs (1000 mm^{-3})	7.3 (1.5)	7.2 (1.4)	0.67

APTT, activated partial thromboplastin time; CRP, C-reactive protein; ETP, endogenous thrombin potential; PT, prothrombin time; SD, standard deviation; t-PA, tissue-type plasminogen activator; WBC, white blood cell. *ETP measured without exogenous triggers and with (TM+) or without (TM−) thrombomodulin. †ETP measured with exogenous triggers and with (TM+) or without (TM−) thrombomodulin.

To estimate permanent effects of PM, we fitted mixed-regression models on data that included the two repeated measures of inflammation and blood coagulation markers, regardless of whether they were measured on samples taken on the first day of work (time 1) or on those taken on the last day of the working week (time 2) (Table 4). We found a significantly shorter PT in association with higher levels of coarse PM (− 0.33 s for an interquartile exposure increase, $P = 0.01$), whereas the association with PM_1 was not statistically significant (− 0.33, $P = 0.08$). PM_1 was significantly associated with increased t-PA (+ 0.72 ng mL^{-1}, $P = 0.01$) and ETP measured without exogenous triggers in the presence of soluble thrombomodulin (+ 98.7 nM min, $P = 0.02$). Coarse PM showed a significant association with t-PA (+ 0.88 ng mL^{-1}, $P = 0.04$) and a borderline association with ETP measured without exogenous triggers in the presence of soluble thrombomodulin (+ 66.2 nM min, $P = 0.05$). No PM effect was observed for ETP measured without exogenous triggers and without thrombomodulin, or for ETP measured with exogenous triggers (Table 4). CRP showed a positive significant correlation with levels of PM_1 (+ 0.59 mg L^{-1}, $P = 0.03$) and coarse PM (+ 0.48 mg L^{-1}, $P = 0.01$). PM exposures were not associated with APTT, D-dimer or WBC count (Table 4).

Discussion

In the present study, based on a population of healthy workers from a steel plant in northern Italy, we found that exposure to PM did not cause any rapid change in a panel of inflammation, coagulation and fibrinolysis markers, as reflected in the lack of difference between measures obtained on blood samples collected on the first and last day of the same working week. However, we showed that the levels of PM exposure were

Table 4 Association of particulate matter (PM) exposure with blood coagulation and inflammation-related markers – repeated-measure models

Outcomes	PM_1			Coarse PM		
	Adjusted β†	SE	*P*-value	Adjusted β‡	SE	*P*-value
PT (s)	− 0.33	0.19	0.08	− 0.33	0.13	0.01
APTT (s)	− 0.25	0.53	0.63	− 0.06	0.39	0.87
t-PA antigen (ng mL^{-1})	+ 0.72	0.28	0.01	+ 0.88	0.43	0.04
D-dimer (ng dL^{-1})	− 16.7	13.0	0.20	− 16.0	9.4	0.09
ETP TM+ (nM min)*	+ 98.6	46.7	0.02	+ 66.2	34.6	0.05
ETP TM− (nM min)*	+ 91.3	75.9	0.25	+ 63.2	59.4	0.29
ETP TM+ (nM min)†	+ 72.6	58.1	0.21	+ 68.4	42.5	0.11
ETP TM− (nM min)†	+ 25.7	49.5	0.60	+ 32.6	36.4	0.37
CRP (mg L^{-1})	+ 0.59	0.27	0.03	+ 0.48	0.20	0.01
WBC (1000 mm^{-3})	− 0.18	0.24	0.45	+ 0.04	0.18	0.83

APTT, activated partial thromboplastin time; CRP, C-reactive protein; ETP, endogenous thrombin potential; PT, prothrombin time; SE, standard error; t-PA, tissue-type plasminogen activator; WBC, white blood cell. *ETP measured without exogenous triggers and with (TM+) or without (TM−) thrombomodulin. †ETP measured with exogenous triggers and with (TM+) or without (TM−) thrombomodulin. ‡Regression coefficients estimating the effect associated with an interquartile range in PM_1 or coarse PM, adjusted for age, body mass index, current smoking, education and non-steroidal anti-inflammatory drug use in the 7 days before blood drawing.

associated with higher systemic inflammation, as reflected in increased circulating CRP, as well as shorter PT, increased thrombin generation measured in the absence of exogenous triggers and in the presence of soluble thrombomodulin, and higher t-PA level. No exposure-related associations were found for the other parameters.

The association of PM levels with coagulation markers and CRP was observed in our study only when the two measurements taken before (time 1) and after (time 2) three consecutive working days were both included in repeated-measure models. In these models, the effects on the two time points were assumed to be similar [27]. This finding, together with the absence of differences between the first and last day of the same working week, suggests that PM operated over an extended timeframe, possibly causing a persistent hypercoagulable state that was not reset to baseline over the 2 days between consecutive working weeks.

The association of PM exposure levels with shortened PT in the present study is consistent with the findings of a previous investigation on ambient air pollution based on healthy volunteers, in which we showed a moderate decrease in PT in association with PM_{10} exposure [11]. Ambient and occupational PM are clearly two different conditions of exposure, so our results cannot be extrapolated to the general population. However, our findings indicate some common mechanisms that may be activated by the two different exposures. Ambient PM exposure has been shown to elicit systemic inflammation [6], which might represent a primary mechanism for its prothrombotic outcomes [2,11,28]. The finding of an association between PM exposure and CRP in the present study points to inflammation as a potential intermediate process that may contribute to modifying coagulability [7].

ETP is defined as the total amount of thrombin that is generated in plasma *in vitro*, and increased levels have been proposed as an index of hypercoagulability [22,23]. In the present study, increased levels of ETP were associated with PM exposure only when the test was performed without the addition of exogenous triggers to the assay system. These findings suggest that PM exposure may induce the release of small amounts of endogenous tissue factor and/or negatively charged phospholipids that may function as triggers of thrombin formation in the assay system. The relatively high concentrations reached in the assay system following the addition of exogenous triggers do presumably blunt the effect of PM-induced increases in the endogenous triggers. Evidence has been provided that endogenous triggers of coagulation (tissue factor and negatively charged phospholipids) may be disseminated into the bloodstream by circulating microparticles stemming from platelets and/or activated monocytes [29], thus supporting our findings. A limitation of our study is that, because of limitations in the quantity of plasma collected, we could not perform any direct measurements of endogenous coagulation triggers.

The thrombin generation assay employed in this study was run with or without thrombomodulin. Thrombomodulin is the main physiologic activator of protein C [30]; it is located on endothelial cells, but not in plasma. Thus, the addition of thrombomodulin to the assay system makes the assay able to mimic much more than any other test the conditions existing *in vivo*. The ratio between the values of the thrombin generation parameter ETP measured with and without thrombomodulin may be regarded as an index of the ability of thrombomodulin to efficiently activate protein C. Accordingly, plasmas displaying high ratios may be regarded as resistant to the action of thrombomodulin, and are therefore associated with hypercoagulability [31]. Increased ETP was associated with PM concentrations when the assay was performed in the presence, but not in the absence, of thrombomodulin. This finding suggests that PM exposure makes plasma resistant to the action of thrombomodulin as a protein C activator.

One limitation of our study is that thrombin generation was measured without the addition to plasma of corn trypsin inhibitor (CTI), which is known to quench contact coagulation factor activation [32]. In the absence of CTI, thrombin generation might be induced by tissue factor, but also by the variable *in vitro* contact factor activation[32]. It is, however, likely that the purported contact factor activation (if any) would affect the investigated population throughout the entire period of exposure to PM, thus leaving unaltered the conclusion of this study.

Our finding of a PM-dependent elevation of t-PA antigen indicates a reduced rather than heightened fibrinolytic activity, because the immunoassay of t-PA measures, to a large extent, the circulating complexes between t-PA and the main fibrinolysis inhibitor plasminogen activator inhibitor-1 [32], and thus also reflects a condition of systemic inflammation.

In our study, we had the advantage of contrasting subjects with a wide range of exposure levels, owing to the differences in PM levels in the different job positions across the work facility. Our study did not include an external reference population of individuals without occupational exposure to PM. However, the lowest PM exposure observed in our study (PM_1 = 1.7 μg m^{-3}, PM_{10} = 74 μg m^{-3}) was relatively low, particularly if compared with the highest level found in our population (PM_1 = 30.5 μg m^{-3}, PM_{10} = 1220 μg m^{-3}). In addition, the lowest PM exposure in our study was only marginally higher than ambient PM levels measured in the geographic area in which the plant is located (average annual ambient PM_{10} levels between 41 and 57 μg m^{-3} were recorded by ambient monitoring stations in the Brescia area [33]). Therefore, although we did not have an external control group, the wide range of exposure makes it possible to consider the subjects in our study with lower exposures as an internal control group. The regression analysis that we used takes full advantage of the extended range of exposures. In addition, it is worth noting that limiting our investigation to individuals who had all been working in the same work facility avoided potential concerns related to the selection of external referents who might have differed from the exposed population in terms of

socioeconomic factors and other characteristics determining hiring into the plant [34].

A further limitation of our study was that individual exposure to PM was based on measures obtained during only one working week. Differences in previous job tasks could have caused misclassification of individual exposure. The study population, however, included workers assigned to specific job tasks repeated regularly every day and who had been employed in the plant for at least 1 year, thus ensuring that the exposure measures used represented the usual ambient exposure of each individual. This was also confirmed by the high correlation between measures of PM exposure obtained 1 year apart from each other for a subset of subjects. In our study, both coarse particles and PM_1 were associated with inflammation and coagulation markers. Because of the strong correlation between coarse and PM_1 personal exposure, our study did not have enough statistical power to identify which portion of PM is the determinant of the effects observed. In addition to PM, workers in foundries may have other exposures, including polycyclic aromatic hydrocarbons [35], carbon monoxide [36], and non-ionizing radiation [37]. Although the participants in our study were in a modern facility with state-of-the-art systems for chemical and physical exposure reduction, we cannot exclude the possibility that these exposures might have contributed to the observed associations.

It is important to note that, although our study showed moderate changes in the average levels of coagulation, inflammation and fibrinolysis markers, none of the subjects showed clinically relevant alterations. Thus, we have no evidence of increased cardiovascular risk among healthy workers exposed to PM levels like the ones we found in this modern steel plant.

In conclusion, our study did not show any change in inflammation and coagulation markers when we contrasted measures obtained on the last day of a working week with those taken on the first day of the same working week. However, the finding that PM exposure levels were associated with moderate changes in PT, thrombin generation and t-PA provides some evidence that PM-induced systemic inflammation, as also reflected in the positive association of PM with plasma CRP, may enhance blood coagulation.

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Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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