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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 2306 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.
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.

1. 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 (U.S. EPA) 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 (U.S. EPA, 2008, 2010, 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

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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). SO_2 may cause oxidative stress to red blood cells and decrease blood viscosity (Baskurt, 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 (U.S. EPA, 2008, 2010, 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.

2. Methods

2.1. 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, 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.

2.2. Air pollutant data

Ambient CO, NO_2 and SO_2 data were obtained from the U.S. EPA air monitoring network. The gases were monitored on an hourly basis. The data downloaded were daily maximum 8-hour average concentrations for CO and one-hour maximum concentrations for NO_2 and SO_2. Fine particles up to 2.5 μm 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 U.S. EPA'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 ft (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).

2.3. 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