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Personal-Level Exposure to Environmental Temperature is a Superior Predictor of Endothelial-Dependent Vasodilatation than Outdoor-Ambient Level

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Abstract

Environmental temperatures influence cardiovascular physiology. However, the majority of time is spent indoors, making outdoor-ambient temperatures inaccurate estimates of true exposures encountered by most individuals. We evaluated in 50 healthy adults the associations between previous 7-day outdoor-ambient (4 occasions) and prior 24-hour personal-level (2 occasions) environmental temperature exposures with blood pressure, heart rate variability, sleep parameters, and endothelial-dependent vasodilatation (brachial flow-mediated dilatation [FMD]) using generalized estimating equations. Participants (34 females; age, 32.1±9.6 years) had normal blood pressures (107.8±13.3/70.2 ± 9.4 mm Hg), FMD (7.4±2.8%), as well as sleep and HRV parameters. Mean 7-day outdoor-ambient (4.6±9.7 °C) differed from personal-level temperature exposures (22.0±3.0 °C). Colder outdoo r-ambient temperatures (per -10°C) over the previous 1-6 days (rolling averages) were associated with decreases in FMD: -0.57% (95% confidence interval [CI] -1.14% to 0.01%, p=0.055) to -0.62% (95%CI -1.07% to -0.18%, p=0.006). However, a 10°C decrease in personal-leve l temperature during the prior 24-hours was associated with a greater decrement in FMD: -2.44% (95%CI -4.74% to -0.13%, p=0.038). Both were also linearly related to FMD during all seasons and without a threshold temperature. Other endpoints were not significantly related to either temperature level in this study. Short-term exposures to colder environmental temperatures reduced endothelial-dependent vasodilatation, supporting the

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epidemiological associations with heightened cardiovascular risk. We show here for the first time that temperature exposures characterized at the personal-level may be more robust predictors of endothelial function than outdoor-ambient levels.

Keywords

Environment; Hypertension; Endothelial Function

Numerous studies conducted worldwide have demonstrated that environmental temperatures during the prior few days are associated with all-cause as well as cardiovascular morbidity and mortality[1-4]. While extreme heat is linked to adverse health effects, a large body of evidence demonstrates that colder temperatures are strongly predictive of increased cardiovascular events[2,4]. This issue is likely to become an even greater public health problem due to global climate change which not only heightens summer heat waves but can promote larger overall variations in temperature and more pronounced winter cold spells across temperate zones[5.6].

Several biological mechanisms may underlie the linkage between temperature and cardiovascular risk[1]. Cold exposure causes adrenal and sympathetic nervous system (SNS) activation as well as thermoregulatory vasoconstriction which may explain the well-established association with elevations in arterial blood pressure (BP)[1,7,8]. In addition, a few studies have shown that temperature and season are related to changes in brachial flow-mediated dilation (FMD), an established measure of endothelial-dependent vasodilatation[9-11]. FMD is an independent predictor of cardiovascular events and as such temperature-induced endothelial dysfunction could be a key pathway explaining the epidemiological associations[12].

It is important to note that the relationship with FMD in the published literature has thus far relied on ambient (i.e., prevailing regional outdoor) temperature values. However, ambient levels are known to be inaccurate metrics of “true” temperature exposures given that most individuals spend the majority (~90%) of their time indoors in regulated environments where the temperature is held relatively constant, particularly in colder regions/seasons and urban locations[13]. We and others have reported greater predictive value of arterial BP by using personal-level environmental temperature (PET) exposures compared to ambient-outdoor levels[8,14-16]. On the other hand, only one study has yet evaluated the differing associations with FMD[14]. Give that endothelial dysfunction plays a fundamental role in cardiovascular diseases[12], we aimed to explore the impact of recent temperature exposures measured by PET versus outdoor-ambient levels on several physiological parameters with a specific focus on FMD.

Methods

This study is a post hoc exploratory analysis of results obtained from the human project component of the Great Lakes Air Center for Integrated Environmental Research (GLACIER) at the University of Michigan. The protocol was designed and powered to evaluate the effect of personal-level $PM_{2.5}$ exposures on primary cardio-metabolic health

endpoints. The study was approved by the Institutional Review Board of the University of Michigan and all participants signed a written informed consent document during a screening visit. Participant inclusion criteria were healthy nonsmoking adults living in nonsmoking households aged 18-50 years without a history of cardiovascular disease or risk factors (screening visit BP < 140/90 mm Hg and fasting glucose < 126 mg/dL). Body mass index (BMI) was calculated from height and weight measured at a screening visit. Subjects were also excluded if they were taking any medication or over-the-counter pill (e.g., cholesterol or BP-lowering medication, fish oil, anti-oxidant) on a routine basis that might alter study outcomes.

Qualifying participants (n=50) were enrolled into a repeated measures panel study, each fully-completing the protocol within a 2 to 3 week-long period (Online supplement, Figure S1). The study was conducted among individuals living in southeast Michigan within a 2-year period during the months of August through October 2014; January through May 5th 2015; November through December 2015; and January through February 2016. There were 2 study blocks, each consisting of 2 visit days in a row when participants came fasting ≥8 hours at 8 am to a temperature-controlled (21-22 °C) outpatient Clinic al Translational Science Award (CTSA) research facility of the University of Michigan (Domino's Farms, Ann Arbor, MI). On visit day 1, cardiovascular outcomes were measured in the order provided in Figure S1 and afterwards participants were discharged with instructions to proceed with usual daily activities (excluding exercise and travel) while wearing a personal environmental monitor. They were also provided with a portable home sleep monitor and instructions on its usage during the upcoming night. The following morning (visit day 2), participants returned to the CTSA. Cardiovascular outcomes were repeated in the same sequence as day 1. Participants were then discharged home and underwent a 6-day (minimum) to 3-week (maximum) washout period. Thereafter, each participant repeated the same process during study block 2.

Cardiovascular Outcomes

Study outcome methods were performed as detailed in our prior experiments and are only be briefly outlined here[14,17]. Seated right upper arm blood pressure (BP) using an appropriate sized cuff was measured by an automated device (BPM-100; http://www.bptru.com/) after participants rested unattended in the exam room for 5 minutes with their arm supported at mid-sternal level. The average of 5 BP readings (2nd to 6th levels using 1 minute intervals) was defined as the BP outcome. Participants next rested supine on a patient exam bed and continuous electrocardiogram monitoring was performed for 6 minutes using a Spacelabs evo Holter system. Time domain (standard deviation of normal-to-normal intervals; SDNN) and frequency domain (high (HF); low (LF) frequency) heart rate variability (HRV) metrics were analyzed using the Spacelabs Pathfinder system (http://www.spacelabshealthcare.com/). Thereafter, resting basal longitudinal brachial artery diameter (BAD) images were measured at a standardized site on the right upper arm using a portable Terason ultrasound system and a 10 mHz linear array transducer (http://www.terason.com/). All images were captured by an electrocardiogram triggered on the R-wave. Digital images were analyzed using a software package employing an edge-detection system (Brachial Analyzer, Medical Imaging Applications; http://www.mia-llc.com/).

Conduit artery endothelial-dependent vasodilation was then measured using the standardized flow-mediated dilatation (FMD) method employing a 5-minute long upper arm cuff occlusion technique. Brachial artery images were captured continuously for 2 minutes during reactive hyperemia. FMD was calculated as the percent increase in BAD from baseline at the largest percent change (FMD-peak). Finally, sleep quality parameters were measured by the portable finger arterial tonometry technique following the manufacturer's directions (http://www.itamarmedical.com/watchpat-main/) starting at bedtime during the night between visit day 1 and 2 on both study blocks. The outcomes analyzed included the apnea-hypopnea index (AHI) and respiratory disturbance index (RDI).

Environmental Exposure Outcomes

The Michigan Department of Environmental Quality operates tapered element oscillating microbalance samplers (Rupprecht & Patashnick TEOM 1400a) to monitor continuous $PM_{2.5}$ levels across Michigan. Outdoor ambient temperature and $PM_{2.5}$ data for this study were averaged over the proceeding 24-hour period from the monitoring site in Ypsilanti, Michigan (ID: 261610008; 42.2406 -83.59972 http://www.michigan.gov/deq/). For assessing outdoor-ambient exposure, each patient had their own unique multiple 24-hour long ambient exposure epochs calculated starting retrospectively from the time in the morning at the start of each of the 4 study visit days. Seven individual 24-hour lag periods were calculated for each patient from each study visit day. In addition, the rolling average of exposures from 1 to 7 days in duration was calculated.

Personal-level particulate exposures and PET were recorded using a battery-powered active personal monitor (Thermo Scientific pDR-1500). Averages were recorded for the 24-hour period prior to the start of visit day 2 in each study block. Average personal exposure to $PM_{2.5}$ mass was calculated from gravimetric determinations using a microbalance (MT-5, Mettler Toledo, Columbus OH) in a temperature/humidity-controlled environment. Sample handling, processing, and analysis took place in a Class 100 ultraclean room at the University of Michigan Air Quality Laboratory.

Statistical Methods

Summary statistics were computed for continuous measures as mean ± standard deviation (SD), as well as median (interquartile range, IQR), and for categorical variables as frequency and proportion (%). All outcomes were evaluated for normality of distribution using the Shapiro-Wilk Normality Test. Correlations between environmental exposures were calculated by Pearson's correlation analysis. Tests for differences between mean values were performed by independent samples t-tests. We evaluated the associations of longitudinal health measurements repetitively obtained with 24-hour average outdoor ambient (4 associations per patient for each lag day and rolling average lag periods) and personal-level temperature exposures (2 associations per patient) using generalized estimating equations (GEEs), where we assumed a very general unstructured correlation structure to account for within subject correlations, and GEEs use data to estimate the within subject correlation matrix. The outcomes of this model are the longitudinal health parameters (e.g., FMD, or BAD). Models were fit with a pool of potential predictors and confounders available in our data collection (such as patient age, sex, BMI, study block, $PM_{2.5}$) and then we perform a

backward model selection procedure with a cut-off p-value as 0.1 to select the final model, which is relatively parsimonious and more stable given the sample size of this study. Our final models, as selected through the backward selection procedure, were adjusted for patient age and prior 24-hour ambient $PM_{2.5}$. Potential non-linear relationships between temperature exposures and FMD-peak were also explored using local polynomial regression (LOESS) analysis, and our results show that assuming this relationship as linear is reasonable in our study. All analyses were performed using the statistical software package R (version 3.3.3).

Results

Study participants were healthy without cardiovascular disease or risk factors. All physiological endpoints including BP, basal FMD, HRV, and sleep parameters were within normal ranges (Table 1). Personal-level versus outdoor-ambient exposures differed for both temperatures and $PM_{2.5}$ concentrations (Table 2). PET was on-average warmer and less variable. The correlations between exposure variables on lag day 1 are provided in Table 3.

Exposures to colder outdoor-ambient temperatures (per -10°C) over the previous week, measured on individual lag days and over rolling averages, were associated with reductions in FMD (Figure 1). Reductions in FMD ranged from -0.57% (95% confidence interval [CI] -1.14% to 0.01%, p=0.055) to -0.62% (95%CI -1.07% to -0.18%, p=0.006) for 1-6 days rolling average temperature changes. However, the same 10°C decreas e in PET exposure during the prior 24-hours (individual lag day 1) was associated with a substantially larger reduction in FMD -2.44% (95%CI -4.74% to -0.13%, p=0.038) (Table 4). Given that PET varied considerably less than outdoor-ambient temperatures, PET is a more precise measurement and more stable predictor of FMD changes. We also compared lag day 1 associations per interquartile range (IQR) change in both exposures. We found similar effects per IQRs, which are representative exposure variations that are likely to occur in the “real world setting”. FMD decreased by -1.01% (95%CI -1.74% to -0.29%, per -16.3 °C) and by -0.93 % (95%CI -1.80% to -0.05%, per -3.8 °C) for each IQR reduction in ambient-outdoor and PET temperatures, respectively. The moderately high correlation (r=0.59) between temperature levels together with our limited sample size make identifying the variable more strongly associated with FMD statistically difficult. Nonetheless, these results taken altogether support a strong predictive ability of PET decreases in relation to FMD reductions and the superiority of PET with regard to measurement precision. Thus, more robust associations with FMD changes can be observed using PET rather than outdoor-ambient temperatures for any given absolute degree change in temperature exposure.

We also explored the potential nonlinear relationship between temperature exposures and FMD through LOESS nonparametric regression method. The graphical associations between changes in both temperature exposures with FMD are presented in Figure 3. The LOESS curves illustrate near-linear associations across the entire exposure ranges (throughout both seasons as well), which confirmed that our model assumptions in GEEs estimations above are reasonable.

A total of 18 participants visited the site during April to October, while 32 participants visited the site during November to March. No participant had visit records across different seasons. During cold seasons (November through March), FMD was significantly lower among participants (6.7 ± 2.7%) compared to other the season (8.4 ± 2.6%) ($p<0.001$). Lag day 1 outdoor ambient temperature (-1.1 ± 7.6 versus 14.8 ± 4.8 °C) and PET (21.0 ± 2.6 versus 24.0 ± 2.6 °C) were also both significantly ($p<0.001$) lo wer during the cold season. There was also no significant effect modification (i.e. non-significant interaction terms in the models) by “cold season” on the PET or outdoor-ambient temperature associations with FMD. These results support that variations in real-world temperatures encountered in both cold-to-temperate (0-23.2°C) and freezing (-13.4 to 0°C) periods remain an influence on FMD. This is despite the fact that PET varied less overall and individuals likely spent even more time indoors during colder seasons. This is supported by the weaker correlation between PET and outdoor-ambient temperature on lag day 1 during cold ($r=0.30$, $p=0.016$) versus the other season ($r=0.71$, $p<0.001$). There was also no significant effect modification by “warm-season”. Finally, we found no significant associations between changes in either temperature levels and other health outcomes studied including BP levels, HRV metrics, and sleep parameters (data not shown).

Discussion

Short-term exposures to colder environmental temperatures were associated with reductions in endothelial-dependent vasodilatation during the ensuing few days. Our results corroborate prior findings[10,11] and provide further mechanistic support for the epidemiological linkages between colder temperatures and increased cardiovascular risk[1-4]. Here, we show for the first time that exposures characterized at the personal-level are likely superior predictors of endothelial function compared with outdoor-ambient levels. This is likely explained by the fact that individuals spend most of their time indoors, particularly in colder environments[13]. PET levels are therefore not only less variable but also represent more reliable estimates of “true” exposures encountered throughout any given day. Nevertheless, there were moderately positive associations between PET and outdoor-ambient temperatures throughout the year. This likely explains why relatively “inaccurate” exposure estimates captured by outdoor temperatures can still significantly predict FMD across all seasons in this as well as prior studies[9-11].

A few studies have reported a relationship between ambient temperature and endothelial function[9-11]. Narwot et al. demonstrated that warmer temperatures were related to impaired FMD. However, in at least 2 other studies, including the Framingham Offspring Cohort[10], FMD was significantly lower in winter after adjusting for clinical covariates, baseline BAD and arterial flow. In the only prior study to evaluate the effect of PET, we did not find an association of same-day levels with FMD[14]. This is likely due to differences in the previous study design, as FMD was performed non-fasting in the late afternoon.

The relationship between environmental temperature exposure and endothelial function is not fully-understood. Possible mechanistic linkages are that colder temperatures activate the sympathetic nervous system and hypothalamic-pituitary-adrenal axis and can also directly trigger thermogenic vasoconstriction. Alone or together these responses could impair

endothelium-dependent vasodilatation[1,10]. While we showed trends to arterial constriction (reduced BAD) in this study, we did not observe cold-induced changes in HRV or BP to support these pathways. This is most likely because that this was a post hoc exploratory analysis of a study not specifically designed to assess the impact of temperature exposures on these outcomes. Future trials will be required to better elucidate the responsible mechanisms.

Cardiovascular mortality is higher during cold and winter months[2-4]. Understanding the underlying reasons is of great clinical and public health importance to help develop preventive strategies given the millions of at-risk individuals worldwide. Our findings support that cold-induced endothelial dysfunction may be at least partially responsible as FMD is a known independent predictor of cardiovascular events[12]. Our observations also accord with a prior meta-analysis showing that indoor is a stronger predictor of BP than outdoor temperature level[8]. This suggests that if personal-level rather than outdoor temperatures were evaluated in epidemiological studies, the associations with cardiovascular events may be even more robust. Our results further suggest that reducing personal-level exposures to cold temperature, regardless of the outdoor-ambient temperatures or season, might be an effective approach to help combat cardiovascular disease. We posit that improved indoor heating and insulation to maintain a stable indoor living temperature, along with avoiding outdoor cold exposures as much as possible in high-risk individuals, may help mitigate excess cardiovascular events.

We recognize a limitation of this study is that it is a post hoc observational analysis and the results should be considered hypothesis-generating. We also examined several outcomes, raising the possibility for type 1 errors. Only FMD was significantly related to temperature levels and the expected association with BP was not observed likely due to the relatively small size of the cohort. Nevertheless, the statistically robust, reproducible, expected, and near linear associations of both temperature values with FMD supports the veracity of our findings. Future studies need to better define the underlying biological mechanisms involved and to test whether interventions to reduce personal-level exposures to colder temperatures can mitigate against endothelial dysfunction. Additional research is also required to determine if the observed temperature-induced changes in FMD are due to alterations in microvascular responses to hyperemia which thereby change the stimuli (shear-stress) induced post cuff release, or due to changes in intrinsic brachial reactivity, or both. Whether these findings extend to high-risk patients with cardiovascular disease or risk factors also remains to be clarified. Finally, in addition to cold temperatures, heat waves are also known to increase cardiovascular morbidity and mortality. We had few days with extreme elevations in temperature in our study (maximum PET: 28.7 degrees Celsius). Whether very hot days (e.g., >35-40 degrees Celsius) trigger adverse events via impaired endothelial function, or by other mechanisms, remains to be determined.

Colder environmental temperatures are associated with reduced endothelial function. Our results show for the first time that exposures characterized at the personal-level are superior predictors of endothelial-dependent vasodilatation than outdoor-ambient temperatures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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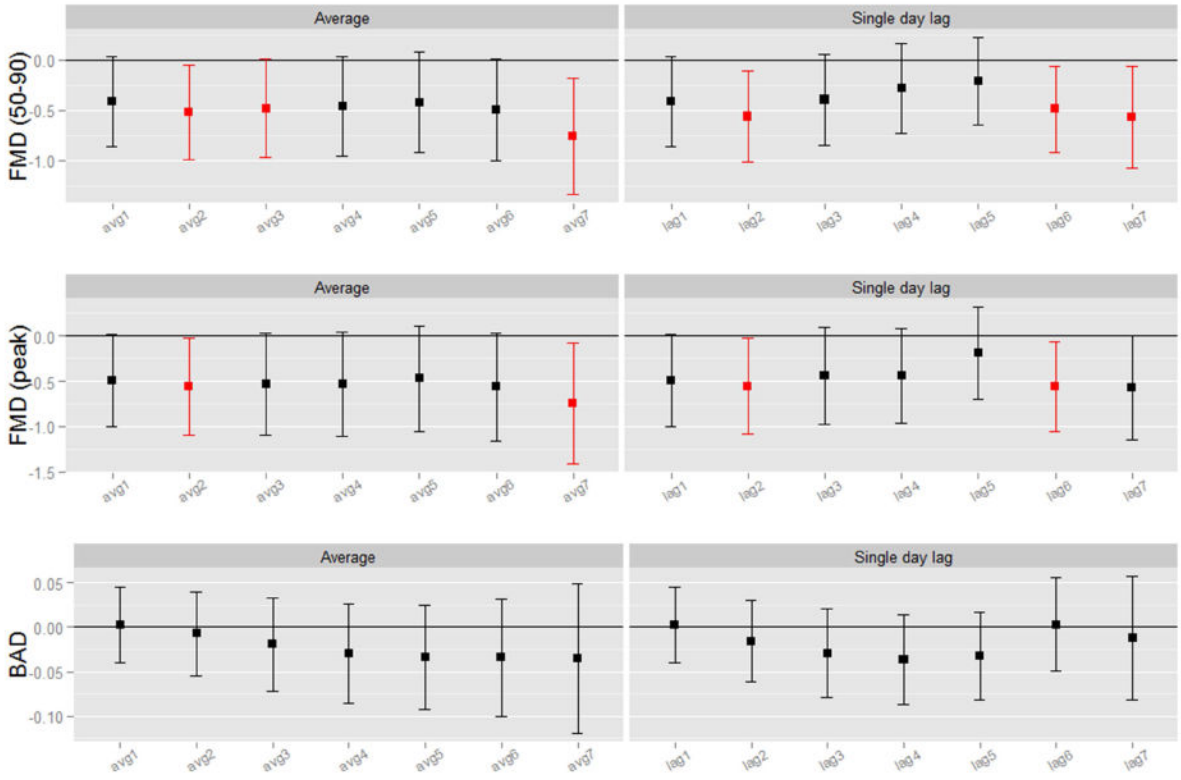

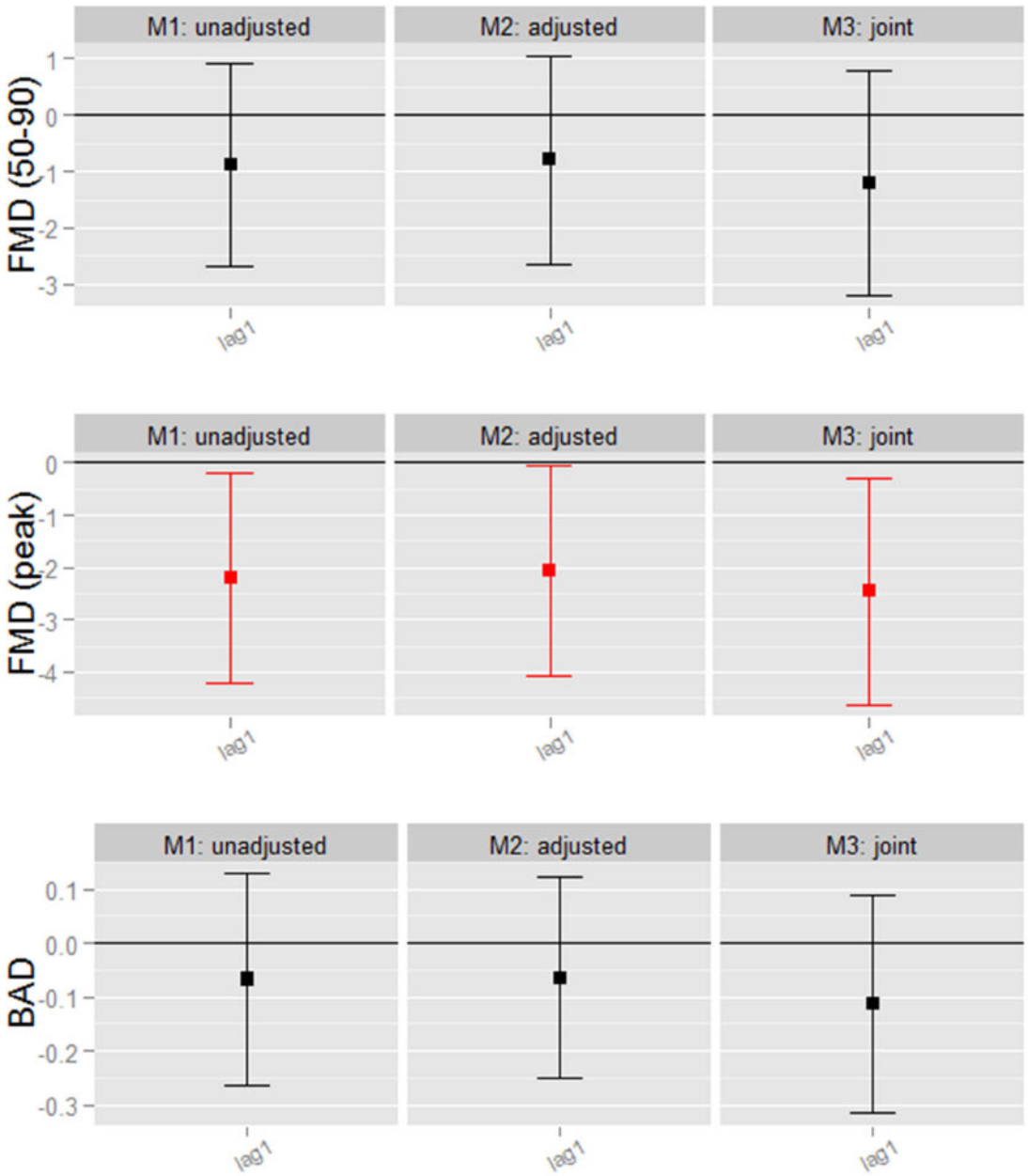

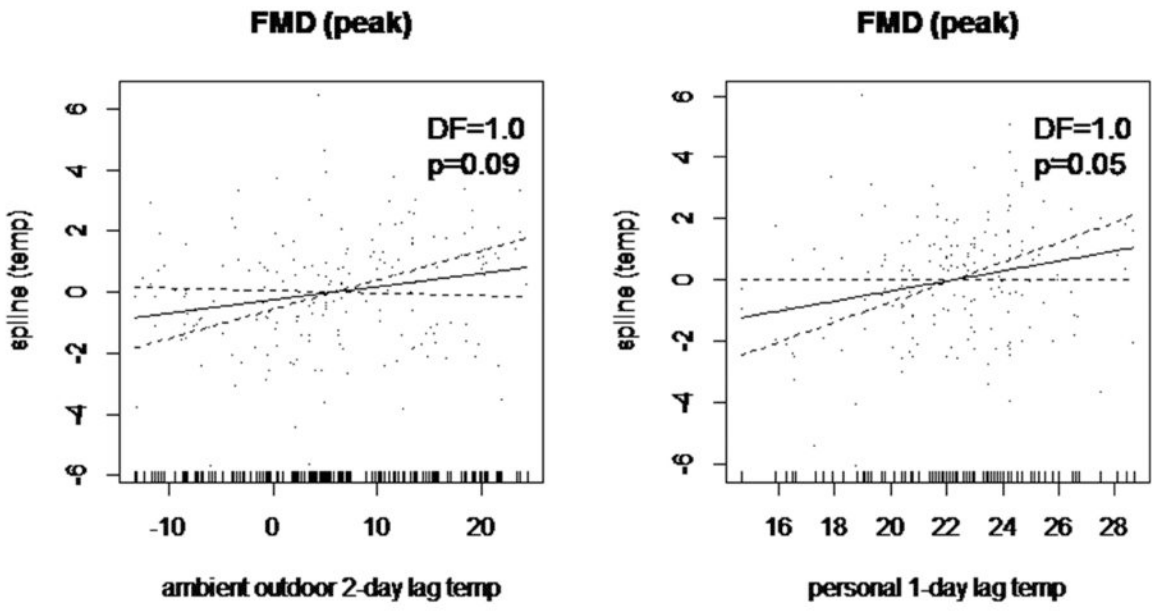

Figure 1. Associations of Colder Ambient-Outdoor Temperatures with Endothelial-Dependent Vasodilatation

Results provided per (-10°C). Average, rolling mean temperature averaged over all exposure days up through lag day(s) 1-6; Single day lag, individual lag day temperature, for lag day 1-6; All models adjusted for age and ambient $PM_{2.5}$ (particulate matter level) during the past 24 hours. FMD (peak), peak flow-mediated dilatation during 120 seconds of reactive hyperemia; BAD, brachial artery diameter at a basal resting state.

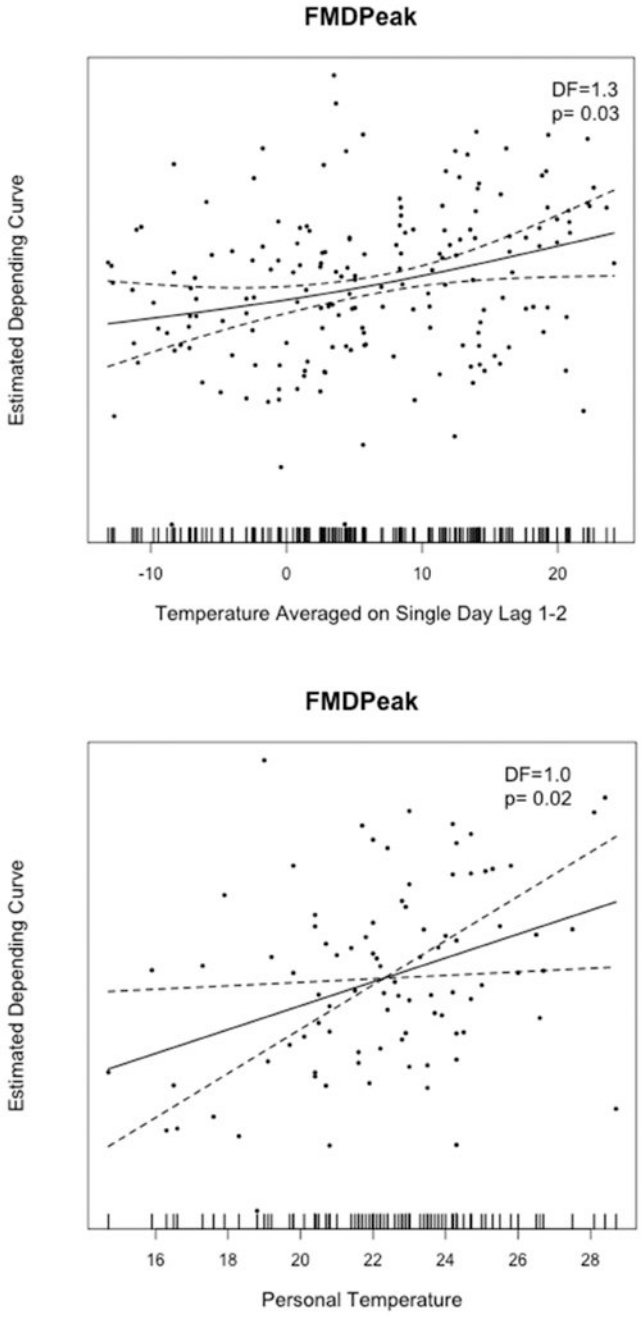

Figure 2. Graphical Associations of Temperature Exposures and Endothelial-Dependent Vasodilatation Using Nonparametric Modeling

Local polynomial regression (LOESS) curve and 95% confidence intervals (hashed lines) for (a) how peak FMD depends on the change of ambient-outdoor temperature averaged over lag day 1 and lag day 2; and (b) how peak FMD depends on the change of personal-level temperature measured during the prior 24 hours.

Table 1

Descriptive Statistics on Study Participant Parameters

Variable	Obs	Mean ± SD	Min	25th percentile	Median	75th percentile	Max
Age (years)	50	32.1 ± 9.6	19.0	24.0	28.5	41.0	50.0
BMI (kg/m^2)	50	26.1 ± 5.7	19.0	21.7	24.9	29.1	43.5
SBP (mm Hg)	200	107.8 ± 13.3	86.0	99.0	105.0	112.0	161.0
DBP (mm Hg)	200	70.2 ± 9.4	50.0	65.0	69.0	75.0	107.0
HR (beats/min)	200	70.6 ± 11.3	44.0	63.0	71.0	78.0	111.0
SDNN	194	79.0 ± 37.1	19.1	53.9	70.1	92.0	225.8
LF	189	1829 ± 1900	66	597	1174	2325	14329
HF	189	2224 ± 4364	23	403	949	1758	38256
LF/HF	189	2.1 ± 2.7	0.1	0.7	1.3	2.6	28.2
FMD 50-90 (%)	185	4.1 ± 2.4	0.0	2.3	3.9	5.8	10.7
FMD peak (%)	185	7.3 ± 2.8	1.5	4.9	7.2	9.6	14.8
BAD (cm)	185	3.7 ± 0.8	2.3	3.1	3.6	4.4	5.2
AHI	93	3.4 ± 4.5	0.0	0.6	1.6	5.0	23.1
RDI	93	11.6 ± 5.6	2.7	7.8	10.5	14.4	32.8

Obs, number of observations; min, minimal value; max, maximal value; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; SDNN, standard deviation of normal-to-normal intervals; LF, low-frequency power variability; HF, high frequency power; FMD, flow-mediated dilatation; BAD, brachial artery diameter; AHI, apnea-hypopnea index; RDI, respiratory disturbance index

Table 2

Descriptive Statistics on Environmental Exposures

	Variable	Obs	Mean ± SD	Min	25th percentile	Median	75th percentile	Max
$PM_{2.5}$ (μg/m^3)	Personal	95	12.2 ± 17.0	0.2	4.0	6.9	13.0	94.0
	Outdoor 7-day average	100	9.2 ± 1.9	5.5	7.7	9.1	10.7	14.2
Temp (°C)	Personal	98	22.0 ± 3.0	13.8	20.4	22.2	24.2	28.7
	Outdoor 7-day average	100	4.6 ± 9.7	-13.4	-3.8	3.1	12.8	23.2

Personal $PM_{2.5}$ and temperature levels were averaged from all available 24-hour long period measurements performed on lag day 1 prior to visit 2 during both study blocks. Outdoor $PM_{2.5}$ and temperature levels were averaged over 7-day long lag periods prior to all study visits.

Table 3
Correlations among Environmental Exposures on Lag Day 1

	Outdoor ambient $PM_{2.5}$	**Personal-level $PM_{2.5}$**	**Outdoor ambient temperature**	**Personal-level temperature**
Outdoor ambient $PM_{2.5}$		0.23 (p=0.001)	0.02 (p=0.77)	0.13 (p=0.07)
Personal-level $PM_{2.5}$	0.23 (p=0.001)		-0.06 (p=0.38)	-0.16 (p= 0.03)
Outdoor ambient temperature	0.02 (p=0.77)	-0.06 (p=0.38)		**0.59 (p<.0001)**
Personal temperature	0.13 (p=0.07)	-0.16 (p= 0.03)	**0.59 (p<.0001)**	

Table 4

Associations of Colder Prior 24-hour Personal-Level Temperature Exposures with Endothelial-Dependent Vasodilatation, adjusted for age and prior 24-hour ambient PM2.5 exposures

Outcome Variable	Covariate in the Model	Coefficient Estimate	Lower CI	Upper CI	P-Value
FDM (peak)					
	Age	-0.091	-0.152	-0.029	0.004
	Prior 24-hour Ambient PM2.5	-0.119	-0.255	0.017	0.086
	Prior 24-hour Personal Temperature	**-2.438**	**-4.743**	**-0.133**	**0.038**
BAD					
	Age	0.028	0.008	0.047	0.005
	Prior 24-hour Ambient PM2.5	0.004	-0.004	0.011	0.331
	Prior 24-hour Personal Temperature	**-0.010**	**-0.158**	**0.139**	**0.899**

Results provided per (-10°C). Model is adjusted for age and ambient $PM_{2.5}$ (particulate matter level) during the past 24 hours. FMD (peak), peak flow-mediated dilatation during 120 seconds of reactive hyperemia; BAD, brachial artery diameter at a basal resting state.