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Association between Gaseous Air Pollutants and Inflammatory, Hemostatic and Lipid Markers in a Cohort of Midlife Women

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Abstract

BACKGROUND—Exposures to ambient gaseous pollutants have been linked to cardiovascular diseases (CVDs), but the biological mechanisms remain uncertain.

OBJECTIVES—This study examined the changes in CVD marker levels resulting from elevated exposure to ambient gaseous pollutants in midlife women.

METHODS—Annual repeated measurements of several inflammatory, hemostatic and lipid makers were obtained from 2,306 midlife women enrolled in the longitudinal Study of Women's Health Across the Nation (SWAN) between 1999 and 2004. Ambient carbon monoxide (CO), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2) data were assigned to each woman based on proximity of the monitoring station to her residential address. Short- and long-term exposures were calculated, and their associations with markers were examined using linear mixed-effects regression models, adjusted for demographic, health and other factors.

RESULTS—Short-term CO exposure was associated with increased fibrinogen, i.e., every interquartile increase of average prior one-week exposure to CO was associated with 1.3% (95% CI: 0.6%, 2.0%) increase in fibrinogen. Long-term exposures to NO_2 and SO_2 were associated with reduced high-density lipoproteins and apolipoprotein A1, e.g., 4.0% (1.7%, 6.3%) and 4.7% (2.8%, 6.6%) decrease per interquartile increment in prior one-year average NO_2 concentration, respectively. Fine particle ($PM_{2.5}$) exposure confounded associations between CO/NO_2 and inflammatory/hemostatic markers, while associations with lipoproteins were generally robust to $PM_{2.5}$ adjustment.

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CONCLUSIONS—Exposures to these gas pollutants at current ambient levels may increase thrombotic potential and disrupt cholesterol metabolism, contributing to greater risk of CVDs in midlife women. Caution should be exercised in evaluating the confounding by $PM_{2.5}$ exposure.

Keywords

Cardiovascular; coagulation; fibrinolysis; carbon monoxide; nitrogen dioxide; sulfur dioxide; lipoprotein

Introduction

Cardiovascular diseases (CVDs) rank number one as the cause of death globally, accounting for about 30% of global deaths (World Health Organization, 2016). Many studies have observed associations between ambient gaseous pollutants and CVD morbidity. Carbon monoxide (CO) has been associated with hospital admissions and emergency department (ED) visits for ischemic heart disease (IHD), and congestive heart failure (CHF) (Lanki et al. 2006; Lee et al. 2007; Rosenlund et al. 2006; Szyszkowicz 2007). Consistent epidemiologic evidence has been reported for increases in incidence of myocardial infarction (MI) and IHD associated with exposure to nitrogen dioxide (NO_2) (Beckerman et al. 2012; Cheng et al. 2009; Lipsett et al. 2011; Rosenlund et al. 2009). Positive associations have also been found for ambient sulfur dioxide (SO_2) concentrations with ED visits and hospital admissions due to CVDs (Guo et al. 2010; Ito et al. 2011; Jalaludin et al. 2006), while some studies have observed negative associations (Chang et al. 2005; Llorca et al. 2005) or results were confounded by co-pollutants (Ballester et al. 2006). Based on an extensive literature review, the United States Environmental Protection Agency (USEPA) concluded that a likely or probable causal relationship existed between short-term exposure to these gases and CVD, but evidence was limited and inconclusive for long-term exposure (USEPA 2008USEPA 2010USEPA 2016).

While evidence for associations between gas exposure and CVDs has been increasing, the mechanisms behind the associations are not fully understood. Previous studies have proposed that CO and NO_2 may cause oxidative stress and airway inflammation, which could migrate to other parts of the body, resulting in systemic inflammation and coagulation and further to development of CVDs (Chuang et al. 2007; Delfino et al. 2008; Riedl et al. 2012). Further, SO_2 may cause oxidative stress to red blood cells and decrease blood viscosity (Baskurt et al. 1988). CO also enters the blood system and forms carboxyhemoglobin (COHb), which could trigger premature angina at high exposure levels (Allred et al. 1989). However, cardiovascular effects of gases at current ambient levels have not been confirmed (Channell et al. 2012; Li et al. 2011; Melin et al. 2005).

Researchers have identified a number of blood indices as CVD markers. Evaluation of these markers may help us better understand the relationship between gas exposures and CVD risks. Some studies have observed positive associations between short-term CO exposure and hs-CRP and fibrinogen (Delfino et al. 2009; Pekkanen et al. 2000), although the findings have been inconsistent across studies (Liao et al. 2005; Rückerl et al. 2007). Positive associations were also reported between short-term NO_2 exposure and hs-CRP (Dadvand et

al. 2014; Delfino et al. 2009), fibrinogen (Bind et al. 2012; Rich et al. 2012; Zhang et al. 2013), and thrombin (a coagulation marker) (Strak et al. 2013); however, the interpretation of these results has been uncertain due to potential confounding by co-pollutants, such as, CO and fine particles. A few studies have observed positive associations of short-term SO_2 exposure with hs-CRP and fibrinogen (Khafaie et al. 2013; Zhang et al. 2013), but results overall have been insufficient and inconsistent, with inadequate control for co-pollutants. Meanwhile, a number of studies have reported no associations of gaseous air pollutants with inflammatory markers (Baccarelli et al. 2007; Langrish et al. 2010; Rückerl et al. 2007; Rudez et al. 2009), and others found a negative association (Rudez et al. 2009; Steinvil et al. 2008). Very few studies have reported an association between ambient gas exposure and lipoproteins (USEPA 2008USEPA 2010USEPA 2016). Evidence about the impact of long-term exposure to these gases on these markers is more scarce and inconsistent (Dadvand et al. 2014; Forbes et al. 2009; Huang et al. 2014; Panasevich et al. 2009). More research is needed to provide additional evidence about the relationship between ambient gas exposure and inflammatory, hemostatic and lipid markers to reconcile the available findings.

The present study was thus conducted using CVD marker data available from the Study of Women's Health Across the Nation (SWAN), a longitudinal multi-site study designed to follow women through the menopausal transition (Sowers et al. 2000). Given the limited and inconsistent evidence mentioned above, we explored new evidence of the associations between exposure to ambient levels of three gaseous air pollutants, including CO, NO_2 and SO_2, and a number of inflammatory, hemostatic and lipid markers, to understand the mechanism and time frame of the adverse cardiovascular effects of each gas.

Methods

Study population

The study design and participant recruitment for SWAN has been previously described in detail (Sowers et al. 2000). The present study included data from six sites: Detroit, Michigan; Chicago, Illinois; Oakland, California; Los Angeles, California; Newark, New Jersey; and Pittsburgh, Pennsylvania. Between 1995 and 1997, SWAN recruited women who were 42 to 52 years of age, had an intact uterus and at least one ovary, were not using exogenous hormones, were not pregnant or lactating, and had at least one menstrual period in the previous three months. Multiple racial/ethnic groups were included, with Caucasians enrolled at every site and African Americans enrolled at three of these six sites and Hispanics, Chinese and Japanese recruited at one site each. Approximately 450 eligible women were recruited at each study site and have been followed up with clinical assessments and questionnaire interviews on a nearly annual basis. The SWAN protocols were approved by the Institutional Review Boards at all participating sites, and all participants provided written informed consent at baseline. The present analyses were based on participants with serum samples collected at SWAN visits 3 through 7 (1999–2004), when both $PM_{2.5}$ measurements and the blood markers of interest were available.

Air pollutant data

Ambient CO, NO_2 and SO_2 data were obtained from the USEPA air monitoring network. The gases were monitored on an hourly basis. The data downloaded were maximum 8-hour average concentrations for CO and one-hour maximum concentrations for NO_2 and SO_2. Fine particles up to 2.5 micrometers in size ($PM_{2.5}$) were a potential confounder of these analyses. $PM_{2.5}$ was typically measured every three days, sometimes daily or every six days, and data were in the format of 24-hour average concentrations. Data for the entire U.S. were downloaded from USEPA's Air Data website (https://www.epa.gov/airquality/airdata, accessed September 2010).

A residential history was maintained for each participant from the baseline visit to visit 7. The coordinate of each residence was geocoded and randomly moved up to 400 feet (about one block) to ensure confidentiality. We created 20 km circular buffer areas around each address using ArcGIS v10.0 (Environmental Systems Research Institute 1995–2016) and assigned exposures for participants within 20 km of monitors. If a participant moved (~13% of all women) during the year prior to her visit, exposure data from multiple addresses were weighted based on the time of move when assigning exposure, or evenly weighted if the move date was not available. More details about exposure assignment can be found in Green et al. (2016).

We calculated average exposure levels for one day, one week, one month, six months, and one year prior to each blood draw. Because $PM_{2.5}$ measurements started in 1999, no matched one-year exposure data were available for some SWAN visits in 1999 and 2000. We, therefore, calculated the six-month average exposure to make use of more biomarker data, and expected similar associations observed for six-month and 1-year average exposures. Month was simplified to 30-day increments, six months to 180 days, and one year to 360 days. A minimum of three daily readings were required to qualify for the one-week exposures; at least nine daily readings were required for the one-month exposures; at least five months were required for the six-month averages; and at least ten months were required for the one-year averages. Otherwise, the specific exposure metric was considered missing. In over 95% of the cases, average exposures were calculated based on daily readings of >80% of exposure duration. We classified the exposure windows as short-term (the prior one-day, one-week, and one-month averages) and long-term (the prior six-month and one-year averages).

Blood measurement and analysis

Blood was drawn at each SWAN clinic visit and assayed for CVD markers as described previously (Green et al. 2016; Thurston et al. 2012). Inflammatory/hemostatic markers examined in this study included high-sensitivity C-reactive protein (hs-CRP), fibrinogen, factor VII coagulant (factor VIIc), tissue-type plasminogen activator antigen (tPA-ag), and plasminogen activator inhibitor Type 1 (PAI-1). When damage occurs to the endothelium of the blood vessels, fibrinogen and factor VIIc help in forming blood clots; tPA activates the fibrinolytic system to break down blood clots; PAI-1 is the major inhibitor of tPA by converting tPA into tPA-PAI-1 complex (Chandler et al. 1997).

We examined lipoproteins that have been linked to CVD risk (Burnett 2004; Kaptoge et al. 2012; Lowe et al. 2004; Smith et al. 2005). These included high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), triglycerides, and total cholesterol, as well as lipoprotein(a) (Lp(a)) and lipoprotein A1 (LpA1). We also assessed apolipoprotein A1 (APOA1) and B (APOB). APOA1 is the primary protein component of HDL and APOB is the major protein component of all other lipoproteins. HDL-related lipoproteins, including HDL, LpA1 and APOA1, are considered to have protective effects on risk for CVDs (Navab et al. 2011), while elevated levels of LDL increases risk of CVD, as does Lp(a), which is an LDL-like particle that is involved in inhibition of fibrinolysis (Nordestgaard et al. 2010).

The majority of markers were measured at each visit, except fibrinogen, Factor VIIc, and LpA1 that were measured only at every other follow-up (Visits 3 and 5) in all women and in a subset of women at visit 7.

Statistical analysis

Summary statistics were calculated for each gas and CVD marker. Marker levels were log-transformed to better meet the normality assumption. Correlations between markers as well as between air pollutants were calculated based on visit 3 data, which has the largest sample size among the visits included.

To study the association between air pollutants and CVD markers, we applied linear mixed-effects regression models with marker concentration as a continuous dependent variable. Each gas metric was included in single-pollutant models along with the visit number. Site was included as a fixed effect, because participants were nested within site. As multiple longitudinal measurements collected from each woman may have been correlated, a random intercept was used to account for the covariance of measurements nested within the same participant. First-order ante-dependence structure was specified for the repeated measurements from each participant (Zimmerman and Núñez-Antón 1997).

In our statistical models, we evaluated a variety of factors for potential confounding, including study site, race/ethnicity, education (high school or less, some college, or college graduate), in addition to the following visit-specific time-varying variables: age at the blood draw (continuous), menopausal status (pre- / early peri- / late peri- / post- / unknown), body mass index (BMI), hormone use (yes/no), active smoking (yes/no) and alcohol consumption in the 24 hours before the blood draw (yes/no). We started with a full model including all covariates and performed a backward elimination of the variables based on statistical significance and Akaike Information Criterion (AIC) value, which allowed us to control for confounding without adding overfitted covariates.

Values of hs-CRP greater than 10 mg/L (9.9% of all observations) were excluded as they may indicate severe infection, major trauma, or chronic inflammatory diseases. For all other markers, values were excluded if they were outside the mean ± 3 times the standard deviations (0.02%-8.2% of observations, varied by markers). Eleven woman-visits conducted after major CVD events, including myocardial infarction, coronary heart failure, stroke, percutaneous coronary intervention and coronary artery bypass graft, were excluded

from the analyses. We also censored the New Jersey data for visit 6 and 7, because only a few participants from that site had data for those two visits. Given the concern over the confounding by diabetes, we included women diagnosed with diabetes in the main analysis but excluded them in a sensitivity analysis.

Using the same data set, Green et al. (2016) reported that $PM_{2.5}$ exposure was associated with levels of hs-CRP, fibrinogen, tPA-ag, and PAI-1. Therefore, we further estimated the associations between each gas exposure and CVD markers adjusting for $PM_{2.5}$ exposure in the same time window (except for one-week window, one-week average $PM_{2.5}$ exposure was not calculated given the $PM_{2.5}$ measurement interval, one-month average $PM_{2.5}$ exposure was used as a substitute). For CO and SO_2, we used two-pollutant models incorporating each of these gases and $PM_{2.5}$ concentrations simultaneously. For NO_2, which was usually highly correlated with $PM_{2.5}$ concentrations, we used a residual analysis to avoid potential collinearity (Bell et al. 2007). As illustrated by the equations below, we predicted $PM_{2.5}$ concentrations by NO_2 concentrations and calculated the residual of $PM_{2.5}$ (r_{pm}), in which r_{pm} and NO_2 concentrations were not correlated. The NO_2 concentration and r_{pm} were entered into the regression model simultaneously with other covariates to estimate marker levels. This procedure was repeated to calculate the residual of NO_2 (r_{NO2}).

$$\mathrm{PM}_{2.5} \sim \mathrm{NO}_2 + r_{pm} \quad \text{CVD marker} \sim \mathrm{NO}_2 + r_{pm} + \text{other covariates}$$

$$\mathrm{NO}_2 \sim \mathrm{PM}_{2.5} + r_{NO2} \quad \text{CVD marker} \sim \mathrm{PM}_{2.5} + r_{NO2} + \text{other covariates}$$

If we found consistent results for NO_2 concentrations and r_{NO2}, we concluded NO_2 results were robust even after controlling for $PM_{2.5}$. Otherwise, the association with NO_2 observed in the base model could have been confounded by $PM_{2.5}$ exposure or other unknown factors. If the $PM_{2.5}$ concentration and r_{pm} were both associated with the outcome in each model, $PM_{2.5}$ exposure was considered to have an association with that particular marker. Only visits 3–7 with matched $PM_{2.5}$ concentrations were included in the analysis, so that the results of single-pollutant models can be compared with those adjusted for $PM_{2.5}$ exposure.

As a sensitivity test, we also examined confounding between gases. Based on the correlation between individual gases, either a two-pollutant model or the residual model was used.

All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC). All tests were two-sided and p-values < 0.05 were considered statistically significant.

Results

Distribution of CVD marker levels

A total of 2,280 women had up to five annual visits between 1999 and 2004. Based on multiple-visit data, we observed that women with higher education levels, lower BMI, and who were premenopausal or early perimenopausal had lower levels of inflammatory and hemostatic markers as well as higher levels of HDL-related lipoproteins and lower levels of

LDL-related lipoproteins and triglycerides (Table 1). Race/ethnicity, smoking, consuming alcohol, and having pre-existing conditions were all related to CVD marker levels.

As expected, some CVD markers were correlated (Table S1). Two inflammatory markers, hs-CRP and fibrinogen, were moderately correlated (Pearson correlation coefficient (r) = 0.46). PAI-1 was correlated with tPA-ag (r = 0.54), and both were positively correlated with triglycerides but negatively correlated with HDL. Lipoproteins were correlated with each other, with highly positive correlations between LDL, APOB and total cholesterol (r = 0.80–0.88) as well as between HDL, LpA1 and APOA1 (r = 0.71–0.80).

Distribution of air pollutant levels

The gas concentrations were similar for different exposure windows; thus, only the prior-day and one-year average gas concentrations, which represented short- and long-term exposures, respectively, are shown stratified by study site (Table 2). For most of the locations, over 75% of the serum samples had matched gas exposure data. Both CO and NO_2 concentrations were higher in Los Angeles and Newark than the other four sites. SO_2 concentrations were remarkably lower in the two California sites than non-California sites, with the highest levels in Detroit.

The CO and NO_2 concentrations matched by exposure window were moderately to highly correlated (r = 0.61–0.78) (Table S2). NO_2 concentrations were also correlated with $PM_{2.5}$ concentrations for the same exposure window (r = 0.39–0.70), while CO was less correlated with $PM_{2.5}$ (r = 0.25–0.41). The SO_2 concentrations were weakly correlated with other gases or $PM_{2.5}$ (r = −0.26–0.36).

Associations between air pollutants and CVD markers

Final regression models between gases and CVD markers were adjusted for study site, race/ethnicity and education, and time-varying visit number, menopausal status, BMI, hormone use, active smoking, and alcohol consumption in the 24 hours prior to blood draw. The associations were expressed as the percent change in marker levels per interquartile increase in the concentration of a gas pollutant, which was 0.68 ppm for CO, 13 ppb for NO_2, and 15 ppb for SO_2. The associations observed for the previous 1-day, 1-week and 1-month exposure windows followed the same trend, as did the previous 6-month and 1-year exposure windows; therefore, results of 1-week and 1-year exposure windows were presented as examples of short- and long-term effects, respectively (Table 3, full results can be found in Table S3–S5).

Short-term exposure to CO and NO_2 were positively associated with fibrinogen and factor VIIc, but negatively associated with tPA-ag (Table 3). For example, an interquartile increase in the one-month average concentrations of CO and NO_2 was associated with 1.3% (95% confidence interval: 0.5%, 2.1%) and 1.4% (0.4%, 2.3%) increases in fibrinogen levels, respectively. After adjusting for $PM_{2.5}$, associations with CO became weaker and the residuals of NO_2 were not statistically significant (Figure 1a). Also, the negative associations of tPA-ag with short-term exposure of CO and NO_2 were confounded by $PM_{2.5}$. $PM_{2.5}$ had associations with fibrinogen, factor VIIc, and tPA-ag in the same direction as NO_2 and with similar magnitude, but the residuals of neither NO_2 nor $PM_{2.5}$ met statistical

significance in most of the cases, making it difficult to differentiate the associations of NO_2 and $PM_{2.5}$ exposures with the markers. In a few cases, $PM_{2.5}$ exposures showed stronger associations than NO_2. Long-term exposure to NO_2 was positively associated with PAI-1, with a 12.4% (-0.1%, 26.6%) increase of PAI-1 levels per an interquartile increase in average prior one-year NO_2 concentration, but this association was also confounded by $PM_{2.5}$ (Figure 1b). Exposure to SO_2 was generally not statistically associated with inflammatory or hemostatic markers we examined, except for a negative association between six-month SO_2 exposure and fibrinogen.

For lipoproteins, long-term exposures to NO_2 and SO_2 were strongly associated with reduced HDL-related lipoproteins (Figure 1c). An interquartile increment of the one-year average NO_2 concentration was associated with an average 4.0% (1.7%, 6.3%) decrease of HDL and 4.7% (2.8%, 6.6%) decrease of APOA1. These negative associations were also observed for six-month and one-week average concentrations of SO_2. Meanwhile, every interquartile increase of the six-month average SO_2 concentration was associated with a 1.9% (0.5%, 3.3%) increase of APOB. SO_2 exposure was also associated with increases in LDL and Lp(a) (Table S5). Short-term CO and NO_2 exposures were associated with increased HDL and decreased triglycerides (Table 3). Results on lipoproteins remained robust or became stronger after adjusting for $PM_{2.5}$.

The sensitivity analysis excluding women diagnosed with diabetes obtained basically same results with stronger statistical significance. Another sensitivity test on the confounding between gases suggested consistent associations with those observed in the single-pollutant models.

Discussion

The multi-site SWAN cohort provided valuable data on a large sample of midlife women to explore the associations between ambient gases and a number of CVD markers while adjusting for covariates. We observed increased levels of fibrinogen associated with short-term CO exposure. Short-term exposure to NO_2 was positively associated with fibrinogen and factor VIIc but negatively associated with tPA-ag, although some associations were difficult to differentiate from the associations with $PM_{2.5}$. These findings suggested increased inflammation and coagulation but suppressed fibrinolysis in association with NO_2 and/or CO. Occurring simultaneously, these gases may increase the risk of thrombosis. Altered vascular reactivity and reduced blood flow may eventually lead to myocardial ischemia and other CVDs (Davies and Thomas 1984). In addition, long-term gas exposures have the potential to lower the “good cholesterol” and increase the “bad cholesterol”. Together, these results suggest ambient gas exposures increase the potential of inflammation and thrombosis and disrupt cholesterol balance, which may further increase the risk of myocardial infarction or other CVDs.

As mentioned earlier, previous findings regarding the associations between short-term gas exposure and inflammatory/hemostatic markers have been inconsistent. For example, Delfino et al. (2009) studied elderly individuals in Los Angeles and found that daily exposure to CO and NO_2 were positively associated with hs-CRP. Bind et al. (2012) found

that an IQR increase in one-day exposure to NO_2 was associated with 1.7% (95% CIs: 0.2, 3.3) increase in fibrinogen but not with hs-CRP, also among elderly men. Based on a large midlife cohort from four centers in the U.S., Liao et al. (2005) did not observe statistically significant association between short-term exposure (1–3 days prior) to CO, NO_2 and SO_2 and fibrinogen. In our study, no statistically signficant association was observed between gas exposure in any window and hs-CRP levels. However, fibrinogen was associated with one-week and one-month exposure to CO and NO_2, which provides evidence that short-term exposure to CO and NO_2 increases the tendency of inflammation.

Only a few studies were available regarding the associations between long-term exposure to the gases and inflammatory/hemostatic markers, with mixed results. Some studies found CO and carboxyhemoglobin (COHb) (a CO product) were positively associated with hs-CRP (Davutoglu et al. 2009; Huang et al. 2014). Panasevich et al. (2009) observed positive but not significant associations of hs-CRP with long-term exposures to CO, NO_2 and SO_2 up to 30 years, but not for fibrinogen or PAI-1. In contrast, two studies found no association between annual average NO_2 or SO_2 and CRP or fibrinogen (Dadvand et al. 2014; Forbes et al. 2009). Our study supports null associations between long-term gas exposure and inflammation/hemostatic markers, except the unexplained negative association between six-month SO_2 exposure and fibrinogen.

Information from prior studies on the relations of ambient gases with lipid markers were even more scarce. Among an elderly population in Taiwan, Chuang et al. (2011) found one-year average NO_2 concentrations were associated with elevated total cholesterol but confounded by $PM_{2.5}$, and no changes were due to exposure to SO_2. Similarly, no stable association with total cholesterol was observed in our study. Instead, we found negative associations between HDL and long-term NO_2 and SO_2 exposure, as well as increased APOB with six-month SO_2 exposure. Both indicate greater risks of CVDs. Furthermore, we observed negative associations of short-term exposures to all gases with triglycerides, which could be confounded by recent diet, although fasting blood samples were used. We note that levels of triglycerides increased as the women entered menopause (Derby et al. 2009), while the gas levels decreased over time during our follow-up period. This may have led to elevated levels of triglycerides at lower gas exposures.

One strength of our study is that multiple exposure windows were examined, shedding light on the time frame required for the body's responses to ambient gas exposure. Previous studies mostly focused on short follow-up times, with lags from hours to several days. USEPA (2010) summarized that CVD outcomes due to CO exposure usually occurred within three days after exposure. Dadvand et al. (2014) found that the associations between NO_2 and inflammatory markers were strongest at lags of 4–5 days but not at lags of 0–2 days. Bind et al. (2012) studied exposure window from hours to a moving average of 28-day lag and found a positive association between CO/NO_2 and fibrinogen from a 1- to a 28-day lag. In the present study, we covered the exposure windows from day and year scales. Given the short half-life of CO in the environment, the associations with markers we examined were mostly observed in short-term exposure windows up to one-month. NO_2 and SO_2 influence human health not only in gas form but also by forming secondary particles, which are temporally more stable, and the associations with CVD markers were observed in both

short- and long-term exposure windows. From the perspective of markers, the inflammatory and hemostatic markers, such as fibrinogen and tPA-ag, responded to gas exposures in all short-term windows we examined from prior one-day to one-month. Repeated inflammation and thrombosis raise the risk of developing chronic cardiovascular outcomes, such as, atherosclerosis (Pearson et al. 2003). In contrast, for lipoproteins, adverse associations were observed for long-term exposure and thus demonstate the long-term impact of ambient gas exposure. Greater variations were observed for apolipoproteins, APOA1 and APOB, than the traditional lipid profile, indicating that they were more sensitive to gas exposure.

We also considered the confounding by $PM_{2.5}$ while evaluating the health impacts of gaseous pollutants. Previous studies showed that the associations of CO with health outcomes generally remained robust in co-pollutant models (USEPA 2010), but for NO_2 and SO_2, such associations of each gas have not been clearly defined with co-pollutants controlled due to potential collinearity issue. Across our analyses with all three gaseous pollutants, $PM_{2.5}$ appeared consistently associated with reduced tPA-ag level in short-term exposure windows as well as increased PAI-1 in long-term exposure windows, indicating risks of thrombosis. We used a residual analysis for NO_2 to avoid collinearity, and found that $PM_{2.5}$ confounded the associations between CO/NO_2 and several inflammatory/hemostatic markers (Table S3–S4). The 1-year average $PM_{2.5}$ exposure was associated with decreased HDL and APOA1; however, the associations between gases and lipoproteins were generally robust and were not confounded by $PM_{2.5}$ exposure.

This study had several limitations to be considered when interpreting the results. First, using the regulatory monitoring network with a 20 km buffer may have introduced exposure misclassification, and thus the ambient gas exposures we obtained were only approximations of personal exposure. The 20 km buffer was selected by taking into consideration the impacts of sample size, exposure misclassification, and population characteristics. By using a larger buffer, we obtained similar exposure estimates to those from the 10 km buffer but a 2–3 times increased sample sizes. A bigger buffer distance also enabled us to keep a diverse population, because areas close to monitors where sources are usually located tend to be low socioeconomic communities (Ebisu et al. 2014). Furthermore, we tracked the changes of participants' home addresses, which maximized accuracy of the exposure estimation.

Secondly, some known cardiovascular risk factors were not considered in this study, such as traffic noise, ultrafine particles, and ozone. As a result of incomplete combustion from traffic, CO may serve as a marker of freshly emitted ultrafine particles, which are considered more toxic than $PM_{2.5}$ (Araujo and Nel 2009). Both CO and NO_2 are involved in ozone formation, and ozone has been shown to affect cardiovascular health (Hoffmann et al. 2012). Future studies with consideration of these factors are warranted. Third, although the SWAN data included many covariates, some potential confounding factors were not included due to the incompleteness of data, e.g., dietary intake and physical activity, which might have resulted in residual confounding. Finally, in this study, participants were recruited with a series of selection criteria and not randomly selected; therefore, the study population may not be representative of the general US female midlife population.

Conclusions

In summary, this study provides valuable additions to the current literature on the associations between ambient gaseous pollutants and CVD markers. Our results suggest that short-term ambient exposures to CO and NO_2 may increase the potential for thrombosis and exposure to NO_2 and SO_2 may affect cholesterol metabolism, suggesting that ambient gas at normally observed level could pose additional CVD risks. One should also be cautious of the confounding of $PM_{2.5}$ exposure on the associations between CO/NO_2 and inflammatory/hemostatic markers, while the associations between gases and lipoproteins were generally robust to $PM_{2.5}$ exposure adjustment.

This study was conducted among midlife women who normally have not been considered as a sensitive population. The disrupted cholesterol levels and increasing vascular inflammation due to menopause make this population more vulnerable to environmental factors that may affect CVD risks. The air pollutant levels below the NAAQS could cause inflammation and coagulation as well as changes in their lipoprotein levels, posing additional cardiovascular burden beyond the impact of menopause.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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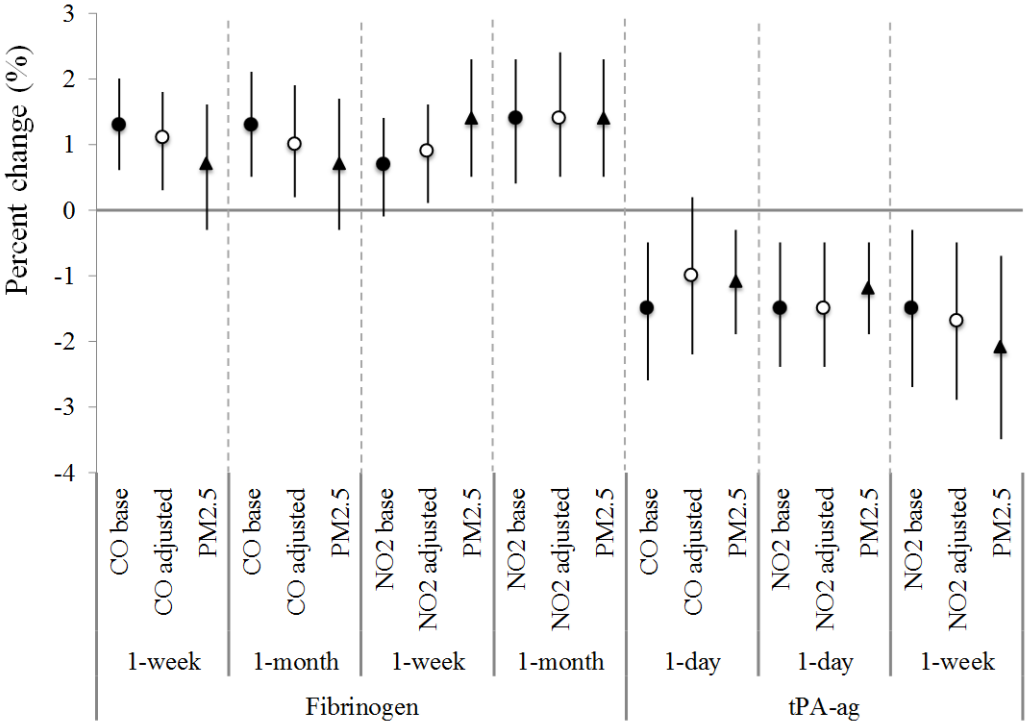
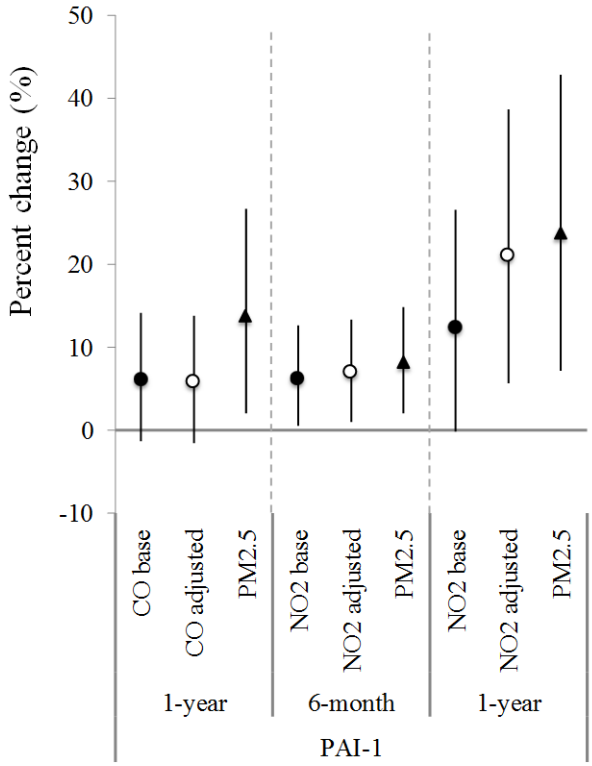
Highlights

- We examined the associations between CVD markers and ambient gases.
- Short-term CO exposure was associated with increased levels of coagulation markers.
- Long-term exposures to NO_2 and SO_2 were associated with reduced HDL and APOA1.
- $PM_{2.5}$ exposure confounded associations between CO/NO_2 and hemostatic markers.
- Exposure to ambient gases at current NAAQS may increase CVD risks in midlife women.





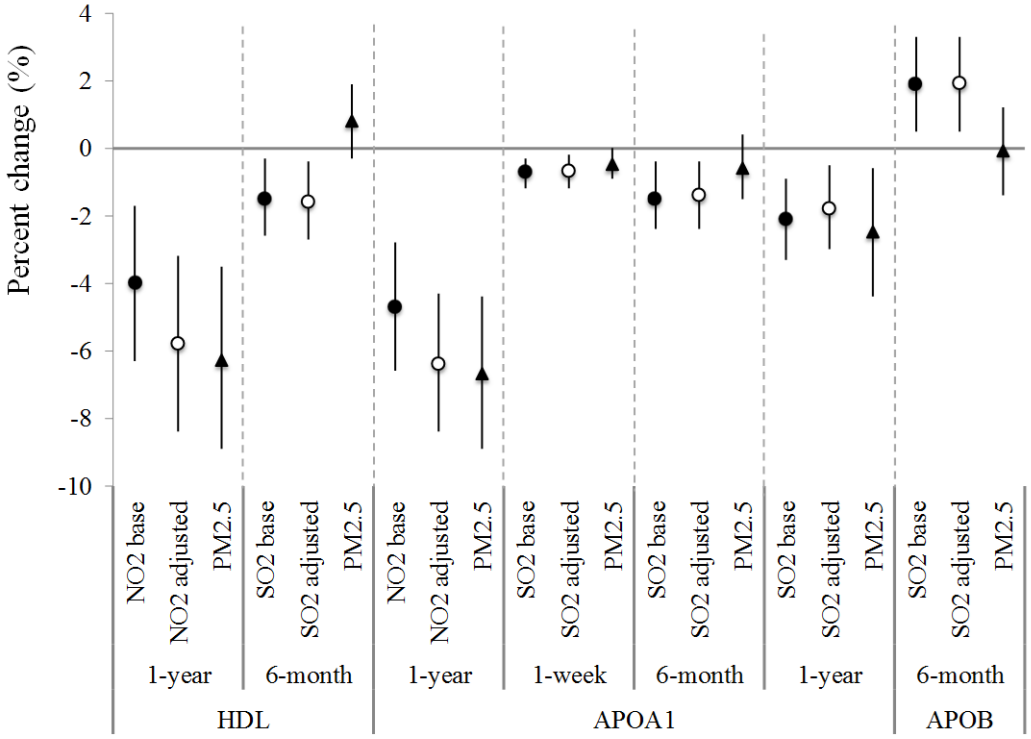


Figure 1.

The association between gas exposure and selected CVD markers in selected exposure windows, before and after adjustment of $PM_{2.5}$ exposure for SWAN cohort, 1999–2004. (Dots/circles/triangles are percent of change in the levels of markers per interquartile increase of exposure, and error bars are 95th% of confidence intervals. Dots - CO / NO_2 / SO_2 base – the change of the gas in the single-pollutant model with one gas only; circles - CO / NO_2 / SO_2 adj by PM – the change of the gas in the two-pollutant model with one gas and $PM_{2.5}$; triangles - PM2.5 – the change of $PM_{2.5}$ in two-pollutant model)

Table 1

Distribution of inflammatory, hemostatic and lipid biomarkers by demographic factors for SWAN cohort, 1999–2004[a]

Variable		N[b]	hs-CRP	Fibrinog en	Factor VIIc	TPA-ag	PAI-1	HDL	LDL	Triglyceri des	Total Choleste rol	Lp(a)	LpA1	APOA1	APOB
(unit)			mg/L	mg/dl	%	ng/ml	ng/ml	mg/dl	mg/dl	mg/dl	mg/dl	mg/dl	mg/dl	mg/dl	mg/dl
N of samples			7951	4039	3930	8382	8309	8902	8549	8665	8900	8386	4432	8761	8683
All participants		2280	1.4 (3.0)	267 (70)	119 (35)	7.0 (4.3)	14 (19)	57 (21)	115 (42)	105 (75)	199 (48)	16 (36)	52 (19)	167 (38)	108 (37)
Race/Ethnicity	African American	26%	2.5 (4.1)	292 (78)	117 (37)	7.8 (4.6)	17 (20)	54 (18)	116 (44)	99 (62)	193 (48)	38 (54)	50 (17)	160 (36)	107 (36)
	Chinese	10%	0.7 (1.1)	262 (58)	118 (31)	6.2 (3.8)	12 (17)	61 (20)	112 (38)	106 (73)	201 (46)	9 (19)	57 (19)	173 (35)	107 (35)
	Hispanic	11%	2.4 (3.8)	279 (74)	117 (35)	8.7 (4.1)	21 (22)	49 (17)	117 (41)	122 (84)	198 (48)	16 (32)	46 (17)	155 (36)	115 (39)
	Japanese	7%	0.5 (1.1)	242 (61)	118 (34)	6.3 (3.6)	10 (16)	62 (20)	117 (42)	109 (77)	205 (45)	12 (20)	55 (18)	175 (34)	111 (35)
	White	46%	1.6 (3.0)	267 (62)	122 (37)	6.8 (4.1)	13 (20)	57 (21)	115 (43)	108 (82)	199 (48)	11 (29)	52 (18)	167 (38)	108 (37)
Education	<12 yrs	24%	1.7 (3.4)	279 (87)	121 (36)	7.4 (4.6)	16 (21)	54 (18)	116 (42)	113 (84)	198 (47)	20 (42)	50 (19)	163 (36)	110 (37)
	some college	33%	1.7 (3.2)	267 (70)	121 (34)	7.3 (4.3)	15 (20)	56 (20)	117 (42)	108 (75)	200 (48)	18 (41)	51 (19)	166 (40)	111 (38)
	college graduated/post grad	43%	1.2 (2.5)	262 (66)	119 (37)	6.5 (4.1)	12 (18)	59 (21)	113 (42)	100 (70)	198 (47)	13 (31)	53 (18)	169 (38)	106 (35)
Menopausal status	Pre	510	1.4 (2.6)	262 (66)	115 (37)	6.8 (4.3)	15 (20)	53 (21)	111 (38)	99 (68)	189 (38)	12 (30)	50 (18)	161 (37)	106 (36)
	Early peri	3419	1.2 (2.5)	267 (66)	115 (31)	6.9 (3.9)	14 (19)	56 (19)	111 (39)	98 (68)	192 (44)	16 (36)	52 (18)	163 (35)	105 (35)
	Late peri	917	1.4 (3.1)	273 (74)	123 (38)	7.4 (4.5)	17 (23)	57 (21)	122 (44)	109 (85)	206 (51)	19 (43)	51 (18)	167 (38)	112 (39)
	Post	3022	1.5 (3.4)	273 (74)	125 (38)	7.1 (4.7)	14 (19)	58 (21)	121 (45)	113 (77)	206 (49)	17 (36)	52 (19)	170 (40)	112 (38)
	Unknown	1050	1.8 (3.5)	262 (62)	123 (39)	6.5 (4.0)	11 (16)	59 (22)	112 (42)	112 (80)	199 (47)	12 (33)	52 (19)	173 (41)	109 (37)
BMI (kg/m^2)	<25, normal/under	3294	0.6 (1.0)	251 (57)	112 (31)	5.3 (3.2)	8.1 (10)	65 (21)	111 (40)	90 (50)	197 (46)	12 (25)	57 (19)	177 (36)	101 (33)
	25–29.9, overweight	2414	1.6 (2.4)	267 (62)	124 (37)	7.0 (3.6)	14 (17)	56 (19)	118 (42)	112 (81)	201 (47)	15 (35)	51 (18)	166 (36)	111 (38)
	≥30, obese	2998	3.7 (4.2)	292 (72)	125 (37)	8.8 (4.1)	23 (24)	50 (16)	118 (44)	124 (92)	198 (49)	22 (47)	48 (16)	157 (33)	113 (38)
Current smoker	Yes	1126	2.0 (3.5)	292 (83)	118 (34)	7.9 (4.4)	18 (23)	52 (19)	117 (45)	117 (85)	197 (50)	21 (45)	48 (18)	161 (40)	113 (41)
	No	7563	1.3 (2.9)	267 (66)	120 (36)	6.8 (4.2)	13 (18)	58 (21)	115 (42)	104 (74)	199 (47)	15 (34)	52 (19)	167 (38)	107 (36)
Alcohol in last 24 hours	Yes	1285	1.2 (2.2)	251 (64)	117 (36)	6.8 (4.3)	13 (17)	65 (22)	113 (43)	94 (63)	200 (47)	13 (37)	56 (18)	180 (38)	106 (36)
	No	7520	1.5 (3.1)	273 (70)	120 (34)	7.0 (4.3)	14 (19)	56 (19)	116 (42)	107 (76)	198 (47)	16 (36)	51 (19)	165 (37)	109 (37)

Variable		N[b]	hs-CRP	Fibrinog en	Factor VIIc	TPA-ag	PAI-1	HDL	LDL	Triglyceri des	Total Choleste rol	Lp(a)	LpA1	APOA1	APOB
(unit)			mg/L	mg/dl	%	ng/ml	ng/ml	mg/dl	mg/dl	mg/dl	mg/dl	mg/dl	mg/dl	mg/dl	mg/dl
N of samples			**7951**	**4039**	**3930**	**8382**	**8309**	**8902**	**8549**	**8665**	**8900**	**8386**	**4432**	**8761**	**8683**
Hormone use since last visit	Yes	1719	1.9 (3.6)	262 (58)	123 (41)	6.2 (4.0)	11 (14)	60 (22)	112 (40)	115 (80)	200 (45)	12 (30)	54 (19)	177 (40)	108 (36)
	No	7201	1.3 (2.8)	267 (70)	119 (34)	7.1 (4.4)	15 (21)	56 (20)	116 (42)	103 (74)	198 (48)	17 (38)	51 (18)	164 (37)	108 (37)
diagnosed diabetes	Yes	704	4.2 (4.7)	300 (89)	131 (35)	9.1 (4.4)	26 (29)	46 (15)	112 (44)	159 (127)	194 (52)	23 (50)	48 (15)	155 (34)	116 (43)
	No	8229	1.3 (2.8)	267 (66)	119 (35)	6.8 (4.2)	13 (18)	58 (21)	116 (42)	103 (70)	199 (47)	15 (35)	52 (19)	168 (38)	108 (35)
Any cardio-vascular event	Yes	104	2.8 (3.6)	308 (72)	135 (30)	8.6 (5.1)	20 (32)	50 (19)	121 (51)	155 (125)	200 (64)	24 (38)	51 (14)	156 (33)	115 (47)
	No	8832	1.4 (2.9)	267 (70)	119 (35)	6.9 (4.3)	14 (19)	57 (21)	115 (42)	105 (74)	199 (48)	16 (36)	52 (19)	167 (38)	108 (36)

[a]Data shown in each grid is median (interquartile range).

[b]For ethnicity/education, the % show in this column are the percentage of participants in each category among all participants. For the visit-specific variables, N is the number of observations, not women; each participant could have data from multiple visits, and could be in different categories at different visits. Sample size varied by biomarkers. Visits without any blood data (N=69) or any matched exposure data (N=5147) were excluded. Visits 6 and 7 in New Jersey site (N=55) were censored due to small sample size. Visits happened after any CVD events (N=11 from 4 participants) were excluded. Marker values out of reasonable ranges (0.02–8.2% varied by markers) were excluded. For hs-CRP, values greater than 10 mg/L (N=863) were not included due to the concern of possible severe inflammation.

Table 2

Distribution of prior one-day and one-year average CO, NO_2, and SO_2 concentrations by SWAN site, 1999–2004

	1-day average concentration						1-year average concentration					
site	**N**	**% *a***	**Mean**	**SD**	**Median**	**IQR**	**N**	**% *a***	**Mean**	**SD**	**Median**	**IQR**
CO (ppm)												
Detroit, MI	758	45	0.58	0.39	0.50	0.40	791	47	0.61	0.16	0.56	0.10
Chicago, IL	1096	77	0.95	0.48	0.90	0.60	1141	80	0.98	0.21	0.96	0.40
Oakland, CA	1670	95	0.90	0.54	0.80	0.70	1674	95	0.95	0.19	0.92	0.31
Los Angeles, CA	1908	95	1.19	1.07	0.80	1.00	1957	97	1.55	0.40	1.43	0.54
Newark, NJ	366	69	1.72	0.86	1.60	1.00	394	75	1.82	0.50	1.79	0.59
Pittsburgh, PA	1333	87	0.99	0.58	0.90	0.80	1462	95	1.02	0.34	1.01	0.64
NO_2 (ppb)												
Detroit, MI	647	39	39.6	17.2	39.0	16.0	607	36	39.1	2.6	39.6	3.2
Chicago, IL	1063	74	40.8	13.0	40.0	18.0	1083	76	39.8	2.1	39.1	2.8
Oakland, CA	1506	86	31.9	13.7	32.0	19.0	1524	87	31.2	2.7	31.4	3.4
Los Angeles, CA	1913	95	44.7	18.5	43.0	19.0	1962	98	48.1	4.3	47.8	5.4
Newark, NJ	374	71	50.7	14.6	50.0	18.0	402	76	49.4	3.9	49.2	6.0
Pittsburgh, PA	1448	94	37.4	12.5	37.0	18.0	1484	97	37.4	3.8	37.6	3.0
SO_2 (ppb)												
Detroit, MI	721	43	24.6	26.5	15.0	33.0	745	44	24.7	4.2	24.6	5.6
Chicago, IL	1295	91	17.6	18.2	12.0	16.0	1360	95	18.0	7.8	15.3	15.5
Oakland, CA	1055	60	4.5	4.1	3.0	4.0	1046	60	4.5	0.9	4.3	0.9
Los Angeles, CA	1851	92	7.5	7.8	6.0	7.0	1910	95	7.5	2.5	8.2	3.2
Newark, NJ	440	83	20.0	13.2	17.0	15.0	448	85	20.1	3.9	21.2	6.9
Pittsburgh, PA	1241	81	22.9	17.3	20.0	17.0	1409	92	23.6	5.1	22.0	4.5

[a]Percentage of blood samples with geographically matched gas concentrations from monitors within 20 km buffer from participants' residences.

Table 3

Adjusted[a] associations between gas exposure and cardiovascular disease markers for SWAN cohort, 1999–2004

Marker	Short-term (1-week)			Long-term (1-year)		
	CO	NO_2	SO_2	CO	NO_2	SO_2
hs-CRP	1.2 (−1.4, 3.8)	0.7 (−1.7, 3.2)	−2.2 (−5.1, 0.7)	1.2 (−6.2, 9.2)	3.9 (−8.4, 17.8)	3.8 (−3.9, 12)
Fibrinogen	1.3 (0.6, 2.0) **	0.7 (−0.1, 1.4)	−0.5 (−1.5, 0.4)	0.05 (−2.1, 2.2)	0.2 (−3.4, 3.9)	−2.0 (−4.6, 0.6)
Factor VIIc	0.9 (0.1, 1.7) *	1.0 (0.1, 1.8) *	−0.6 (−1.8, 0.5)	−1.0 (−3.5, 1.7)	2.1 (−2.3, 6.7)	−1.6 (−4.6, 1.5)
tPA-ag	−1.4 (−2.6, −0.2) *	−1.5 (−2.7, −0.3) *	−0.2 (−1.6, 1.2)	3.3 (−0.3, 7.1)	−1.6 (−7.2, 4.5)	3.1 (−0.6, 6.9)
PAI-1	0.1 (−2.2, 2.6)	0.9 (−1.4, 3.4)	0.4 (−2.4, 3.3)	6.1 (−1.3, 14.1)	12.4 (−0.1, 26.6)	−3.4 (−10.3, 4.0)
HDL	0.9 (0.4, 1.4) **	0.2 (−0.2, 0.7)	−0.6 (−1.1, 0) *	−1.2 (−2.6, 0.3)	−4.0 (−6.3, −1.7) **	−1.3 (−2.7, 0.1)
LDL	−0.02 (−0.7, 0.6)	−0.03 (−0.7, 0.6)	0.2 (−0.5, 1.0)	1.9 (−0.3, 4.0)	0.7 (−2.6, 4.2)	0.3 (−1.7, 2.4)
Triglycerides	−1.4 (−2.5, −0.4) *	−1.6 (−2.6, −0.5) **	−0.6 (−1.8, 0.7)	1.2 (−2.2, 4.7)	3.1 (−2.6, 9.1)	−0.7 (−4.0, 2.7)
Total cholesterol	0.1 (−0.3, 0.6)	−0.2 (−0.6, 0.3)	−0.1 (−0.6, 0.4)	0.7 (−0.6, 2.0)	−0.6 (−2.7, 1.6)	−0.3 (−1.6, 1.0)
APOA1	0.3 (−0.1, 0.7)	−0.3 (−0.7, 0.1)	−0.7 (−1.2, −0.3) **	−0.8 (−2.0, 0.4)	−4.7 (−6.6, −2.8) **	−2.1 (−3.3, −0.9) **
APOB	0.1 (−0.4, 0.7)	−0.2 (−0.7, 0.3)	−0.05 (−0.7, 0.6)	1.5 (−0.2, 3.3)	−1.2 (−3.9, 1.6)	1.6 (−0.1, 3.3)
Lp(a)	−0.6 (−2.3, 1.1)	−0.5 (−2.1, 1.1)	1.4 (−0.5, 3.4)	−0.9 (−6.4, 5.0)	−3.4 (−12.3, 6.5)	5.7 (0.2, 11.5) *
LpA1	0.7 (−0.1, 1.5)	−0.1 (−1.0, 0.7)	−0.1 (−1.2, 1.1)	−0.8 (−3.3, 1.8)	−0.7 (−5.0, 3.7)	−0.1 (−3.3, 3.3)

Note: Results shown are percent of change in biomarker level per an interquartile increase of exposure, which is 0.68 ppm for CO, 13 ppb for NO_2, and 15 ppb for SO_2.

[a] Analyses were based on log-transformed biomarker levels, adjusted for study site, visit number, race/ethnicity, education, menopause status, BMI, active smoking status, hormone use since last visit, alcohol consumption in the past 24 hours before blood draw.

* $p<0.05$;

** $p<0.01$