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Short-term effects of air temperature on plasma metabolite concentrations in patients undergoing cardiac catheterization

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ABSTRACT

Background: Epidemiological studies have shown associations between air temperature and cardiovascular health outcomes. Metabolic dysregulation might also play a role in the development of cardiovascular disease.
Objectives: To investigate short-term temperature effects on metabolites related to cardiovascular disease.
Methods: Concentrations of 45 acylcarnitines, 15 amino acids, ketone bodies and total free fatty acids were available in 2869 participants from the CATHeterization GENetics cohort recruited at the Duke University Cardiac Catheterization Clinic (Durham, NC) between 2001 and 2007. Ten metabolites were selected based on quality criteria and cluster analysis. Daily averages of meteorological variables were obtained from the North American Regional Reanalysis project. Immediate, lagged, and cumulative temperature effects on metabolite concentrations were analyzed using (piecewise) linear regression models.
Results: Linear temperature effects were found for glycine, C16-OH:C14:1-DC, and aspartic acid/asparagine. A 5 °C increase in temperature was associated with a 1.8% [95%-confidence interval: 0.3%; 3.3%] increase in glycine (5-day average), a 3.2% [0.1%; 6.3%] increase in C16-OH:C14:1-DC (lag of four days), and a −1.4% [−2.4%; −0.3%] decrease in aspartic acid/asparagine (lag of two days). Non-linear temperature effects were observed for alanine and total ketone bodies with breakpoint of 4 °C and 20 °C, respectively. Both a 5 °C decrease in temperature on colder days (< 4 °C)and a 5 °C increase in temperature on warmer days (≥ 4 °C) were associated with a four day delayed increase in alanine by 6.6% [11.7; 1.8%] and 1.9% [0.3%; 3.4%], respectively. For ketone bodies we found immediate (0-day lag) increases of 4.2% [−0.5%; 9.1%] and 12.3% [0.1%; 26.0%] associated with 5 °C decreases on colder (< 20 °C) days and 5 °C increases on warmer days (≥ 20 °C), respectively.
Conclusions: We observed multiple effects of air temperature on metabolites several of which are reported to be involved in cardiovascular disease. Our findings might help to understand the link between air temperature and cardiovascular disease.

1. Introduction

In recent years, the influence of weather conditions, such as air temperature, on population health has received greater attention. Emphasis has been placed on the effects of heat waves (Astrom et al., 2011; D'Ippoliti et al., 2010; Son et al., 2012) as well as the short-term effects of changes in moderate temperature on cardiovascular morbidity and mortality (Baccini et al., 2008; Basu, 2009; Bhaskaran et al., 2009; Gasparrini et al., 2015; Yu et al., 2012). Authors have reported a U- or J-shaped association between air temperature and myocardial infarctions or mortality. Thus, cool as well as warm temperatures increase the number of adverse

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cardiovascular events and days with a mean temperature between 15 °C and 30 °C (depending on the geographical region) have the smallest association with cardiovascular events (Baccini et al., 2008; Gasparrini et al., 2015).

It is assumed that the elderly, women, and individuals with diabetes or cardiovascular disease are particularly vulnerable to temperature changes or temperature extremes (Analitis et al., 2008; Benmarhnia et al., 2015; Medina-Ramon et al., 2006; Oudin Astrom et al., 2015; Schwartz, 2005; Son et al., 2011; Yu et al., 2010). Therefore, it is important to investigate temperature effects in these potentially susceptible populations.

Underlying mechanisms for associations between short-term temperature changes and cardiovascular morbidity and mortality potentially include acute changes in cardiovascular disease risk factors/predictors such as blood pressure, blood markers of inflammation (e.g. C-reactive protein, interleukin-6) and coagulation (e.g. platelets, fibrinogen, factor VII), and heart rate variability. Recent panel studies reported higher blood pressure (Chen et al., 2015; Halonen et al., 2011; Lanzinger et al., 2014) and changes in blood markers of inflammation and coagulation (Halonen et al., 2010; Hampel et al., 2009, Schäuble et al., 2012; Schneider et al., 2008) on days with lower air temperature. Furthermore, researchers showed reduced heart rate variability in association with increases in air temperature (Wasserman et al., 2014; Wu et al., 2013).

A relatively new analytical strategy to identify novel biomarkers of cardiovascular disease is metabolomic profiling (Barderas et al., 2011). Metabolic profiling is defined as the simultaneous measurement of a wide range of low-molecular weight metabolites in biological specimens that reflects the dynamic response to genetic modification, physiological, pathophysiological, developmental and/or external stimuli (Clarke and Haselden, 2008; Shah et al., 2012a). Altered metabolic profiles may play a role in the development of cardiovascular disease (Shah et al., 2012a). In 2012, Shah et al. (2012b) performed a principal component analysis of 69 metabolites in 2023 participants undergoing cardiac catheterization. They reported independent effects of five metabolite factors (medium-chain acylcarnitines, short- and long-chain dicarboxylacylcarnitines, branched-chain amino acids, and fatty acids) on all-cause mortality and of three metabolite factors (short- and long-chain dicarboxylacylcarnitines and fatty acids) on mortality or subsequent myocardial infarction.

Despite advances in linking the ambient environment, metabolomics, and disease there remains a lack of epidemiological studies investigating the effects of air temperature on metabolomics in potentially susceptible populations. Therefore, the aim of this study is to use a susceptible population of individuals, those undergoing cardiac catheterization, to assess the influence of air temperature on selected metabolites and to determine whether the resultant associations are modified by participant or life style characteristics.

2. Material and methods

2.1. Study population

This study was conducted using data from the catheterization genetics (CATHGEN) cohort, a large cohort of 9334 individuals recruited sequentially at the Duke University Hospital Cardiac Catheterization Laboratory (Durham, NC) from 2001 to 2011 (Kraus et al., 2015). Clinical data and patient characteristics were provided by the Duke Databank for Cardiovascular Disease (DDCD), a database of patients undergoing catheterization at Duke University since 1969. Residential addresses were obtained from medical records and geocoded by the Children's Environmental Health Initiative (http://cehi.snre.umich.edu/) for 8017 of the 9334 study participants. Metabolomic profiling was performed for 3878 CATHGEN patients between 2001 and 2007. We restricted our analysis to 2869 participants residing in North Carolina who had complete information on exposure, covariates and metabolomic profiling.

The Duke University Institutional Review Board approved the CATHGEN study and written informed consent was obtained from all subjects. None of the samples in CATHGEN were collected from catheterizations performed in the context of an acute coronary syndrome as informed consent could not be obtained in these cases.

More detailed information on the design, collection, and analysis of the CATHGEN cohort can be found elsewhere (Kraus et al., 2015).

2.2. Metabolite data

Metabolomic profiling was performed for 3873 individuals. Subjects were fasting for a minimum of six hours before blood collection. Blood was drawn from the femoral artery at the time of arterial access for catheterization, immediately processed to separate plasma, and frozen at −80 °C. The concentrations of 45 acylcarnitines, 15 amino acids, ketone bodies (total and β-hydroxybutyrate) and total free fatty acids were quantitatively determined using a targeted mass spectrometry–based approach (Shah et al., 2012a). Proteins were first removed by precipitation with methanol; aliquoted supernatants were dried and esterified with hot, acidic methanol (acylcarnitines) or n-butanol (amino acids). For analysis, tandem mass spectrometry with a Quattro Micro instrument (Waters Corp, Milford, MA) was used. Adding mixtures of known quantities of stable-isotope internal standards facilitated the quantification of “targeted” intermediary metabolites. Assay ranges are 0.05–50 μmol (acylcarnitines) and 5–1000 μmol (amino acids). Ketone bodies and total free fatty acids were assayed on a Beckman-Coulter DxC600 clinical chemistry analyzer with reagents from Wako (Richmond, VA). Methodologies, coefficients of variation, and intra-individual variability have been reported previously (Shah et al., 2010, 2009). Two acylcarnitines did not meet the quality standards and were excluded because more than 25% of values were below the limit of detection (LOD).

2.3. Meteorology and air pollution data

Daily mean air temperature, relative humidity, and barometric pressure were obtained from the North American Regional Reanalysis (NARR) project (Mesinger et al., 2006). Patients' geocoded addresses were matched to the meteorological data based on spatial location and date. Daily predictive surfaces of particulate matter with an aerodynamic diameter $< 2.5\ \mu m$ ($PM_{2.5}$) (daily average in $\mu g/m^3$) and ozone (daily 8-h maximum in ppb) were provided by the U.S. Environmental Protection Agency (U.S. EPA) for the years 2001–2008 (www.epa.gov/esd/land-sci/lcb/lcb_faqsd.html). Details and descriptions of the modeling technique and predictive performance can be found elsewhere (Berrocal et al., 2010a, 2010b, 2012; Gray et al., 2013). Geocoded residential addresses of the study participants were assigned the exposure as estimated at the closest census tract centroid based on spatial location and date. Daily averages of meteorological variables and air pollutants on the day (lag 0) of the clinical examination as well as one (lag 1) to four days (lag 4) before the examination were assigned to each individual. Additionally, for each individual the 5-day average (lag 0–4) of the exposure variables were calculated. Daily minimum and maximum temperature were also determined.