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The association between short and long-term exposure to $PM_{2.5}$ and temperature and hospital admissions in New England and the synergistic effect of the short-term exposures

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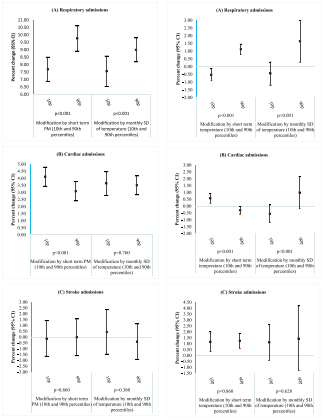
HIGHLIGHTS

- Associations between short and long-term exposures were observed for all outcomes.
- Long-term exposures to particulate matter < 2.5 μm ($PM_{2.5}$) had stronger effects than short-term exposures.
- Short-term $PM_{2.5}$ related respiratory risk was larger on warmer days.
- Short-term $PM_{2.5}$ related cardiac in risk was larger on colder days.
- Short-term $PM_{2.5}$ risks were larger in months of higher temperature variability.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Particulate matter < 2.5 μm in diameter ($PM_{2.5}$) and heat are strong predictors of morbidity, yet few studies have examined the effects of long-term exposures on non-fatal events, or assessed the short and long-term effect on health simultaneously.
Objective: We jointly investigated the association of short and long-term exposures to $PM_{2.5}$ and temperature with hospital admissions, and explored the modification of the associations with the short-term exposures by one another and by temperature variability.
Methods: Daily ZIP code counts of respiratory, cardiac and stroke admissions of adults ≥65 (N = 2,015,660) were constructed across New-England (2001−2011). Daily $PM_{2.5}$ and temperature exposure estimates were obtained from satellite-based spatio-temporally resolved models. For each admission cause, a Poisson regression was fit on short and long-term exposures, with a random intercept for ZIP code. Modifications of the short-term effects were tested by adding interaction terms with temperature, $PM_{2.5}$ and temperature variability.
Results: Associations between short and long-term exposures were observed for all of the outcomes, with stronger effects of long-term exposures to $PM_{2.5}$. For respiratory admissions, the short-term $PM_{2.5}$ effect (percent increase per IQR) was larger on warmer days (1.12% versus −0.53%) and in months of higher temperature variability (1.63% versus −0.45%). The short-term temperature effect was higher in months of higher

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temperature variability as well. For cardiac admissions, the $PM_{2.5}$ effect was larger on colder days (0.56% versus −0.30%) and in months of higher temperature variability (0.99% versus −0.56%).
Conclusions: We observed synergistic effects of short-term exposures to $PM_{2.5}$, temperature and temperature variability. Long-term exposures to $PM_{2.5}$ were associated with larger effects compared to short-term exposures.

1. Introduction

Particulate matter air pollution and heat are strong predictors of cardiovascular (Yitshak-Sade et al., 2015; Kloog et al., 2012; Kloog et al., 2015; Brook et al., 2010; Barnett et al., 2006; Peters et al., 2001; Ye et al., 2012; Michelozzi et al., 2009; Schwartz et al., 2004) and respiratory (Kloog et al., 2012; Michelozzi et al., 2009; Bell et al., 2008; Kloog et al., 2014a) morbidity and mortality. It is, therefore, important to correctly identify their joint effect on health outcomes, especially in light of the ongoing process of climate change (McMichael et al., 2006; Li et al., 2017). In most studies that assessed the effects of temperature and particulate matter smaller than 2.5 μm in diameter ($PM_{2.5}$) on health, temperature was treated as a confounder rather than a modifier (Li et al., 2017). Those that did assess modification by temperature mostly focused on the estimation of short-term PM effects with stratification by temperature or season. Very little evidence is currently available on synergism (that is, on the joint effects of temperature, temperature variability and air pollution) (Zanobetti and Peters, 2015). In addition, examination of the health effects of temperature has been almost exclusively focused on short-term exposures (days to a few weeks). However, recent studies of mortality cohorts have indicated that there are chronic effects of longer-term temperature exposure, and that temperature variability is a key predictor of health (Shi et al., 2016a; Shi et al., 2015; Anderson and Bell, 2009; Breitner et al., 2014; Guo et al., 2016). Such exposures have not, to our knowledge, been studied for hospital admissions for acute events.

The underlying mechanism explaining the interaction between temperature and PM may be related to different exposure patterns to PM across the range of temperature (i.e. different PM composition in warmer and colder temperatures) (Stafoggia et al., 2008) or to physiological stress that may increase susceptibility (Li et al., 2015a). Regarding temperature variability, there is strong evidence of adaptation to usual temperatures (Zanobetti et al., 2012), and because the effect of climate change is seen both in the increases of the average values and the variability of temperature (Stocker, 2014), it is important to investigate the health impacts of unstable weather and its interaction with PM.

The majority of studies that examined the interaction between temperature and PM focused on mortality (Li et al., 2017; Breitner et al., 2014; Stafoggia et al., 2008; Li et al., 2015a; Kioumourtzoglou et al., 2016; Sun et al., 2015; Li et al., 2015b; Analitis et al., 2014; Burkart et al., 2013; Kim et al., 2015a; Dholakia et al., 2014; O'Neill et al., 2003; Shi et al., 2016b; Wang et al., 2017). The evidence regarding hospital admissions, emergency room visits or other measures of morbidity are scarce, and the direction of the interaction varies by the outcome tested and the geographic location. A study by Pan et al. assessed the modification of the association between temperature and measures of cerebrovascular hemodynamics, by $PM_{2.5}$. The authors found significantly weaker effects of temperature on resting blood flow velocity at higher $PM_{2.5}$ concentrations (Pan et al., 2015). A recent study has found an increased risk of stroke associated with $PM_{2.5}$ on the day of the event, with stronger associations on warmer days (Huang et al., 2016). A study in New York, which included hospital admissions due to cardiovascular diseases, found stronger associations with $PM_{2.5}$ in the winter and in low temperatures (Hsu et al., 2017). For respiratory admissions, a study of 204 US urban counties found stronger effects of $PM_{2.5}$ in warmer regions (Dominici et al., 2006). Another study, however, found stronger short-term $PM_{2.5}$ effects in the winter (Bell et al., 2008).

Another gap is that most previous research examined either acute or chronic exposure rather than investigating the effect of both exposures simultaneously (Zanobetti and Peters, 2015). Examining the simultaneous effect of both exposures will provide the effect of each exposure independently from the other. Kloog and colleagues addressed this in a series of studies, where they investigated both acute and chronic effect of air pollution on several health outcomes and found increases of short and long-term exposure to $PM_{2.5}$ to be associated with increases in cardiovascular, respiratory and stroke admissions rate (Kloog et al., 2012; Shi et al., 2016b; Kloog et al., 2013), but further examination of the potential interactions of these effects is clearly needed.

In this study, we aim to investigate the association between short and long-term exposures to $PM_{2.5}$ and temperature simultaneously, with cardiac, stroke and respiratory hospital admissions, while using spatio-temporally resolved satellite based exposure models (Kloog et al., 2014b; Kloog et al., 2014c). In addition, we aim to explore the modification of the associations with the short-term exposures by one another and by temperature variability, which may limit physiological adaptation to temperature.

2. Methods

2.1. Study population and main outcomes

This study was approved by the Harvard School of Public Health Institutional Review Board. The study population comprised New England residents between the years 2000 and 2011, 65 years or older, who were Medicare beneficiaries and enrolled in the fee-for-service program. For each eligible subject, individual-level data on gender, age, race, country of residence, Medicaid eligibility, dates of hospital admissions, the International Classification and Disease, Ninth Revision (ICD 9) code for the primary cause of hospitalization and the date of death were extracted. Cases were defined as emergency admissions with a principal discharge code of all respiratory diseases (ICD 9: 460–519), all cardiac diseases (ICD 9: 390–429) or ischemic stroke (ICD 9: 432–435). From this data, we constructed daily counts of the number of hospital admissions for each admission cause and each zip code.

2.2. Exposure

Temperature data were obtained from a spatiotemporally resolved prediction model generating predictions of daily average temperatures at a 1 × 1 KM spatial resolution, described previously in detail (Kloog et al., 2014c). In brief, daily MODIS (Moderate resolution imaging spectroradiometer) land surface temperatures (LST) data, in grid cells where both air temperature and LST were available for that day, were calibrated using mixed effect models. The model covariates included LST, land use regression (LUR) variables (percent urban, elevation, normalized difference vegetation index) and a random intercept and slope for surface temperature for each day. Information from neighboring grid cells was used to estimate air temperature when no surface temperature data are available. Out-of-sample ten-fold cross-validation was used to quantify the accuracy of the model predictions, showing

excellent model performance for both days with available satellite data (mean out-of-sample $R^2 = 0.947$) and days without satellite observations (mean out-of-sample $R^2 = 0.940$). For more in depth information refer to Kloog et al. (2014c).

$PM_{2.5}$ data were obtained from a hybrid satellite based model incorporating daily satellite remote sensing data and classic LUR methodologies at 1×1 km spatial resolution. In brief, in days where both monitor PM data and Aerosol Optic Depth (AOD) values were co-located, mean daily $PM_{2.5}$ concentrations in each grid cell were estimated by calibrating the AOD-PM relationship using mixed effect models with a random slope for day and nested regions, in addition to the spatial and temporal predictors such as in a classic LUR. Then, a second model was built to estimate exposures on days when AOD measures were not available using calibration fits. The model used the regional mean of $PM_{2.5}$ monitoring stations, with a smooth function of latitude and longitude and a random intercept for each cell that takes advantage of associations between grid cell AOD values and PM data from monitors located elsewhere, and associations with available AOD values in neighboring grid cells. Again, Out-of-sample "ten-fold" cross-validation was used to quantify the accuracy of the model predictions, showing excellent model performance for both days with available satellite data (mean out-of-sample $R^2 = 0.88$) and days without satellite observations (mean out-of-sample $R^2 = 0.87$). For more in depth description please refer to Kloog et al. (2014b).

The exposure values of all grid cells located within each of the 1823 ZIP codes and their 500 m buffer surrounding, were averaged daily and exposure data was assigned to ZIP codes using ArcGIS based on spatial location and date.

2.3. Covariates

The following ZIP code level socioeconomic variables were obtained through the U.S Census Bureau from the US Census 2000 and the American Community Survey (ACS) 5-year estimates of 2009–2013: median household income, percent black, percent Hispanic, percent living in poverty and percent of residents with no high school education. Using both Census and ACS data we applied a linear interpolation obtaining yearly values for each variable.

2.4. Statistical methods

Associations between cause-specific admissions and short and long-term exposure to $PM_{2.5}$ and temperature were assessed using Poisson regression with proportional hazard model with a piecewise constant hazard for each day (Laird and Olivier, 1981) and a random intercept for each ZIP code. This model combines the classic Poisson time series analysis with proportional hazard model where the hazard is allowed to vary each time period, allowing its estimation using a Poisson regression. This allows the simultaneous assessment of the associations with both short and long-term exposures. Each time interval in the model has a separate hazard, allowing the baseline hazard to vary with time, and an offset representing the person-time at risk in that ZIP code. Since the time intervals are small, the time-interval intercepts approaches a smooth function of time, and therefore can be replaced with a smooth function of time incorporated in the Poisson model (Kloog et al., 2012).

Previous work done by our team found stronger associations with $PM_{2.5}$ measured over the current and previous day of hospitalization, compared to same day exposure (Kloog et al., 2012). We, therefore, used the moving average of $PM_{2.5}$ at lag days 0–1 for the calculation of the short-term exposure to $PM_{2.5}$. For temperature, previous studies found stronger effects of colder temperatures at lag 1–5 (Nordio et al., 2015) and of warmer temperatures at lag 0 (Anderson et al., 2013), we therefore a priori defined three potential exposure windows (lag 0, lag 0–1 and lag 1–5) and tested the associations with each. Moreover, the association with temperature is commonly nonlinear. To assess the linearity of the associations with the four main exposures, we regressed the cause specific admissions rate against the aforementioned exposures using penalized splines. Then, we compared the Akaike's and Bayesian information criteria between the models to assess the best fit.

To ensure that the short-term effect estimates only capture short-term variation within ZIP code and not spatial differences between ZIP code, the short-term exposures were defined as the difference between the defined exposure window and the average ZIP code exposure across the entire study period. This also assures that the short-term effects cannot be confounded by spatially varying population characteristics. Long-term exposure was defined as the annual average of exposures (Kloog et al., 2012). To capture temperature variability, we computed the monthly standard deviation of daily temperatures, separately for each ZIP code.

All models were built off of a base model, which included the short and long-term exposures to $PM_{2.5}$ and temperature, with adjustment for a smoothed function of time (using natural cubic splines with 5 degrees of freedom per year) (Kloog et al., 2012), day of the week, and ZIP code level socioeconomic variables (age, percent minorities, median household income, percent poverty and percent people with no high school education). We then fit a series of separate models, which each added additional terms to the base model as follows: (Yitshak-Sade et al., 2015) base model plus interaction terms between the two short-term exposures, (Kloog et al., 2012) base model plus interaction terms between short-term exposure to $PM_{2.5}$ and the measure of temperature variability, and (Kloog et al., 2015) base model plus interaction terms between short-term temperature and the measure of temperature variability. Since the variation in the long-term exposures is smaller, a longer follow-up period was needed to examine interactions of long-term exposures. Because of the limited number of years of follow-up in our study (10 years), we did not examine these interactions in our analysis.

Results are presented as percent change for inter-quartile range (IQR) increase of the exposures. The effect of the long-term exposure to temperature was modeled using penalized splines, we therefore computed the percent change in admissions rate per IQR increase (and 95% Confidence Intervals (CI)) in the 10th (8 °C) and 90th (12 °C) percentile of temperature.

For the effect modification analysis, the results are presented as percent change in cause-specific admissions for an IQR increase in the exposure at the 10th and 90th percentile of the distribution of the modifier.

3. Results

Descriptive statistics of the 2,015,660 admissions included in the study are presented in Table 1. The patient population was about 80 years old on average, 44.6% were males and the majority was white. Table 2 shows the summary statistics of short and long-term exposures to $PM_{2.5}$ and temperature across the study area. The two-day average concentration of $PM_{2.5}$ was 8.92 $\mu g/m^3$ on average (IQR = 5.65–11.05), and the two-day temperature average was 9.94 °C (IQR = 7.62–12.83). Supplementary Fig. 1 shows the mean annual $PM_{2.5}$ and temperature predictions generated by our models averaged within ZIP codes. For $PM_{2.5}$, the mean annual concentrations in the study period ranged between 6.7 and 11.6 $\mu g/m^3$, with higher values in urban areas. Hence, any association is entirely below the current National Ambient Air Quality Standard for $PM_{2.5}$. The average temperature ranged between 5.5 and 13.0 °C. The standard deviation of monthly temperature ranged between 0.15 and 7.9 °C with the highest variability observed between December–January and lowest variability observed between July–September. The correlation between the exposures was low to moderate with the highest correlation observed between long-term exposures to temperature and $PM_{2.5}$ ($r = 0.46$, $p < 0.001$).

Of the exposure windows tested, the average temperature at the same day yielded the best fit based on the Akaike's and Bayesian

information criteria. We therefore used the same day exposure for the calculation of the short-term exposure to temperature. As seen in Supplementary Fig. 2, showing the associations between the smoothed functions of short and long-term exposures to temperature and hospital admissions, the association with short-term exposure to temperature was close to linear throughout most of the exposure distribution, with a slight curve only in the 98th percentile of short-term temperature (10 °C). For long-term exposure however, the dose-response curves for all three outcomes were nonlinear. We therefore treated the association with short-term exposure to temperature as linear and used penalized splines for the long-term exposure.

Table 3 presents the associations between short and long-term exposures to $PM_{2.5}$ and temperature and each cause of admission estimated from the base model. Short-term exposure to temperature was associated with an 8.63% (95% CI: 7.88; 9.39) increase in respiratory admissions rate and 3.63% (95% CI: 3.01; 4.25) increase in cardiac admissions rate for an IQR (9.2 °C) increase in temperature, but not with stroke. Increases of long-term temperature in the 10th percentile were associated with higher admissions rate per IQR increase (2.2 °C), compared to the 90th percentile, for respiratory (6.24% and 1.37%, respectively), cardiac (−2.15% and − 1.69%, respectively) and stroke (7.32% and 0.15%, respectively) admissions.

For $PM_{2.5}$, an IQR (5.4 μg/m^3) increase in short-term exposure to $PM_{2.5}$ was associated with a 0.41% (95% CI: 0.16; 0.65) increase in respiratory admissions and a 1.20% (95% CI: 0.71; 1.69) increase in stroke admissions rate. Larger and statistically significant associations with IQR (2.3 μg/m^3) increases of long-term exposure to $PM_{2.5}$ were observed for respiratory (4.09% increase (95% CI: 3.31; 4.87) and cardiac (6.58% increase (95% CI: 5.90; 7.26) admissions rate.

Figs. 1 and 2 show the interaction of the short-term exposures and the modification of these exposures by monthly standard deviation of temperature. For respiratory admissions (Fig. 1), the effect of short-term exposure to temperature was stronger on days of higher $PM_{2.5}$ concentration (9.75%, 95% CI 8.91;10.60 in the 90th percentile) compared to days of lower concentration (7.68%, 95% CI 6.87;8.49 in the 10th percentile, interaction $p < 0.001$); and in months of higher temperature variability (8.99%, 95% CI 8.19;9.80 in the 90th percentile) compared to lower temperature variability (7.55%, 95% CI 6.53;8.57 in the 10th percentile, interaction $p < 0.001$). For cardiac admissions, the effect of short-term exposure to temperature was stronger on days of lower $PM_{2.5}$ concentration (4.12%, 95% CI 3.44; 4.79 in the 10th percentile) compared to days of higher concentration (3.08%, 95% CI 2.40; 3.77 in the 90th percentile, interaction $p < 0.001$).

The short-term effect of $PM_{2.5}$ on respiratory and cardiac admissions was significantly modified by short-term exposure to temperature and temperature variability (Fig. 2). For respiratory admissions, the effect of short-term exposure to $PM_{2.5}$ was stronger on hotter days (1.12%, 95% CI 0.78;1.45 in the 90th percentile) compared to colder days (−0.53%, 95% CI -0.92;-0.14 in the 10th percentile, interaction $p < 0.001$); and in months of higher temperature variability (1.63%, 95% CI 0.29;2.99 in the 90th percentile) compared to lower temperature variability (−0.45%, 95% CI -1.19;0.29 in the 10th percentile, interaction $p < 0.001$). For cardiac admissions, the effect of short-term exposure to $PM_{2.5}$ was stronger on colder days (0.56%, 95% CI 0.21;0.91 in the 10th percentile) compared to hotter days (−0.30%, 95% CI -0.57;-0.03 in the 90th percentile, interaction $p < 0.001$); and in months of higher temperature variability (0.99%, 95% CI -0.16;2.15 in the 90th percentile) compared to lower temperature variability (−0.56%, 95% CI 0.21;0.91 in the 10th percentile, interaction $p < 0.001$).

Table 1
Population characteristics.

Population characteristics	All respiratory (n = 750,694)	All cardiac (n = 1,053,731)	Ischemic stroke (n = 211,235)
Male gender, %(n)	44.50 (334,056)	45.28 (477,170)	41.40 (87,445)
Race, %(n)			
White	94.33 (708,106)	94.35 (994,171)	93.58 (197,677)
Black	2.96 (22,196)	3.13 (32,979)	3.70 (7806)
Other	2.71 (20,392)	2.52 (26,581)	2.72 (5752)
Age, Mean ± SD	79.99 ± 8.12	79.85 ± 8.03	80.77 ± 7.84

Table 2
Summary statistics for hospitalization day, 2-day average and annual moving average of exposure to $PM_{2.5}$ and temperature.

Exposure	Mean	SD	IQR
$PM_{2.5}$			
Lag 0	8.92	5.38	5.22;11.31
Lag 0–1 MA	8.92	4.76	5.65;11.05
Annual average	8.92	1.63	7.82;10.08
Temperature			
Lag 0	9.94	6.17	5.63;14.80
Lag 0–1 MA	9.94	4.45	7.62;12.83
Annual average	9.94	1.55	8.88;11.13

MA = moving average; IQR = inter-quartile range; SD = standard deviation.

4. Discussion

Our study shows associations between both short and long-term exposures to $PM_{2.5}$ and temperature and increased risk of hospital admissions, and evidence of synergy between the short-term exposures. Increased risk for respiratory admissions was associated with the short and long-term exposures, with larger effects of short-term exposure to $PM_{2.5}$ on warmer days, and larger effects of both short-term exposures to $PM_{2.5}$ and temperature on days of higher temperature variability. Increased risk for cardiac admissions was associated with long-term exposure to $PM_{2.5}$, and both short and long-term exposures to temperature, with smaller effects of short-term exposure to $PM_{2.5}$ on warmer days, and larger effects on days of higher temperature variability. A significantly increased risk of ischemic stroke was associated with the short-term exposure to $PM_{2.5}$ and long-term exposure to temperature, but the associations were not modified by $PM_{2.5}$, temperature or temperature variability. The finding of substantially larger effect sizes for longer-term exposure to $PM_{2.5}$ on incidence of ischemic stroke and on cardiac admissions than of shorter-term exposures is important, because it indicates that $PM_{2.5}$ exposure does not simply advance the

Table 3
The association between short and long-term exposure to $PM_{2.5}$ and temperature and cause specific admissions.

Cause	Exposure	Percent change (95% CI)
Respiratory	$PM_{2.5}$ short term	0.41% (0.16%; 0.65%)**
	$PM_{2.5}$, long term	4.09% (3.31%; 4.87%)**
	Temperature, short term	8.63% (7.88%; 9.39%)**
	Temperature, long term (10th p)	6.24% (6.54%; 5.93%)**
	Temperature, long term (90th p)	1.37% (1.28%; 1.47%)**
Cardiac	$PM_{2.5}$, short term	0.02% (−0.18%; 0.23%)
	$PM_{2.5}$, long term	6.58% (5.90%; 7.26%)**
	Temperature, short term	3.63% (3.01%; 4.25%)**
	Temperature, long term (10th p)	−2.15% (−2.36%; −1.93%)**
	Temperature, long term (90th p)	−1.69% (−1.77%; −1.60%)**
Ischemic stroke	$PM_{2.5}$ short term	1.20% (0.71%; 1.69%)**
	$PM_{2.5}$, long term	0.82% (−0.68%; 2.35%)
	Temperature, short term	−0.08% (−1.49%; 1.34%)
	Temperature, long term (10th p)	7.32% (6.68%; 7.96%)**
	Temperature, long term (90th p)	0.15% (−0.04%; 0.34%)

Results are presented as percent change and 95% Confidence Intervals (CI) for an IQR increase in short term PM2.5 (5.4 μg/m^3), long term $PM_{2.5}$ (2.3 μg/m^3), short term temperature (9.2 °C) and long term temperature (2.2 °C). The effect of the long-term exposure to temperature was modeled using penalized splines, results are therefore presented as percent change and 95% Confidence Intervals (CI) for IQR increases in the 10th (8 °C) and 90th (10.2 °C) percentile of temperature. We used the moving average of $PM_{2.5}$ at lag days 0–1 for the calculation of the short-term exposure to $PM_{2.5}$, temperature ta lag day 0 for the calculation of short-term temperature and annual averages for the long-term exposures of $PM_{2.5}$ and temperature.

** $p < 0.05$.

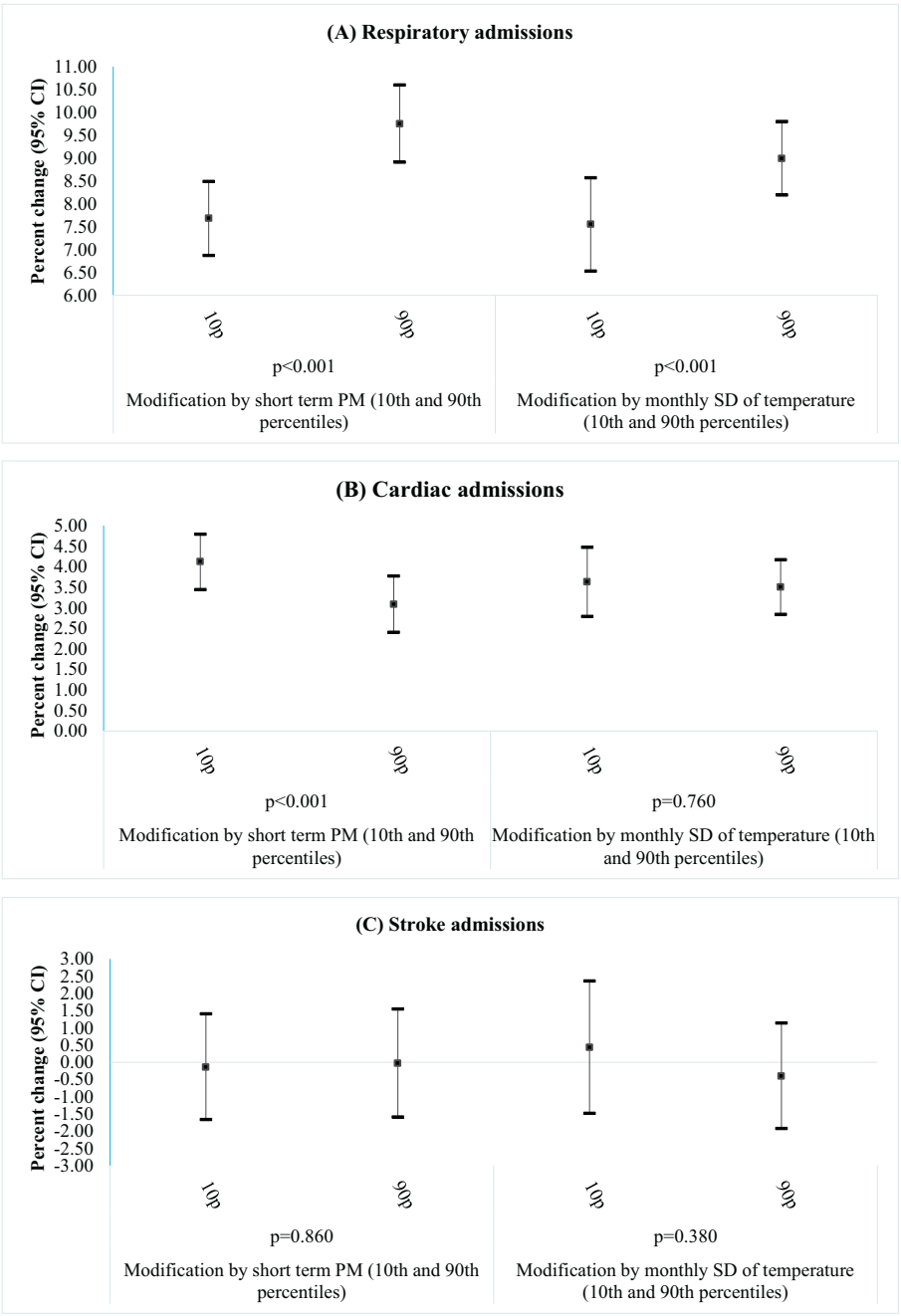

Fig. 1. The effect of short-term temperature across the range of short-term $PM_{2.5}$ and monthly standard deviation (SD) of temperature. Results are presented as percent change and 95% Confidence Intervals (CI) for an IQR increase in temperature at the 10th and 90th percentiles of the distribution of short-term exposure to $PM_{2.5}$and monthly standard deviation of temperature.

timing of these events, it increases the incidence rate. This is consistent with mortality studies, which show considerably larger effect size estimates for long-term $PM_{2.5}$ exposure than for short-term exposure (Kim et al., 2015b; Lu et al., 2015; Zhao et al., 2017). Current risk assessments by the U.S. EPA and WHO only estimate the effect of short-term exposure to $PM_{2.5}$ (or temperature) on these events, and the evidence from our study suggests these may be substantial underestimates. In addition, the $PM_{2.5}$ associations we found were entirely below the current U.S. annual standard of 35 μg/m^3 (Kim et al., 2015b), indicating those standards are inadequate to protect public health.

In recent decades, studies have suggested that extreme temperatures may have a significant health impact. Multiple studies have reported an excessive number of cardiac and respiratory hospitalizations during episodes of heat waves (Schwartz et al., 2004; Knowlton et al., 2009; Empana et al., 2009). Depending on the climate, episodes of extreme cold may also pose a threat to health in high latitude countries (Phung et al., 2016; Shaposhnikov et al., 2014). Studies of the associations between heat and hospital admissions show inconsistent results. A previous study performed among this study population (but for the entire country) found a higher risk for renal failure and heat stroke and a lower risk for congestive heart failure, associated with heat waves; no association was found with respiratory illness (Bobb et al., 2014). Other studies did find, however, an increased risk for respiratory admissions in this elderly population associated with extreme heat or increased temperatures (Anderson et al., 2013; Gronlund et al., 2014). Regarding cardiac admissions, a recent meta-analysis reported an increase in the risk for hospitalizations associated with short-term exposures to both extreme heat and cold (Phung et al., 2016). Another

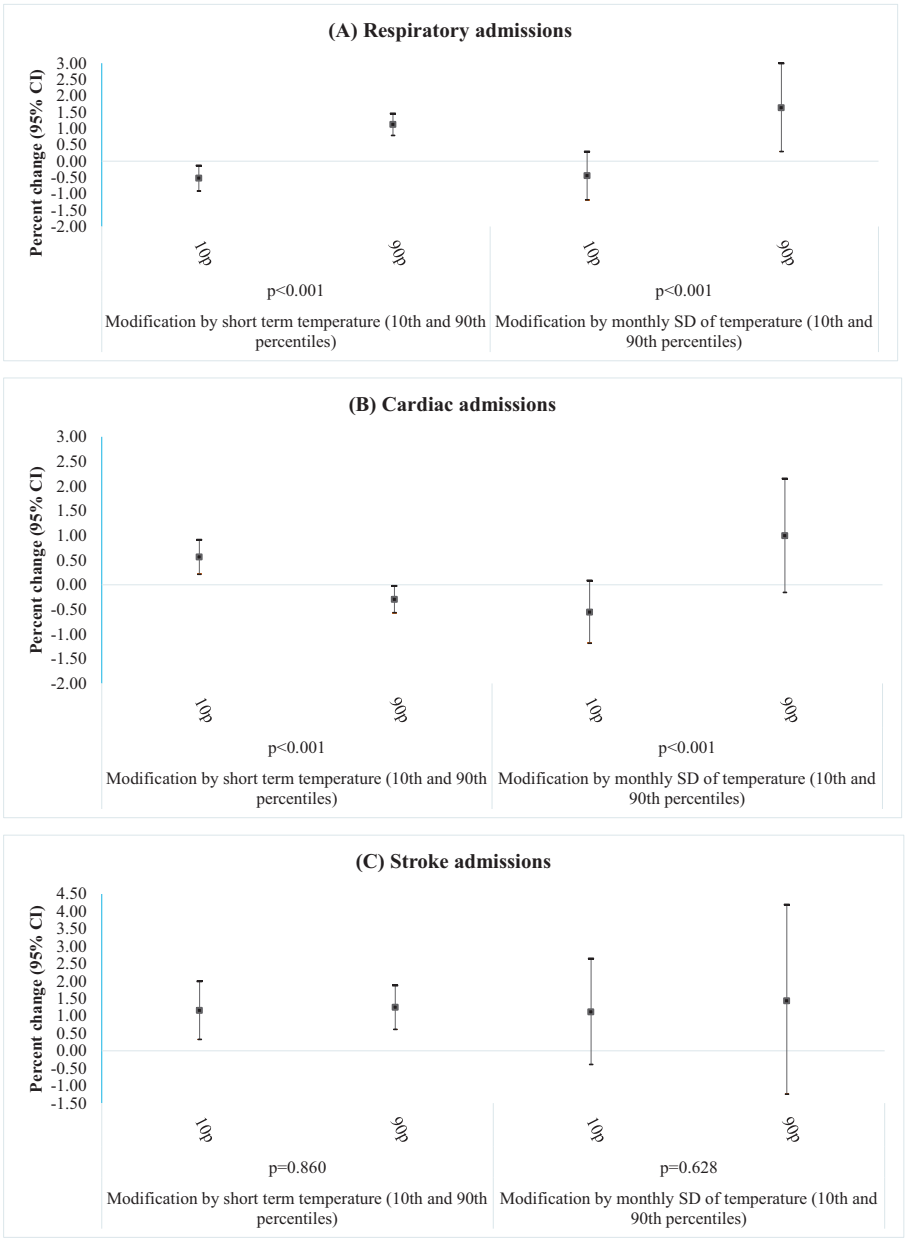

Fig. 2. The effect of short-term $PM_{2.5}$ across the range of short-term temperature and monthly standard deviation (SD) of temperature. Results are presented as percent change and 95% Confidence Intervals (CI) for an IQR increase in short-term exposure to $PM_{2.5}$ at the 10th and 90th percentiles of the distribution of short-term exposure to temperature and monthly standard deviation of temperature.

review found heat exposure to be associated with increased risk of cardiac, cerebrovascular and respiratory mortality, but not cardiac or cerebrovascular morbidity (Song et al., 2017). The evidence on the association between $PM_{2.5}$ and hospital admissions is more consistent, with evidence of links to cardiac (Dominici et al., 2006; Luo et al., 2015; Zanobetti et al., 2009) respiratory (Bell et al., 2008; Zheng et al., 2015) and stroke admissions (Yitshak-Sade et al., 2015; Wang et al., 2014).

All of the above studies assessed associations with either acute or chronic exposure. A key finding of this study is the independent effects of short and long-term exposures to $PM_{2.5}$ and temperature while accounting for both windows of exposure simultaneously. For all the cause-specific admissions tested, the long-term effect estimate of $PM_{2.5}$ was larger than the short-term effect. Interestingly, for respiratory and stroke admissions, the short-term effect was still present independently of the long-term effect. Both short and long-term effects of $PM_{2.5}$ on health are biologically plausible. PM exposure can directly affect the airways, bronchiole, and alveolus through inhalation, decreasing lung function and inducing pulmonary inflammation and oxidative stress (Ren et al., 2006; Pope and Dockery, 2006). Cardiovascular symptoms can be directly induced through the effect of PM on receptors of the lungs, blood and cardiovascular system or indirectly mediated through inflammatory pathways and oxidative stress (Brook et al., 2010). The stronger effect of the long-term exposures can be explained by cumulative damage of these prolonged exposures (Kloog et al., 2012).

Our findings show a larger increase in PM related respiratory admission rate on warmer days and days of higher temperature variability. Several theories were suggested to explain this synergistic effect with respect to cardiorespiratory morbidity and mortality. Stafoggia et al. hypothesized that the modification, of PM-associated mortality, by temperature is mainly due to higher exposure to air pollution during warmer temperatures (Stafoggia et al., 2008). Another theory is that temperature exposure can cause physiological stress and alter the response to the air pollutants, especially among more vulnerable

individuals (Li et al., 2015a). We also observed a larger increase in temperature related respiratory admission rate on months of higher temperature variability. Unstable temperatures may modify the population response to temperature exposure by affecting heart rate, blood pressure, blood viscosity, peripheral vasoconstriction and the autonomic nervous system. Different countries may present different patterns of association with temperature variability depending on the climate (Guo et al., 2016).

For cardiac admissions, larger effects of $PM_{2.5}$ were observed at lower temperatures. These results are in accordance with previous findings of larger $PM_{2.5}$ related increases in cardiac disease admission rate during the winter season (Bell et al., 2008; Hsu et al., 2017). These findings may be explained by the extensive use of coal, oil, diesel or wood burn based heating during colder temperatures. This, alongside a tendency to stay indoors with poor ventilation, may increase the PM effect (Hsu et al., 2017). Furthermore, the toxicity of $PM_{2.5}$ may vary by its composition, which may vary seasonally and affect differently on human health (Peng et al., 2009), specifically on cardiac and respiratory outcomes. Interestingly, similar to respiratory admissions, larger $PM_{2.5}$ effects were also observed on months of higher temperature variability. Which, again, may be related to the body response to unstable temperatures.

A major limitation of this study is its ecological nature, which did not allow us to control for individual level potential confounders such as age, diet, socioeconomic status etc. To minimize the potential confounding within the limits of this study, we have used area level socioeconomic variables. In addition, the assignment of exposure based on ZIP code rather than geocoded addresses may introduce some exposure misclassification into our study. To address that, we averaged the predictions obtained from our high spatially resolved satellite-based models, within the limits of each ZIP code.

In conclusion, our findings indicate associations between $PM_{2.5}$, temperature and respiratory, cardiac and stroke admissions rate, with stronger effects of long-term exposure to $PM_{2.5}$. We observed synergistic effects of the short-term exposures, and of $PM_{2.5}$ and temperature and monthly temperature variability, with respect to respiratory and cardiac admissions. These findings emphasize the importance in assessing the joint effect of air pollution and climate parameters when investigating their effect on health.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2018.05.181.

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