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The cold effects on circulatory inflammation, thrombosis and vasoconstriction in type 2 diabetic patients☆

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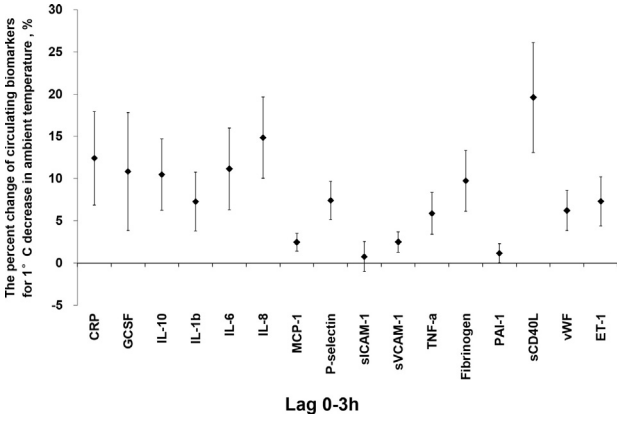
HIGHLIGHTS

- Few studies have examined the acute effect of temperature at the individual level.
- The biologic mechanisms remain largely unknown.
- We found cold effects on biomarkers of inflammation, thrombosis and vasoconstriction in T2D patients.
- First study to find hourly effects of temperature on circulating biomarkers in T2D patients
- These findings add evidence to the health effects of ambient temperature.

GRAPHICAL ABSTRACT



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ABSTRACT

Short-term associations between temperature variation and adverse cardiovascular outcomes have been well documented. However, it remains unclear whether these temperature-related cardiovascular effects are reflected in circulating biomarkers. We aimed to examine the associations between ambient temperature and circulating biomarkers of inflammation, coagulation and vasoconstriction. We collected 207 blood samples from a panel of 35 type 2 diabetes mellitus patients. Sixteen biomarkers of inflammation, coagulation and vasoconstriction were repeatedly measured over six follow-ups. The short-term associations between air temperature and these biomarkers were assessed by mixed-effect models with controls of demographic characteristics and main air pollutants. We found significant and acute effects of temperature on circulatory biomarkers occurred

Abbreviations: BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; CVD, cardiovascular disease; ET-1, endothelin-1; GCSF, Granulocyte-colony stimulating factor; IL-1b, interleukin-1b; IL-6, interleukin-6; IL-8, interleukin-8; IL-10, interleukin-10; MCP-1, monocyte chemoattractant protein-1; O_3, ozone; PAI-1, plasminogen activator inhibitor-1; $PM_{2.5}$, particulate matter less than 2.5 μm in diameter; RH, relative humidity; sCD40L, soluble CD40 ligand; sVCAM-1, soluble vascular cell adhesion modecule-1; sICAM-1, soluble intercellular adhesion molecule-1; T2D, type 2 diabetes; TNF-α, tumor necrosis factor-α; vWF, von Willebrand factor.

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as early as 3 h after exposure, peaked at 25–48 h and lasted until 72 h after exposure. For example, a 1 °C decrease in the 25–48 h average of air temperature was associated with 2.2%–15.1% increases in biomarkers of inflammation, 1.4%–24.5% of coagulation and 8.2% of vasoconstriction. Our results provided significant evidence that a temperature decline results in a response in biomarkers of inflammation, coagulation and vasoconstriction biomarkers, suggesting them to be the potential biologic mechanisms underlying the cardiovascular effects of temperature variation, and may have implications for disease prevention.

Abbreviations: CRP, C-reactive protein; GCSF, Granulocyte-colony stimulating factor; IL, interleukin; MCP-1, Monocyte chemoattractant protein-1; sVCAM-1, soluble vascular cell adhesion modecule-1; sICAM-1, soluble intercellular adhesion molecule-1; TNF-α, tumor necrosis factor-α; PAI-1, plasminogen activator inhibitor-1; PAI-1, plasminogen activator inhibitor-1; sCD40L, soluble CD40 ligand; vWF, von Willebrand factor; ET-1, Endothelin-1.

1. Introduction

Exposure to cold has been worldwide associated with cardiovascular outcome (Kysely et al., 2009; Phung et al., 2016). Previous studies have observed increased risks of myocardial infarction (Bhaskaran et al., 2010), stroke (Fustinoni et al., 2013) and hypertension (Jansen et al., 2001) when temperature declines. However, the exact mechanisms of these associations are not well understood.

Systemic inflammation, thrombosis and vasoconstriction are among the proposed mechanisms advancing cardiovascular events. There is ample human evidence showing that increased levels of C-reactive protein (CRP) (Blake and Ridker, 2002) and fibrinogen (Corrado et al., 2010) could strongly predict cardiovascular events. However, the potential for outdoor temperature to affect systemic inflammation, thrombus formation and/or vasoconstriction as parts of the mechanisms leading to cardiovascular mortality has scarcely been studied. To our knowledge, only a few studies from North America and Western Europe have evaluated associations between ambient temperature and biomarkers related to cardiovascular outcomes, and their findings were inconsistent (Schneider et al., 2008; Hampel et al., 2010; Halonen et al., 2010; Lanzinger et al., 2014; Schauble et al., 2012). More importantly, these associations have rarely been examined in Asian countries (Hong et al., 2012) and none have been conducted in China, where the climatic conditions probably differ from other areas. Furthermore, most of existing studies reported effects of temperature in scales of daily or weekly variation (Schneider et al., 2008; Halonen et al., 2010; Analitis et al., 2008); however, very acute (such as hourly) effects have never been investigated. A better understanding on the time windows of the health effects of temperature may have public health implications, especially for vulnerable populations.

We therefore hypothesize that biomarkers of inflammation, coagulation and vasoconstriction are associated with short-term ambient temperature variations. We also hypothesize that response of these biomarkers to ambient temperature changes are acute. To test these hypotheses, we conducted a panel study among patients with type 2 diabetes (T2D). T2D patients were selected because this population has been found to be susceptible to temperature change (Schwartz, 2005); moreover, they have greater risks of cardiovascular disease (CVD) (Emerging Risk Factors, C., 2010).

2. Methods

2.1. Study population

This panel study was conducted in Tianping Community, which is located in the central urban area of Shanghai, China. Patients older than 18 years, who were physician-diagnosed with T2D for at least 3 months, and had been resident in Tianping Community for at least 1 year, were recruited. Inclusion and exclusion criteria of participation were described elsewhere (Wang et al., 2015). In brief, the following patients were excluded: (1) subjects with overt diabetic complications; (2) those who are current tobacco smokers or alcohol addicts; (3) those with congestive heart failure and uncontrolled hypertension; and (4) those who had undergone surgical procedures. T2D patients who were not taking antihypertensive or lipid-lowering medications were recruited; while those who were taking a stable dose of these medications for at least 6 months with documented blood pressure and lipid control were eligible. The study protocol and data used were approved by the Institutional Review Board of the School of Public Health at Fudan University. Information of this study was given to all subjects and all participants provided written informed consents before the study started.

2.2. Clinical measurements

The patients were scheduled for six clinical visits between April 13th and June 30th. All visits were conducted at Tianping Community Health Center (TCHC) with an interval of 2 weeks. At the first visit, a baseline questionnaire was administered regarding health status, pulmonary and cardiac symptoms, medication and smoking history. Information on height, weight, and fasting blood glucose levels was also collected using standard procedures. For each visit, venous peripheral blood samples were drawn during the morning hours (8:30 A.M. to 10:00 A.M.). Coagulant vacuum tubes were used and serum samples were isolated and stored at −80 °C for further analysis. Blood sample collection was performed on the same day of the week and at the same time of the day to control for possible circadian rhythm of biomarkers and day-of-week effects.

Sixteen biomarkers that have been identified to be related to temperature variation or particulate air pollution in previous studies were measured in this study, including C-reactive protein (CRP) (Hampel et al., 2010; Hong et al., 2012), Granulocyte-colony stimulating factor (GCSF) (Masubuchi et al., 1998), interleukin-1b (IL-1b) (Schauble et al., 2012), interleukin-6 (IL-6) (Halonen et al., 2010), interleukin-8 (IL-8) (Halonen et al., 2010), interleukin-10 (IL-10) (Zuurbier et al., 2011), monocyte chemoattractant protein-1 (MCP-1) (Shaw et al., 2011), P-selectin (Delfino et al., 2009), soluble vascular cell adhesion modecule-1 (sVCAM-1) (Halonen et al., 2010), soluble intercellular adhesion molecule-1 (sICAM-1) (Hampel et al., 2010), tumor necrosis factor-α (TNF-α) (Wilker et al., 2012), fibrinogen (Schauble et al., 2012), plasminogen activator inhibitor-1 (PAI-1) (Schauble et al., 2012), von Willebrand factor (vWF) (Lanzinger et al., 2014), soluble CD40 ligand (sCD40L) (Hampel et al., 2010) and endothelin-1 (ET-1) (Wilker et al., 2012).

All biomarkers were measured by commercial Millipore MILLIPLEX™ MAP human cytokine/chemokine kit (Millipore Corp., Billerica, MA), which is based on the Luminex® xMAP® technology. The concentration of each biomarker was simultaneously quantified by the MagPix system and xPONENT software (Luminex). More details on biomarkers measurement and data quality control can be found elsewhere (Wang et al., 2015).

2.3. Exposure measurement

Hourly and daily mean temperature and relative humidity (RH) measurements were derived from a meteorological station of Shanghai Meteorological Bureau located approximately 2 km from TCHC.