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Estimating the associations of apparent temperature and inflammatory, hemostatic, and lipid markers in a cohort of midlife women

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ABSTRACT

Associations between temperature and cardiovascular (CVD) mortality have been reported, but the underlying biological mechanisms remain uncertain. We explored the association between apparent temperature and serum biomarkers for CVD. Using linear mixed effects models, we examined the relationships between residence-proximate apparent temperature (same day and 1, 7, and 30 days prior) and several inflammatory, hemostatic, and lipid biomarkers for midlife women from 1999 through 2004. Our study population consisted of 2,306 women with mean age of 51 years (± 3 years) enrolled in Study of Women's Health Across the Nation (SWAN) in Chicago, Illinois; Detroit, Michigan; Los Angeles and Oakland, California; Newark, New Jersey; and Pittsburgh, Pennsylvania. Mean daily apparent temperature was calculated using temperature and relative humidity data provided by the National Climatic Data Center and the US Environmental Protection Agency, while daily data for fine particles, ozone, carbon monoxide, and nitrogen dioxide from the US Environmental Protection Agency Air Quality Data Mart were considered as confounders. All analyses were stratified by warm and cold seasons.

More significant ($p < 0.10$) negative associations were found during the warm season for various lag times, including hs-CRP, fibrinogen, tissue plasminogen activator antigen (tPA-ag), tissue plasminogen activator antigen (PAI-1), Factor VIIc, high-density lipoprotein (HDL), and total cholesterol. During the cold season, significant negative associations for fibrinogen and HDL, but significant positive associations for tPA-ag, PAI-1, and triglycerides were observed for various lag times. With the exception of ozone, pollutants did not confound these associations. Apparent temperature was associated with several serum biomarkers of CVD risk in midlife women, shedding light on potential mechanisms.

1. Introduction

Associations between temperature and morbidity (Turner et al., 2012; Ye et al., 2011) and mortality (Basu, 2009; Basu and Samet, 2002b) have been demonstrated in several studies throughout the world. Consistently, cardiovascular disease (CVD) including acute myocardial infarction (Basu and Ostro, 2008; Bhaskaran et al., 2009; Madrigano et al., 2013; Wichmann et al., 2013), congestive heart failure (Basu and Ostro, 2008; Kolb et al., 2007; Wilker et al., 2012), and ischemic heart disease (Basu and Ostro, 2008; Basu et al., 2012), as well as cerebrovascular outcomes such as stroke (Basu et al., 2012; Miyatake et al., 2011) have been associated with higher ambient temperature. Few studies, however, have been conducted to examine serum markers associated with these CVD outcomes, which may help clarify the mechanisms involved with temperature-induced mortality and morbidity from CVD (Halonen et al., 2011a, 2011b; Hampel et al., 2010; Hong et al., 2012; Schauble et al., 2012; Schneider et al., 2008; Wilker et al., 2012).

While previous research has investigated the hypothesis that inflammatory, hemostatic and/or lipid markers may be associated with higher ambient temperature, they have yielded mixed results. For example, positive, negative and no associations between temperature and high-sensitivity C-Reactive Protein (hs-CRP) have been reported in several studies, but these inconsistent results may be partially explained by the differences in populations studied and the temperature ranges examined as well as control or lack of control of other

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confounding factors (Halonen et al., 2010; Hampel et al., 2010; Hong et al., 2012; Schauble et al., 2012; Schneider et al., 2008; Wilker et al., 2012). Furthermore, many studies were conducted among patients with pre-existing diseases or among other vulnerable populations such as the elderly, while fewer were conducted among healthy populations or younger age groups (Benmarhnia et al., 2015). The body's thermoregulatory capacity and activity patterns may be different between healthy people and people with pre-existing diseases who may spend less time outdoors. Also a large degree of spatial heterogeneity occurs with temperature exposures. Heat impacts may also vary by area due to people's adaptation to the regional climate, and vectors for diseases are sensitive to different temperature thresholds (Ye et al., 2011). Thus, the effects of temperature on serum biomarkers for CVD are not fully understood.

The Study of Women's Health Across the Nation (SWAN) is a large multi-racial/ethnic cohort study in the US originally designed to follow middle-aged women approximately annually through menopausal transition. The data provided a unique opportunity to explore the association between temperature and serum biomarkers in a healthy population of women in six geographic locations in the US. We examined the associations between both short- and intermediate-term exposure to temperature, while updating residential addresses annually to capture the relevant exposure over time. The following serum inflammatory/hemostatic biomarkers and lipid blood markers were considered: hs-CRP, plasminogen activator inhibitor-1 (PAI-1), tissue plasminogen activator antigen (tPA-ag), factor VII coagulant activity (Factor VIIc), fibrinogen, total cholesterol, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), Lipoprotein A (LPA), and Lipoprotein A-1 (LPA1).

2. Methods

2.1. Study population

The study design and recruitment of participants for the SWAN cohort has been described in detail previously (Green et al., 2016). Six of the seven clinical SWAN sites participated in this specific study of temperature specifically: Chicago, Illinois; Detroit, Michigan; Los Angeles, California; Newark, New Jersey; Oakland, California; and Pittsburgh, Pennsylvania. This study was based on a longitudinal analysis of temperature and inflammatory, hemostatic, and lipid markers assessed at clinical visits 3 (1999) through 7 (2004). Non-Hispanic white women were examined at each site as well as women selected from the following racial/ethnic groups for specific sites: African-American in Pittsburgh, Detroit, and Chicago; Chinese in Oakland; Japanese in Los Angeles; and Hispanic in New Jersey.

Approximately 450 eligible women at each of the study sites were recruited for the longitudinal cohort study, which conducted annual clinical assessments. hs-CRP values > 10 mg/L were excluded because they may have resulted from severe infection, major trauma, or chronic inflammatory diseases (9.9% of all observations). For other inflammatory, hemostatic, or lipid markers, extreme values (outside the mean $\pm$3 standard deviations) were excluded from the study.

All women provided signed, written informed consent for the SWAN protocols at study recruitment between 1995 and 1997, and the Institutional Review Boards at all six participating sites approved the SWAN protocols for this study of temperature specifically.

2.2. Exposure assignment

A residential history was abstracted for each participant throughout the study period. Addresses were geocoded as described in Green et al. (2016).

The main exposure in this study, mean daily apparent temperature, was calculated using temperature and relative humidity data provided by the National Centers for Environmental Information (NCEI) ((NOAA), 2012) and the US Environmental Protection Agency (EPA). Data for 24-hour average fine particles ($PM_{2.5}$), 8-hour average ozone (O_3) and carbon monoxide (CO), and 1-hour maxium nitrogen dioxide (NO_2) were abstracted from the US EPA's Air Quality System Data Mart (US EPA, 2014) to be examined as confounders. Typically, apparent temperature and gaseous pollutants were measured hourly, while $PM_{2.5}$ was measured every three days but sometimes every six days or daily. Participants with air pollution monitors located within a 20 km radius of each residential address and apparent temperature within 30 km and 12 km for short and intermediate-term exposures, respectively, were included in the study. Short-term apparent temperature exposures consisted of same day (lag0), lag of one day prior (lag1), and cumulative average lag of prior seven days (lag0-6/week), while intermediate-term was defined as a cumulative average of lag 30 days prior (lag0-29/month), inclusive of the blood draw date. ArcGIS v10.0 (Environmental Systems Research Institute, 2014) was used to assign these exposures. When multiple monitors were available, the monitor that minimized the distance but maximized the number of measurements was selected (Green et al., 2016).

Because $PM_{2.5}$ began to be routinely monitored in mid-1999 and 2000, our study period began at visit 3, which corresponded to visits starting in 1999. Previous studies examining $PM_{2.5}$ using the same data found an association with some of these biomarkers, so we wanted to make sure that we adjusted for it in our models (Green et al., 2016; Ostro et al., 2014). The same monitor chosen was used for the 30-d and 7-d metrics to maintain comparability between the exposure periods. However, we allowed single-day lag measurements (0-d and 1-d) to come from different monitors because daily measurements were less available for some exposures. For apparent temperature calculations and gaseous pollutants, if a 30-d period had at least nine days of data, then an average was assigned for the month. For the week-long window, a minimum of three days were required. For $PM_{2.5}$, if a 30-d period had at least three days of data, then an average was assigned for the month. However, over 75% of the 30-d periods had nine or more measurements. If the participant moved during the year prior to her visit, we took an average of both locations when assigning exposures.

2.3. Data analysis

To study the association between apparent temperature and the serum markers, we used SAS 9.4 Proc Mixed (SAS Institute, Inc., 2014) for linear mixed effects regression analyses with first-order autoregressive structure to account for the correlation between repeated measurements for each woman.

We included the serum markers in the regression models as response variables. Study site, race/ethnicity (Caucasian, African-American, Japanese, Chinese and Hispanic) and education (high school or less, some college, or college graduate) were included as time-invariant variables in a base model with the following visit-specific variables: hormone use since last visit, active smoking (yes/no), body mass index (BMI) (continuous) and alcohol consumption in the 24 h prior to the blood draw (yes/no). In addition, we considered participant's time-varying age, menopausal status (pre-/early peri-/late peri-/post-/surgically induced/hormone user), and visit number in combination and separately to determine which variable(s) were significant in an effort to adjust for changing trends over time. We stratified all analyses by season of blood draw (warm/cold season). Warm season was defined as May through October for Los Angeles and Oakland and June through September for all non-California sites; cold season was defined as November through April for Los Angeles and Oakland and October through May for all non-California sites. Differences in seasonal definitions by study location were chosen based on local climatology.

We excluded visits for women who reported having any previous CVD event, such CVD accident, heart attack, stroke, congestive heart