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Long- and Short-Term Exposure To Air Pollution and Inflammatory/Hemostatic Markers in Midlife Women

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Abstract

Background—Studies have reported associations between long-term air pollution exposures and cardiovascular mortality. The biological mechanisms connecting them remain uncertain.

Methods—We examined associations of fine particles ($PM_{2.5}$) and ozone with serum markers of cardiovascular disease risk in a cohort of midlife women. We obtained information from women enrolled at six sites in the multi-ethnic, longitudinal Study of Women's Health Across the Nation, including repeated measurements of high-sensitivity C-reactive protein (hs-CRP), fibrinogen, tissue-type plasminogen activator antigen (tPA-ag), plasminogen activator inhibitor Type 1 (PAI-1), and Factor VIIc (Factor VII coagulant activity). We obtained residence-proximate $PM_{2.5}$

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and ozone monitoring data for a maximum five annual visits, calculating prior year, six-month, one-month, and one-day exposures and their relations to serum markers using longitudinal mixed models.

Results—For the 2,086 women studied from 1999 through 2004, $PM_{2.5}$ exposures were associated with all blood markers except Factor VIIc after adjusting for age, race/ethnicity, education, site, body mass index, smoking, and recent alcohol use. Adjusted associations were of the strongest for prior year exposures for hs-CRP (21% increase per 10 μg/m^3 $PM_{2.5}$, 95% CI: 6.6, 37), tPA-ag (8.6%, 95% CI: 1.8, 16), and PAI-1 (35%, 95% CI: 19, 53). An association was also observed between year prior ozone exposure and Factor VIIc (5.7% increase per 10 ppb ozone, 95% CI: 2.9, 8.5).

Conclusions—Our findings suggest that prior year exposures to $PM_{2.5}$ and ozone are associated with adverse effects on inflammatory and hemostatic pathways for cardiovascular outcomes in midlife women.

Introduction

Fine particulate matter (particles less than 2.5 microns in diameter, or $PM_{2.5}$) has been associated with a variety of adverse health effects. Consistent associations have been observed between $PM_{2.5}$ and cardiovascular disease (CVD) mortality and morbidity. [1-3] Because particulate matter (PM) mass and some PM constituents have been reported to have pro-inflammatory properties, researchers have posited that a likely mechanism for cardiovascular effects involves pulmonary and systemic inflammation leading to increased coagulation and thrombotic potential, and, ultimately, ischemic events. [4,5]

A number of known blood markers lie on this proposed pathway and can be used to explore the importance of this mechanism. Acute phase-proteins involved in inflammatory response, such as C-reactive protein (CRP) and fibrinogen, have been found to be consistent and clinically useful long-term predictors of cardiovascular risk. [6-8] Cohort studies have also identified links between hemostatic markers governing blood viscosity and clot formation, such as tissue-type plasminogen activator antigen (tPA-ag), plasminogen activator inhibitor-1 (PAI-1), and Factor VIIc (Factor VII coagulant activity), and cardio- and cerebrovascular endpoints like coronary heart disease and stroke.[9-14] However, evidence directly linking air pollution exposure with these markers is limited, and primarily focuses on inflammation and short-term effects. [15,16] CRP has been linked to long-term traffic and $PM_{2.5}$ exposure,[17,18] though other markers have not demonstrated strong associations in previous studies.[19,20] A weakness of these long-term pollution studies is that they have relied on one residential address per participant.

The Study of Women's Health Across the Nation (SWAN), a large multi-ethnic cohort study in the U.S. of women followed through the menopausal transition, collected yearly residential location and measurements of a number of inflammatory and hemostatic blood markers, specifically high-sensitivity CRP (hs-CRP), PAI-1, tPA-ag, Factor VIIc and fibrinogen. In our analysis, we examined the relationship between these inflammatory/hemostatic markers and both short- and long-term exposure to $PM_{2.5}$ and ozone in the

SWAN cohort. A previous paper [21] examines effect modification by demographic and health status variables for long-term exposure to $PM_{2.5}$ specifically for hs-CRP.

Methods

Participants

SWAN is a longitudinal, multi-racial/ethnic cohort study designed to follow women through the menopausal transition. The design of the study has been described in detail elsewhere.[22] Six of the seven clinical SWAN sites participated in our air pollution study: Chicago, Illinois; Detroit, Michigan; Los Angeles, California; Newark, New Jersey; Oakland, California; and Pittsburgh, Pennsylvania. Recruitment at each site included White women as well as women from one of the following racial/ethnic groups: African-American in Pittsburgh, Detroit, and Chicago; Chinese in Oakland; Hispanic in New Jersey and Japanese in Los Angeles. Women were recruited for the study between 1995 and 1997 at which time 16,065 women completed a screening interview. The inclusion criteria for the cohort study at baseline (visit 0) were: being age 42 to 52 years, having an intact uterus and one or more ovaries, not being pregnant or lactating, not using reproductive hormones in the past 3 months and having had at least one menstrual period in the past 3 months. Approximately 450 eligible women at each of the study sites were recruited for the longitudinal cohort study, which included annual clinical assessments. This study consists of a longitudinal analysis of $PM_{2.5}$ and ozone levels and inflammatory/hemostatic markers assessed at clinical visits 3 (1999) through 7 (2004). Although the markers were available at earlier visits, $PM_{2.5}$ monitors were just becoming available during visit 3. Institutional Review Boards at all six participating sites approved the SWAN protocols and the air pollution study, and all women provided signed, written informed consent for the SWAN protocols.

Blood assays

Blood was drawn at each annual visit and assayed as described previously.[23] The hs-CRP values > 10 mg/L were excluded from the primary analyses because they may have been an indication of active, obvious inflammatory processes, such as severe infection, major trauma, or chronic inflammatory diseases (9.9% of all observations). For all other markers, extreme values (outside the mean ± 3 standard deviations after log transformation) were excluded (0.9%, 1.4%, 1.2%, and 2.3% of observations for tPA-ag, PAI-1, fibrinogen, and Factor VIIc, respectively) from the study because of suspected laboratory error.

Exposure assignment

A residential history was maintained for each participant from the baseline visit to the most recent visit. We received a total of 4,506 addresses from the sites, of which 4,402 were successfully geocoded using batchgeocode.com, now known as Batchgeo (Batchgeo LLC, Seattle, WA), with one site (Oakland) using MapMarker Plus v12 (Pitney Bowes, Stamford, CT), for 2,849 women. The remaining addresses were not geocoded because they were post office boxes, out of country, out of state for the Oakland site, unable to be located using the software, or a work address. Another program was applied to each coordinate to randomly move the location of each residence up to 400 feet (about a block) to ensure confidentiality, and a 20 km circular buffer was created around each address.

$PM_{2.5}$ and ozone monitoring measurements came from the AQS DataMart.[24] Participants with $PM_{2.5}$ monitors located within their 20 km buffers were assigned exposures. During the study period, $PM_{2.5}$ was typically measured every three days, but sometimes every six days or daily. Monitor readings were used to calculate average exposures for the year, six months, 30 days, and one day prior to each visit. We simplified months to 30-day increments, so that six months covered 180 days, and one year covered 360 days. If a 30-day period had at least three days of data, an average was assigned for the month. However, over 75% of the 30-day periods had nine or more measurements. Otherwise, monthly exposure was considered missing. A six-month average required at least five months of data, and 10 months were required for a year average. We used these criteria for the longer-term exposure measures to ensure that all possible seasons were at least partially covered.

We used a nearly-identical procedure to create daily 8-hour maximum ozone exposure metrics, limiting monitor assignment to those within 20 km of the residence. These data were typically monitored on a daily basis, so we required that each 30-day period have at least nine daily readings to qualify as a month with identical requirements to $PM_{2.5}$ for the longer exposure periods. Some monitors, most notably in Michigan, only measured ozone in the summertime. We only created ozone exposure metrics when a corresponding $PM_{2.5}$ metric was available for a woman at a particular visit.

Often, multiple monitors, with varying dates in service and completeness of data, were located within 20 km of a woman's residence during our study period. For residences with multiple monitors within 20 km, one monitor was selected to represent exposure. Selection was based on criteria balancing the number of women's clinic visits with available exposure data for a monitor versus the distance to the monitor. Preference was typically given to the closer monitor. However, for example, if a monitor was located twice as far away as the closest monitor, it would be chosen if it more than doubled the number of clinic visits included in the study. The same monitor chosen was used for the one-year, six-month, and 30-day metrics to maintain comparability between metrics. However, we allowed the one-day prior measurement to come from a different monitor because daily measurements were less available, and left it missing for the instances where no prior day measurements were made. If the participant moved during the year prior to her visit, we considered both locations when assigning exposure. For example, if the participant moved eight months prior to her visit, the year average was calculated using the four months of measurements from the first address and eight months of measurements from the second address. If we did not have a move date, we assumed she spent six months at the first address and six months at the second address.

Data Analysis

To study the association between air pollution levels and the inflammatory/hemostatic markers, we used SAS 9.1 Proc Mixed (SAS Institute, Cary, NC) to perform linear mixed effects regression analyses with first-order autoregressive structure to account for the correlation among the repeated measurements for each woman. The models included a random intercept, allowing us to ascribe a “woman-specific” interpretation to model parameters.

We included the inflammatory/hemostatic markers in the regression models as response variables. To account for design issues and potential confounders, study site, race/ethnicity and education (high school or less, some college, or college graduate) were included in a base model in addition to the following visit-specific variables: age (continuous), active smoking (yes/no), body mass index (BMI) (continuous) and alcohol consumption in the 24 hours prior to the blood draw (yes/no). We used the base model for all four averaging times for both $PM_{2.5}$ and ozone.

We also explored possible effect modification by individual health traits, specifically BMI (below vs. equal to or above 25kg/m^2), diabetes, and current menopause transition stage (early & late peri-menopausal vs. post-menopausal), because some of these groups may have enhanced inflammatory responses and, consequently, higher risk for cardiovascular disease endpoints.[23,25,26] For models stratified by BMI, BMI was not included as a predictor.

Stratifying variables were omitted from these models. Effect modification was determined to exist if the difference in effects between two subgroups of each of the characteristic variables was statistically significant at $p < 0.05$ using a t-test. In a previous paper[13] hs-CRP was further explored as a binary variable (greater than 3 mg/l) and effect modification by the following variables was examined for past year exposure to $PM_{2.5}$: age, marital status, income, education, BMI, smoking, alcohol use, hormone therapy, statin use, menopausal stage, hypertension, diabetes, and distance to an air pollution monitor.

For each visit, we excluded women who reported a previous heart attack or stroke because these conditions could potentially affect markers of inflammation or hemostasis. We also excluded women who did not fast 12 hours before the blood draw. We ran one model without BMI and several models without diabetes because these variables may be on the causal pathway between air pollution exposure and inflammation.[25,27] For fibrinogen and Factor VIIc, which were only measured at visits 3, 5 and 7, medical conditions reported at the measured visit or the previous visit were included in the statistical models. If a covariate, such as physical activity, was systematically not measured at each visit, we assigned the value from the previous visit or the average of the previous visit and the following visit. Due to the small numbers of New Jersey participants for visits 6 and 7, we censored those visits while keeping women from that site in the model for visits 3, 4, and 5. Except for fibrinogen, which was normally distributed, the other cardiovascular markers were log transformed, and the results were expressed as the percent change in inflammatory/hemostatic marker per 10 μg/m^3 $PM_{2.5}$ using the formula $[100 \times (\exp^{(\beta \text{ per unit pollutant } *10)} - 1)]$. To examine whether $PM_{2.5}$ was confounded by ozone, or vice versa, we considered both pollutants in the base models. For these models, the same averaging time was used for each pollutant.

We conducted several sensitivity analyses for the $PM_{2.5}$ exposure. First, we used the base model but restricted it to women who were non-smokers at each visit. Second, we added season of blood draw (Jan-Mar, Apr-Jun, Jul-Sep, Oct-Dec) to adjust for possible seasonality of the inflammatory/hemostatic markers. Third, we conducted analyses including all the hs-CRP values because of the possibility that $PM_{2.5}$ could cause extreme inflammation in sensitive subjects. Fourth, we used the base model but restricted to women who had all five

visits to consider effects of loss to follow-up. Finally, we conducted analyses for the one-year pollutant averages in which we created several other models by adding to the base model one or more of the following variables that have been shown to be associated with inflammatory/hemostatic markers in the literature and in previous SWAN investigations of other exposures: time of blood draw between 8 am and 10 am (yes/no); menopausal status; menopausal hormone therapy use; use of cholesterol medications; other heart medications or anticoagulant use; use of steroids or pain medications; marital status; depression; non-work physical activity; hypertension based on treatment and/or systolic and diastolic blood pressure; and diabetes based on treatment and/or fasting glucose levels.

Results

Of the 2,849 women who filled out the original questionnaire at the six sites, 245 women were excluded from the analysis because they did not live within 20 km of a working $PM_{2.5}$ monitor, 375 because they did not have at least one visit between visits 3 and 7, 54 because they had a heart attack or stroke prior to visit 3, and 89 because they were missing information on covariates in the base model. The final study population thus consisted of 2,086 women, ranging from 457 in Los Angeles to 249 in New Jersey, with mean age of 46.3 years (2.7 years standard deviation). Thirty-six percent changed addresses between visit 0 (baseline) and visit 7. For visit 4, with the highest number of participants, the number of monitors by site ranged from 7 to 13 for $PM_{2.5}$, and 7 to 11 for ozone. The highest percentage of participants assigned to a particular monitor ranged from 33% in Pittsburgh to 79% in Chicago for $PM_{2.5}$ and from 53% in Oakland to 97% in Pittsburgh for ozone.

Tables 1 and 2 summarize descriptive statistics. Average $PM_{2.5}$ levels over the study period were higher for Japanese women and lower for Chinese women (Table 1) due to their selection at the particular sites. For example, the Japanese women were all from the Los Angeles site where air pollution levels were higher over the study period. $PM_{2.5}$ levels averaged over the past year were highest in Chicago and Los Angeles at visit 3, and they declined at all sites over the study period (Table 2). Yearly ozone levels were highest in New Jersey, Pittsburgh and Los Angeles at visit 3 and increased or stayed the same thereafter. The correlation between $PM_{2.5}$ and ozone over the study period was 0.51.

Variability was greater for the short-term metrics compared to their long-term analogues (Table 3). The number of yearly estimates was smaller because $PM_{2.5}$ monitors were just becoming available during the Visit 3 year. The interquartile range width (IQR_w) for 1-day $PM_{2.5}$ was 11.5 $\mu g/m^3$, and 4.1 $\mu g/m^3$ for 1-year $PM_{2.5}$. Similarly, the 1-day ozone IQR_w was approximately 3 times its 1-year IQR_w. One-day $PM_{2.5}$ variability was additionally impacted by lower counts due to decreased availability of prior day measurements.

In general, the base model results for the relation of the average levels of the pollutant to the five inflammatory/hemostatic markers were most robust for the one-year and six-month averages of either $PM_{2.5}$ or ozone (Table 4). For each 10 $\mu g/m^3$ increase in the yearly average for $PM_{2.5}$ we observed a 21% (95% confidence interval (CI), 6.6% to 37%) increase in hs-CRP, an 8.6% (95% CI 1.8% to 16%) increase in tPA-ag and a 35% (95% CI 19% to 53%) increase for PAI-1. The corresponding yearly associations with $PM_{2.5}$ based on IQR_w

were about 50% less. A 10 μg/m^3 increase in the average $PM_{2.5}$ concentration of the previous year was associated with a 5.2 mg/dL (95% CI −4.5 to 15) increase in fibrinogen level. The estimate for the 30-day $PM_{2.5}$ average concentration for fibrinogen was elevated (β × 10=3.5; 95% CI 0.4 to 6.6). Factor VIIc appeared to be inversely associated with $PM_{2.5}$ concentration for the six-month and 30-day averages.

We considered $PM_{2.5}$ and ozone in single pollutant models and two-pollutant models (Table 4 and Figure 1). In the single pollutant model, ozone did not show as many associations as $PM_{2.5}$. However, Factor VIIc was positively associated with yearly ozone exposure (% increase per 10 ppb increase: 5.7% (95% CI 2.9 to 8.5)). hs-CRP was positively associated with the 6-month ozone average concentration, 3.2% (95% CI 0.1 to 6.5), but associations were imprecise for the other averaging times. Associations of six-month and yearly averages of $PM_{2.5}$ concentration with biomarkers persisted and were slightly greater with the addition of ozone exposure to the model (Figure 1). Adding $PM_{2.5}$ to the ozone models similarly enhanced or had no impact on the original associations we found for ozone exposure.

In sensitivity analyses to test robustness of results to restricting the cohort demographics, adding potential confounders to the model or including extreme hs-CRP values, associations were not changed appreciably. Compared to the base model, adding season or restricting analysis to non-smokers for PM2.5 did not change the results (not shown). The effect estimates for the one-day and 30-day $PM_{2.5}$ and ozone exposure averages did not change when including all the hs-CRP values over 10 mg/l (not shown). However, when including all hs-CRP values, the estimates for the 6-month and one-year $PM_{2.5}$ averages were reduced to 2.4 (−5.0 , 10) and 17 (2.3 , 33). For ozone, when including all hs-CRP values, the 6-month and one-year ozone averages were reduced to 1.7 (−1.5, 5.1) and −0.6 (−8.3, 7.7), respectively. When the population was restricted to women who contributed to all five visits, the effect estimates were somewhat greater for the associations of long-term $PM_{2.5}$ exposure and hs-CRP, tPA-ag and PAI-I (not shown). The results of the yearly average $PM_{2.5}$ concentration and the inflammatory/hemostatic markers did not change appreciably by model specification (eTable 1).

eTable 2 presents results for yearly exposure to either $PM_{2.5}$ or ozone for all five imflammation/hemostatic markers when stratifying by BMI, diabetes status, or menopausal status. Effect modification was only observed for $PM_{2.5}$ exposure. The effect of $PM_{2.5}$ exposure on tPA-ag was significantly greater ($p_{interaction}$=0.003) for women with BMI < 25 that those with BMI >=25, and the effect on hs-CRP was significantly greater ($p_{interaction}$=0.047) for post-menopausal versus peri-menopausal women.

Discussion

In this multi-racial/ethnic, five-year follow-up study of midlife women, we found that several of the inflammatory/hemostatic markers studied were associated with $PM_{2.5}$ levels over the past year. In general, the associations were strongest for longer-term averages (six-month or yearly) versus shorter-term averages (1-day or 30-day), though comparisons between short- and long-term effects may appear exaggerated due to our scaling by a 10 μg/m^3 increment, a substantial proportion of the annual metric range but a smaller portion of

daily metric range. Still, effects were more apparent using long-term PM metrics. hs-CRP and PAI-1 levels were associated with increased $PM_{2.5}$ levels in the past six months and year, while tPA-ag was positively associated only with the $PM_{2.5}$ levels in the past year. The results for the yearly $PM_{2.5}$ averaging time were robust to further adjustment for other variables not included in the base model. Exposure to ozone also was associated with several of the inflammatory markers and did not appear to confound the relationship between $PM_{2.5}$ and any of the markers. Annual average ozone was associated with Factor VIIc, while the 6-month average was associated with hs-CRP.

Our study found positive associations with short-term effects of $PM_{2.5}$ and hs-CRP. CRP has been positively associated with short-term exposures to PM in some[15,16,28] but not all studies.[29,30] In a German cohort, exposure to $PM_{2.5}$ over the past 5 days was associated with increased CRP and fibrinogen in men, but not women.[31] A panel study of college students in Shangai found an association between exposures to PM a few hours prior to blood draw and CRP and fibrinogen, and between exposures to $PM_{2.5}$ up to 2 days prior and PAI-1.[32] A more complete review of the the CRP studies can be found in Li et al.[33]

In our study, estimates for Factor VIIc and fibrinogen were not as precise as those for hs-CRP, tPA-ag and PAI-1, because Factor VIIc and fibrinogen were only measured at visits 3, 5, and 7. No association was found in a Canadian panel study between short-term $PM_{2.5}$ and fibrinogen but the authors suggest the ambient $PM_{2.5}$ levels may have been too low.[34] Similar to fibrinogen, the association of $PM_{2.5}$ with Factor VIIc has been less conclusive in previous studies than with some other inflammatory markers. It also has a less well-established association with cardiovascular events.[35] Much of the literature examining the relationship between Factor VIIc and PM exposure considers PM_{10} (particles less than 10 microns in diameter) as opposed to $PM_{2.5}$. Although we found no relationship between short-term $PM_{2.5}$ averages and Factor VIIc, a couple of studies have found an inverse relationship between PM and Factor VIIc levels.[35,36]

Few studies have also examined long-term exposure; almost all have been cross-sectional and reported mixed results. Ostro et al.[21], in a previous analysis of the same cohort, further explored effect modification for yearly $PM_{2.5}$ exposure and hs-CRP, both as a continuous and categorical variable (hs-CRP > 3 mg/l). Larger effects were observed among those living closer to the $PM_{2.5}$ monitors, diabetics, the unmarried, those with low income, high blood pressure, or who were using hormone therapy, with indications of a protective effect for those using statins or consuming moderate amounts of alcohol.[21] Rioux et al.[17] reported an association between residential exposure to traffic and CRP among older Puerto Rican adults in Boston, while a German study found an association between $PM_{2.5}$ exposure and both CRP and fibrinogen in men but not in women[31] and no association with measures of traffic. However, Forbes et al.[19] and Adar et al.[37] found no association between PM_{10} exposure and either CRP or fibrinogen. A study conducted among diabetics in Belgium[20] failed to find an association between PM_{10} exposure in the past year and Factor VIIc. In our study $PM_{2.5}$ exposure appeared to be inversely related to Factor VIIc for the longer averaging times, although the estimates were imprecise. The one longitudinal study, across multiple US cities and multiple ethnicities found no association between $PM_{2.5}$ of one-year duration and either CRP or fibrinogen.[38]

Clot-formation is governed, in part, by tPA-ag. Although we found an association between long-term exposure to $PM_{2.5}$ and increased tPA-ag, we saw a negative association for the one-day and 30–day exposure periods. A panel study by Graff et al.[39] also found decreased levels of tPA-ag after short-term exposure to concentrated ambient particles. Decreased tPA-ag could inhibit the breakdown of clots, leading to increased odds of thrombosis. Longer-term exposure to $PM_{2.5}$ may cause tPA-ag levels to increase in response to clot formation. More studies are needed to fully explain the mechanisms involved and replicate the findings for both short- and long-term exposures.

All short-term ozone exposures had imprecisely measured effect estimates that were usually in the negative direction. To date, a limited number of studies have examined the association between ozone exposure and inflammatory/hemostatic markers. Associations of two-day average ozone concentration and repeated measured of CRP, PAI-1 and fibrinogen were observed among college students in Taiwan [40] and CRP was associated with a three-day lag of ozone concentration among patients with a recent coronary event. [41] In a U.S. study of middle-aged men and women, an association with daily ozone exposure was found for fibrinogen but not the inflammatory markers. [42]

We observed positive associations of six-month ozone exposure with hs-CRP and one-year ozone exposure with Factor VIIc. All other estimates of risk associated with inflammatory/hemostatic markers and ozone in our study were imprecisely measured and were usually in the negative direction. A few cross-sectional studies have examined the association of one-year exposure to ozone with inflammatory/hemostatic markers. Chuang, et al. [43] reported an association with IL-6 using data on older adults in Taiwan. However, in an English study no association was observed with either CRP or fibrinogen. [19] We observed associations of six-month ozone exposure with tPA-ag and one-year ozone exposure with Factor VIIc.

This study was, to our knowledge, the first to examine associations of $PM_{2.5}$ and ozone with inflammatory/hemostatic markers in a relatively young population of women without pre-existing cardiovascular disease. The following are several strengths of our study. We had $PM_{2.5}$, ozone and inflammatory/hemostatic marker measurements for an average of 3.6 visits per woman, and for five consecutive yearly visits for 50% of women. A complete residential history was available for all participants during the study period, allowing us to estimate exposures even if a woman changed addresses during the study period. We were able to create long-term as well as short-term exposure measurements. We had access to six of the seven SWAN sites with differing air pollution levels and racial/ethnic and other personal characteristics. The correlation between yearly ozone and $PM_{2.5}$ levels was modest, allowing us to examine $PM_{2.5}$ while controlling for ozone. We also had a relatively large study population with data on several potential confounders including menopausal hormone therapy use and menopausal status.

The study also had limitations. Confounding may have been present due to unmeasured variables. We could not investigate effect modification by race/ethnicity because, by original study design, race/ethnicity was tied to the site. Also, because no time-activity patterns or indoor measurements of air pollution were collected, the exposure assessment was somewhat imprecise. Additionally, because exposure assessment was tied to residence, it did

not account for exposures away from home. Studies in California have shown that adults spend approximately 60 to 70 percent of time at home indoors.[44] Exposure misclassification was likely non-differential, which would have biased the results toward a weaker association. Indeed, the stronger association between $PM_{2.5}$ and hs-CRP when we limited our population to women living within 9 km (median distance) of a monitoring station suggests that home exposures were important and that assessment improved with residential proximity of the monitor.[21] The results could have been affected by loss to follow-up, since the women for whom there was data for all 5 visits tended to be thinner, more educated, less likely to be diabetic or smokers, had higher income than those with fewer visits, and included no Hispanics (since the only site that had Hispanics was New Jersey, and that site contributed to at most 3 visits). The study was limited to the six participating sites and may not have been representative of all women in the U.S. However, the study was racially/ethnically diverse, and the sites had differing air pollution levels, which may translate to other urban areas of the U.S. It should be noted that the inflammatory/hemostatic markers we used are not equivalent predictors of cardiovascular disease, with fibrinogen, hs-CRP, and tPA-ag being more strongly tied to heart disease [6,9] than Factor VIIc and PAI-1. This should be taken into consideration when assessing any study using these biomarkers to evaluate possible mechanistic links between exposure and poor cardiovascular outcomes.

Conclusions

The results of this study indicated that, in a cohort of racially/ethnically diverse, middle-aged women followed for five years, higher long-term exposures (one-year) to $PM_{2.5}$ and ozone were associated with higher levels of some inflammatory/hemostatic markers. Effects for $PM_{2.5}$ were robust to a number of model specifications adjusting for medical and demographic characteristics, and to the inclusion of ozone in the model. Our findings support the hypothesis that air pollutants may act through inflammatory and hemostatic pathways to cause cardiovascular illness.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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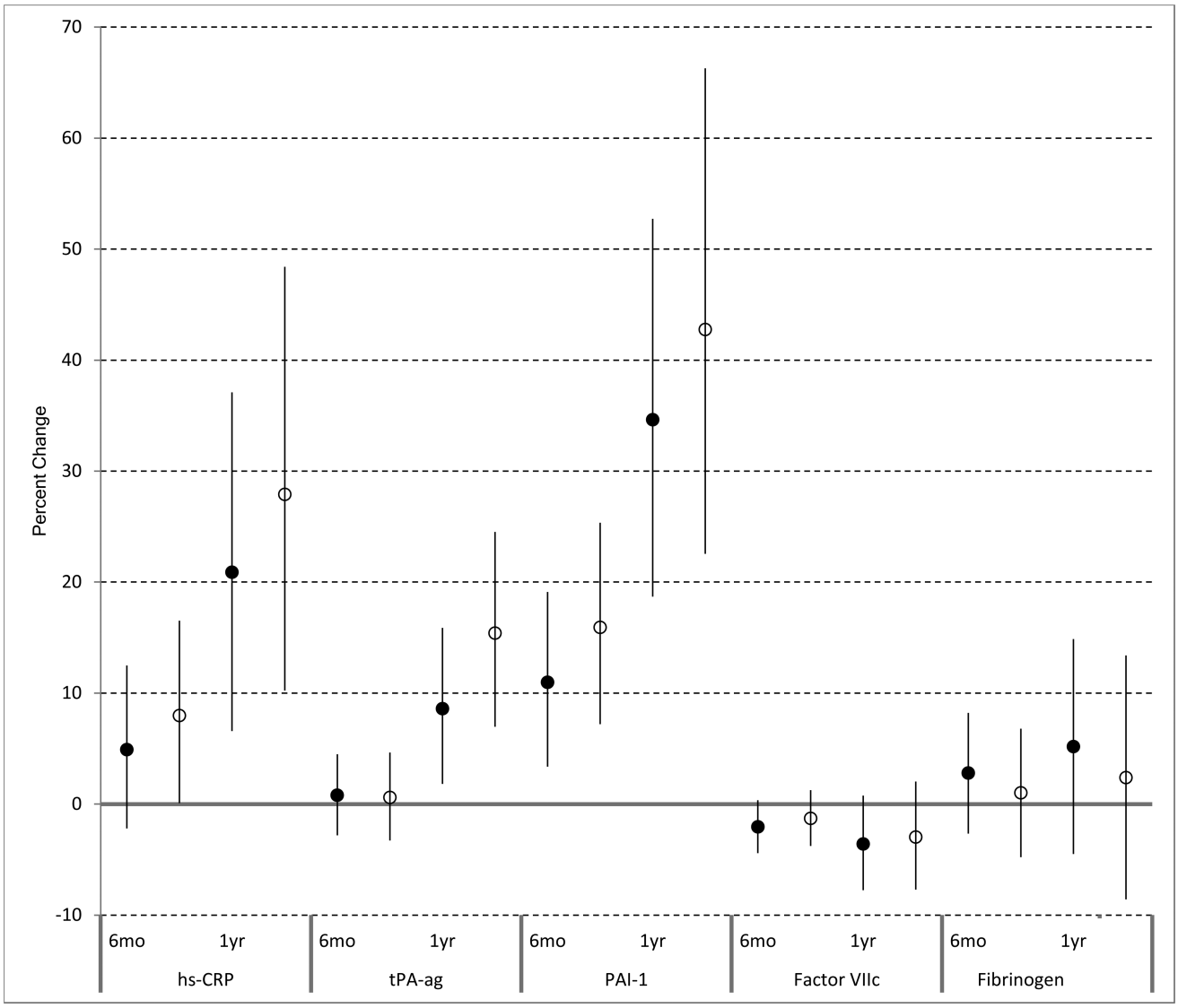

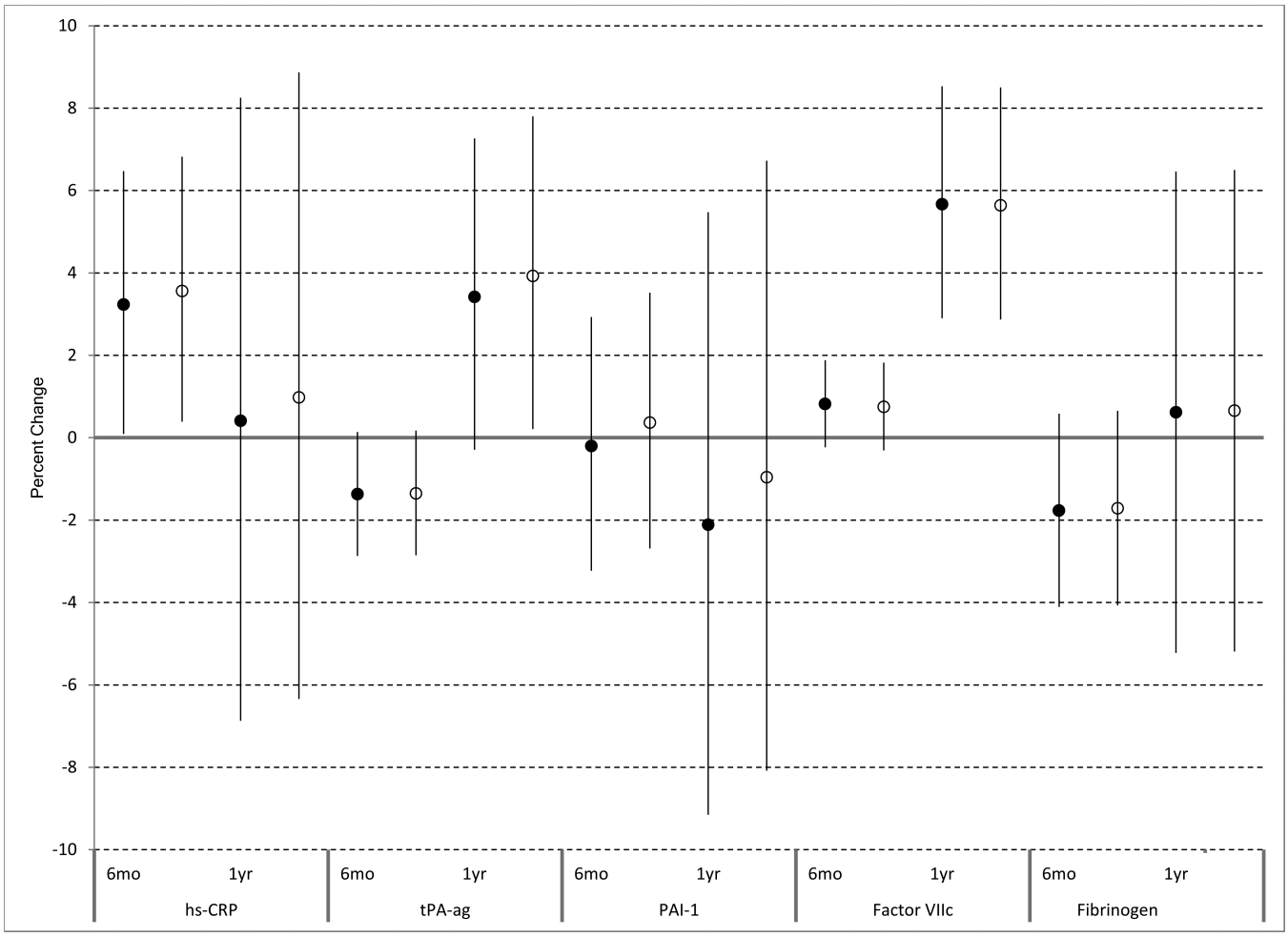

Figure 1.

Associations between hemostatic markers and (A) $PM_{2.5}$ alone (solid circles) and $PM_{2.5}$ with ozone (open circles) in the model with a 10 μg/m^3 change in $PM_{2.5}$ and a 10 ppb change in ozone, and (B) ozone alone (solid circles) and ozone with $PM_{2.5}$ (open circles). Bars around estimates represent 95% confidence intervals. The estimates for fibrinogen are not percent changes, but instead are unit changes per 10 unit change in air pollutant. Adjusting for time invariant variables: site, ethnicity, and education; and time variant variables: smoking status, age, body mass index and alcohol use in the last 24 hours.

Factor VIIc, Factor VII coagulant activity

hs-CRP, high sensitivity C-reactive protein

PAI-1, plasminogen activator inhibitor Type 1

$PM_{2.5}$, fine particles or particles less than 2.5 microns in diameter

tPA-ag, tissue-type plasminogen activator antigen

Table 1

Characteristics of the SWAN Cohort at the 6 Participating Sites

	Visit 0[e] Women included in Air Pollution Study N=2086	Yearly Pollution Averaged Over Visits 3-7 for Air Pollution Study mean (SD)	
		PM2.5 (μg/m^3)	Ozone (ppb)
Body mass index (kg/m^2), N[a] (%)[b]			
Obese (>30)	628 (30)	15.9 (3)	33.2 (5)
Overweight (25-30)	546 (27)	16.5 (3)	33.3 (5)
Normal/under (<25)	886 (43)	16.7 (4)	33.1 (6)
Race/ethnicity, N[a] (%)[b]			
African-American	540 (26)	15.9 (2)	32.9 (3)
Chinese	196 (9)	12.0 (1)	25.7 (6)
Hispanic	147 (7)	16.1 (1)	35.6 (7)
Japanese	242 (12)	21.3 (2)	36.8 (4)
White	961 (46)	16.1 (3)	33.6 (6)
Education, N[a] (%)[b]			
High school grad or less	491 (24)	16.0 (3)	33.4 (6)
Some college	679 (33)	16.6 (3)	34.0 (5)
College grad/postgrad	916 (44)	16.3 (4)	32.7 (6)
Health History, N[a] (%)[b]			
Diabetes			
Yes	102(5)	16.0 (3)	32.0 (6)
No	1890 (95)	16.4 (3)	33.3 (6)
Insulin			
Yes	45 (2)	15.7 (3)	32.1 (6)
No	2032 (98)	16.4 (3)	33.2 (6)
Steroids			
Yes	31 (1)	16.2 (3)	33.5 (6)
No	2046 (98)	16.4 (3)	33.2 (6)
Blood pressure medications			
Yes	222 (11)	16.2 (3)	33.3 (5)
No	1855 (89)	16.4 (4)	33.2 (6)
Smoker			
Yes	327(16)	16.7 (3)	34.1 (5)
No	1742 (84)	16.3 (3)	33.1 (6)
Inflammatory/hemostatic markers		CV Between Subjects[c]	CV Within Subject[d]
hs-CRP (mg/L), median (IQR_w)	1.4 (3.8)	102.1	6
tPA-ag (ng/mL), median (IQR_w)	7.1 (4.4)	49.3	6

	Visit 0[e] Women included in Air Pollution Study N=2086	Yearly Pollution Averaged Over Visits 3-7 for Air Pollution Study mean (SD)	
		PM2.5 (μg/m^3)	Ozone (ppb)
PAI-1 (ng/mL), median (IQR_w)	19.8 (21.6)	106.1	6.5
Factor VIIc (%), median (IQR_w)	113.0 (33.0)	21.8	4
Fibrinogen (mg/dL), mean (SD)	286.4 (58.1)	19.3	3

CV, coefficient of variation

Factor VIIc, Factor VII coagulant activity

hs-CRP, high sensitivity C-reactive protein

IQR_W, interquartile range width

PAI-1, plasminogen activator inhibitor Type 1

$PM_{2.5}$, fine particles or particles less than 2.5 microns in diameter

NA, not applicable

SD, standard deviation

SWAN, Study of Women's Health Across the Nation

tPA-ag, tissue-type plasminogen activator antigen

[a] N may not add to total due to missing

[b] Percentages may not add to 100% due to rounding

[c] Average of the average for each visit that marker was analyzed

[d] Estimates from Thurston et al (2011) using CV associated with mean. Blood draws from Visit 0, Visit 1 and Visits 3-7 (except Factor VIIc and Fibrinogen had no analytes from Visits 4 and 6)

[e] Demographic characteristics at baseline (visit 0) are shown because all the women in the air pollution study attended that visit.

Table 2

Yearly averages of $PM_{2.5}$ and ozone by SWAN site and visit

	$PM_{2.5}$ ($\mu g/m^3$) Yearly Averages Visit					Ozone (ppb) Yearly Averages Visit				
Site Location	**3**	**4**	**5**	**6**	**7**	**3**	**4**	**5**	**6**	**7**
Detroit, MI	16.1	15.6	15.5	15.4	14.7	31.1	38.9	39.1	39.8	37.9
Chicago, IL	17.8	17.2	16.4	15.3	15.0	30.6	29.5	29.3	30.7	31.2
Oakland, CA	13.4	12.4	12.5	12.0	10.7	25.5	23.2	24.3	30.9	32.4
Los Angeles, CA	21.1	21.3	22.2	20.7	19.2	35.6	35.7	36.9	38.3	37.3
Hackensack, NJ[a]	16.0	16.6	15.1	-	-	36.3	35.0	36.2	-	-
Pittsburgh, PA	16.6	16.4	16.2	15.7	15.4	36.8	33.7	35.0	36.8	35.4

$PM_{2.5}$, fine particles or particles less than 2.5 microns in diameter

SWAN, Study of Women's Health Across the Nation

[a]Visits 6 and 7 censored from study

Table 3

Descriptive statistics for $PM_{2.5}$ and ozone by averaging time for Visits 3 to 7 for all SWAN sites in this study, 1999-2004

Pollutant	Averaging Time	Average # visits with hs-CRP, tPA-ag or PAI-1[a]	Average # visits with Factor VIIc and fibrinogen[b]	Mean	Standard Deviation	Maximum	Minimum	Interquartile range width
$PM_{2.5}$ ($\mu g/m^3$)								
	1 day	4,918	2,214	17.2	10.7	115.2	1.7	11.5
	30 days	7,016	3,323	15.9	5.5	43.7	3.9	6.6
	6 months	6,861	3,152	16.0	3.8	29.6	6.7	4.0
	1 year	6,361	2,724	16.4	3.4	26.1	7.7	4.1
Ozone (ppb)								
	1 day	4,100	1,827	35.2	17.2	122.0	2.0	24.0
	30 days	6,058	2,873	35.9	13.1	73.8	6.6	20.8
	6 months	5,516	2,587	34.3	9.7	71.4	9.9	16.2
	1 year	4,558	1,957	33.2	5.8	54.8	17.4	7.0

Factor VIIc, Factor VII coagulant activity

hs-CRP, high sensitivity C-reactive protein

PAI-1, plasminogen activator inhibitor Type 1

$PM_{2.5}$, fine particles or particles less than 2.5 microns in diameter

SWAN, Study of Women's Health Across the Nation

tPA-ag, tissue-type plasminogen activator antigen

[a] These biomarkers were systematically measured at every visit once per year.

[b] These biomarkers were only measured at visits 3, 5 and 7.

Table 4

Association of $PM_{2.5}$ and ozone with inflammatory/hemostatic markers[a]

	hs-CRP	tPA-ag	PAI-1	Factor VIIc	Fibrinogen
	% change (95% CI)	% change (95% CI)	% change (95% CI)	% change (95% CI)	β × 10 (95% CI)
$PM_{2.5}$ Averaging Time					
1 day	0.1 (−1.7, 1.9)	−1.7 (−2.6, −0.7)	−0.5 (−2.4, 1.4)	0.7 (−0.1, 1.5)	1.4 (−0.3, 3.1)
30 days	0.6 (−3.0, 4.3)	−2.4 (−4.2, −0.5)	0.7 (−3.0, 4.4)	1.2 (−0.2, 2.6)	3.5 (0.4, 6.6)
6 months	4.9 (−2.2, 12)	0.8 (−2.8, 4.5)	11 (3.4, 19)	−2.1 (−4.4, 0.4)	2.8 (−2.6, 8.2)
1 year	21 (6.6, 37)	8.6 (1.8, 16)	35 (19, 53)	−3.6 (−7.8, 0.8)	5.2 (−4.5, 15)
Ozone					
1 day	0.4 (−1.0, 1.8)	0.1 (−0.6, 0.9)	−1.1 (−2.5, 0.4)	−0.4 (−1.0, 0.1)	−0.4 (−1.6, 0.8)
30 days	−0.2 (−2.2, 1.7)	0.8 (−0.1, 1.8)	−0.6 (−2.5, 1.3)	−0.7 (−1.3, −0.0)	−1.0 (−2.5, 0.4)
6 months	3.2 (0.1, 6.5)	−1.4 (−2.9, 0.1)	−0.2 (−3.2, 2.9)	0.8 (−0.2, 1.9)	−1.8 (−4.1, 0.6)
1 year	0.4 (−6.9, 8.2)	3.4 (−0.3, 7.3)	−2.1 (−9.2, 5.5)	5.7 (2.9, 8.5)	0.6 (−5.2, 6.5)

CI, confidence interval

Factor VIIc, Factor VII coagulant activity

hs-CRP, high sensitivity C-reactive protein

PAI-1, plasminogen activator inhibitor Type 1

$PM_{2.5}$, fine particles or particles less than 2.5 microns in diameter

tPA-ag, tissue-type plasminogen activator antigen

[a]For all outcomes except fibrinogen (which was not log transformed), regression coefficients were back transformed using [100 × (exp (β *10) −1)] to calculate the percent change in the outcome associated with a 10 μg/m^3 change in $PM_{2.5}$ or a 10 ppb change in ozone. Absolute change in fibrinogen multiplied by 10 to correspond with a 10 unit air pollution change. Adjusting for time invariant variables: site, ethnicity, education; and time variant variables: smoking status, age, body mass index and alcohol use in the last 24 hours.