Association between Ambient Temperature and Blood Biomarker of Systemic Inflammationin (C-reactive protien) in Diabetes Patients

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Abstract

Background: Climatic conditions, especially changes in temperature are associated with cardiovascular (CV) events but underlying mechanisms are not well understood. We investigated association between air temperature and C-reactive protein (CRP), in type 2 diabetes patients.

Methods: The subjects were resident of Pune city and suburbs (n=1700). The relationships between air temperature at lag 0-5 and different averaging time periods (3 and 7 days) and CRP concentration were analyzed using robust regression models. Sensitivity of our result to possible influence of additional adjustments for season, and air pollutants variable including PM_{10}, NO_x, and SO_2 were investigated.

Result: Mean daily air temperature during study period varied between 15°C to 34°C. A 5°C decrease in the air temperature was associated with significant increase of 15.26% (95% CI=4.42 to 24.88) in geometric mean of CRP concentration with a lag of 1-day.

Conclusion: This study suggests that decrease in temperature is associated with change in CRP which is important risk factor for CV. We need to investigate physiological and environmental mediators of this association to help improve CV risk.

Keywords: Air temperature; C-reactive protein; Diabetes patients

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Introduction

The association between change in ambient temperatures and health related events has been investigated in several studies [1-3]. However, the mechanisms underlying the temperature-related health effect are still poorly understood. To date, several biomarkers have been reported to be associated with temperature [2]. Many of these markers are implicated in the causal pathway for the development of cardiovascular events, and mortality.

C-reactive protein, is associated with greater risk for adverse CV events [4]. However, the potential for outdoor temperature to affect systemic inflammation (i.e. CRP) as part of the mechanism leading to CV mortality has scarcely been studied [5]. Previously we have shown that air pollution increased the number of inflammatory markers in the circulation [6] and number of

metrological variable were important in these association. We therefore studied possible associations between temperature

and CRP using data from Wellcome Genetic (WellGen) Study, controlling for personal and environmental confounders.

Material and Methods

Subjects

Type 2 diabetes patients enrolled for Wellcome Genetic (WellGen) study, a clinical based study of genetics of Indian which is ongoing in Diabetes Clinic of the King Edward Memorial Hospital (KEMH), Pune. In brief, type 2 diabetes patients who were not more than 46 years age at time of diagnostic were recruited. Subjects who fulfilled the clinical criteria of fibrocalculous pancreatic diabetes (FCPD), maturity-onset diabetes of the young (MODY), type 1 diabetes, and pregnant women were excluded from the study. The study design and area has been described in detail elsewhere [6,7]. The study was approved by the Institutional Ethics Committee and all patients gave a written informed consent.

Clinical measurements

The patients were appointed for a visit between March 2005 and May 2007. The visits were conducted though out the week except Sunday and national holidays. Patients suffering from acute inter-current illness were reappointed after 4 weeks. At the visit, a standard questionnaire was administrated which provided information regarding medical history, medication intake, and smoking history. In addition clinical examination included measurement of height, weight, waist and hip circumferences were performed. Fasting blood serum sample was drawn to assess C-reactive protein.

Meteorological and air pollution data

The meteorological parameters minimum and maximum air temperature, relative humidity (rh), mean sea level pressure (mslp), dray bulb (dbt) and dew point temperature (dpt) for the city of Pune during the period of the study were obtained from national data center, meteorological department. Arithmetic mean air temperatures were computed from the daily minimum and maximum temperature, also apparent temperature (at) was calculated, as: at = -2.653+(0.994 × dbt)+(0.0153 × dpt^2).

Furthermore, NO_x, SO_x and PM_{10} (particulate matter with an aerodynamic profile ≤ 10 µm) from 3 stations situated around city center admissible as per APHEA protocol [8] were used for current study. Missing air pollution data was imputed by linear interpolation technique with respect to nature of missing data (short length of gaps and overlay less than 22% missing variable) [9].

Meteorological and air pollutants parameters for each person's day of visit or blood collection (lag 0), and upto 5 days before (lag 0 to lag 5) as 24 hours exposure have been computed. Furthermore, moving average of 3 days and 7 days before blood collection were computed as a cumulative exposure.

Statistical analysis

Data was presented as mean (±SD) when normally distributed and median (25th, 75th percentile) when not normally distributed. The plasma CRP needed to be log 10- transformed to fulfil the model

assumption of residual normality. Specific confounder models for CRP without meteorological parameter were built separately. Variables considered affecting the average CRP concentration such age, gender, education, Body Adiposity Index (BAI, calculated as (hip)/height^1.5 - 18) [10], medication, duration of diabetes are included. Additionally we adjust for short term time trend (day of week) and long term time trend. Relative humidity and mean sea level pressure with the same day lag and moving average as air temperature terms were used in the models. Final models were built by minimizing Akaik's Information Criterion (AIC) [11]. After completion of confounder models, the effects of air temperature were investigated using robust linear regression. We present effect estimates as percent changes in CRP for a 5ºC decrease in air temperature. The significance threshold was P=0.05 in all analyses. Sensitivity of our result to possible influence of additional adjustments for air pollutants variable including PM_{10}, NO_x, and SO_2 were investigated. All statistical analyses were performed using STATA version 11.1 software (STATA Corporation, College Station, TX).

Result

Study Population

The study population comprised 1700 type 2 diabetes patients who fulfilled the inclusion and exclusion criteria and who had results for at least one of blood samples. **Table** 1 presents the baseline characteristics of the study participants.

Biomarkers

Biomarkers of 1700 collected blood sample, measurements of CRP were available for 1392 patients. Concentrations of biomarkers are shown in **Table 1**. CRP concentration was significantly associated with fasting plamsa glucose (FPG) (0.13, p<0.01) but not related with Hb concentration (after adjustment for age and gender). FPG and Hb also were inter-correlated (r=0.09, p<0.01).

Metrological and air pollutants data

Meteorological measurements were available for all the days during the study period. Out of the total of 822 days of study, 175 missing air pollution data was imputed. Air temperature was inversely correlated with air pollutants concentration, rs ranging from -0.13 to -0.22 (P<0.001) but positive only with PM_{10} during monsoon (rs=0.12, P=0.002). Relative humidity showed negative correlations with ambient pollutants, rs ranging from -0.28 to -0.45 (P<0.001) **(Table 1)**.

Regression analysis

We studied the association between air temperature at lag0-5 and different averaging time periods (3 and 7 days) and concentration of biomarkers **(Figure 1)**. The model and adjustment procedures have been described in the statistical analysis. We found that decrease in ambient air temperature was associated with a significant increase in CRP concentrations. We estimated a 15.26% (CI=4.42% to 24.88%) increase in geometric mean of CRP per 5°C decrease in ambient air temperature (1-day preceding blood collection).

Table 1 Characteristics of study subject and local levels of environmental variables (air pollutants and meteorological measurment).

N	1700
Male sex, n (%)	943 (55.47)
Age (years)	46.15 (9.20)
Body Mass Index (kg/m²)	26.06 (4.21)
Waist-Hip ratio	0.94 (0.07)
Body Adiposity Index	31.17 (6.59)
C-Reactive Protein (mg/L)	3.59 (1.79, 7.75)
Fasting Plasma Glucose (mg/dL)	153 (125, 203)
Hemoglobin (g/dL)	13.20 (1.83)
HbA1c (%)	8.91 (2.09)
Duration of diabetes (yrs)	7 (3, 14)
Current smoking n (%)	170 (10.06)
Current Alcohol usage, n (%)	345 (20.41)
Thiazolidinediones n (%)	427 (25.12)
Statin n (%)	384 (22.59)
Aspirin n (%)	670 (39.41)
SO_2 ($\mu g/m^3$)	21.81 ± 5.36
NO_x ($\mu g/m^3$)	39.67 ± 7.63
PM_{10} ($\mu g/m^3$)	114.14 ± 37.20
Relative humidity (%)	61.19 ± 19.08
Air temperature (°C)	25.21 ± 3.37
Apparent temperature (°C)	27.60 ± 4.26
Barometric pressure (hPa)	1008.69 ± 3.99

PM_{10}, particles ≤ 10 μm in aerodynamic diameter; SO_2, sulfur dioxide; NO_x, oxides of nitrogen.
Values are presented as mean ± SD or No (%), except CRP, FPG, and duration of diabetes which presented as median (25th-75th percentile)

Regression analysis

Adjustment for air pollution (i.e. PM_{10}, NO_x, and SO_2) did not show any significant effect on the results (**Figure 2 and supplementary Table 1**).

Discussion

More than half of patients had CRP concentrations in the high coronary risk zone (i.e. >3 mg/L). The meteorological factors (temperature and relative humidity) varied with season. The ambient pollutant levels were highest in winter and lowest in monsoon. It would appear that all these factors have a complex effect on circulating CRP which was highest in cool season and lowest in warm season. We showed that levels of air temperature a day preceding blood collection is inversely and significantly associated with CRP concentration and the results were robust to additional adjustment for air pollution

To date, several biomarkers have been reported to be associated with temperature [2]. Many of these markers such CRP [4], Hb (≥17 or <13 g/dL) [12,13], and FPG concentration [14] are implicated in the causal pathway for the development of cardiovascular events, and mortality. However, few studies have investigated the subclinical changes due to air temperature [15-18] also results are inconsitante. For instance unlike our finding which indicate cold stress (lower temperature) could rise CRP, Wilker [18] reported 21.6% (95% CI: 2.5, 44.2; p=0.03) increase in CRP concentration for a 5°C increment in air temperature.

The effect of air pollution on mortality in patients with cardiovascular disease and coexisting diabetes has been shown to be greatest in warm seasons [15]. Short-term effects of air pollution across seasons have not always been well characterized and show inconsistent results [19-23]. Also in our previous study we showed that effect of PM_{10} was more significant in summer [6]. However we did not observed a seasonal variation in the association for SO_2 and NO_x. It is unclear whether temperature are confounders or effect modifier of the air pollutants-biomarker association. We found a significant effect of air pollution even in multivariate regression model, after adjustment for temperature and other potential confounding factors. There was no interaction between air pollution and temperature in association with CRP **(Supplementary Figures S1 and S2)**. Therefore we assumed temperature as an important confounding factor and not effect-modifier of air pollution health effect.

The potential of the effect of ambient temperature on levels of systemic biomarkers as part of the mechanism leading to CV mortality has scarcely been studied [3]. It is known that lower temperature is associated with a higher blood pressure [24,25] and an increase of thrombogenic factors, such as C-reactive protein [18]. furthermore CV effects could be mdiated by stimulation of sympathetic nervous activity [26]. Our results suggest that the
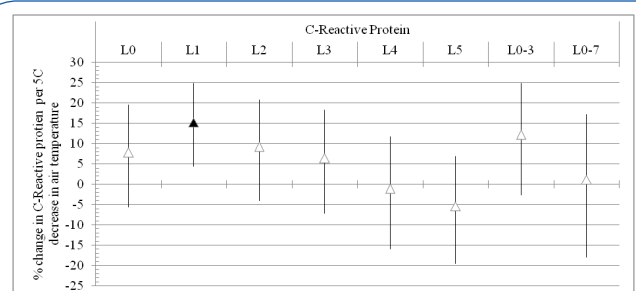
Figure 1 Association between ambient air temperature and CRP. Error bar indicate 95% CI. Black triangle indicate significant association (p<0.05).
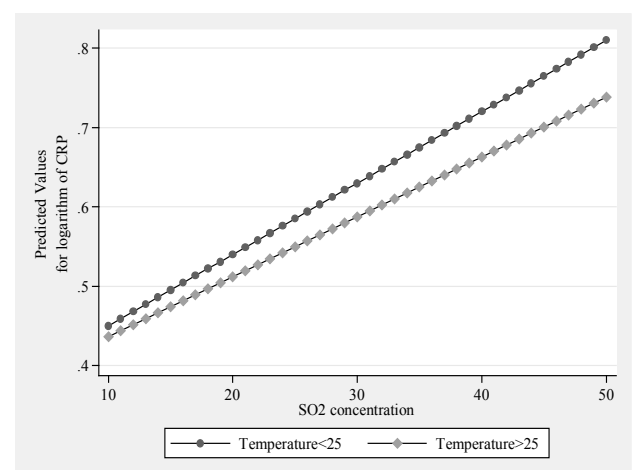
Figure 2 Confounding effects of temperature in the association between air pollution and CRP.

effects of environmental variables on the cardiovascular system should be investigated in future prospective cohort studies.

Our study is unique in its kind and indicates that change in temperature might lead to increase concentration of CV risk biomarkers (i.e. CRP) suggesting a biological mechanism for the temperature related cardiovascular mortality.

Acknowledgments

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