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Association between $PM_{2.5}$ exposure and heart rate variability for the patients with cardiac problems in Japan

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Abstract

A reduction in heart rate variability (HRV) is reportedly associated with an increased risk of cardiovascular mortality and morbidity. In previous studies, an inverse association was noted between HRV and particulate air pollution, but the sample populations were small and most consisted only of elderly individuals. We examined the association between 24-h HRV and fine particulate matter ($PM_{2.5}$) in a large study population spanning 7 prefectures in Japan from April 2010 through March 2013. Meta-analysis was also performed. In total, 59,493 records of 24-h HRV for patients aged 20–90 years with symptoms/signs suggestive of heart disease were included in this analysis. Air pollution data were obtained from the National Institute for Environmental Studies. Regression models were used to examine the association between daily concentration of $PM_{2.5}$ and HRV indices (e.g., standard deviation of normal-to-normal (SDNN), SD of average NN internals calculated over short periods (SDANN), very low frequency (VLF), and ultra-low frequency (ULF)). The model was adjusted for age, sex, temperature, and relative humidity. We examined the lagged association for single (up to lag3) and moving average (up to lag03). We found that decreases in HRV indices, especially for SDNN, SDANN, VLF, and ULF, were associated with $PM_{2.5}$ in Hokkaido, Chiba, Tokyo, and Kanagawa. In contrast, there was no clear association between HRV with $PM_{2.5}$ in Saitama and Aichi. Meta-analysis revealed significant decreases in SDNN, SDANN, VLF, and ULF were associated with $PM_{2.5}$. Short-term exposure to $PM_{2.5}$ was associated with lower 24-h HRV in patients with symptoms/signs suggestive of heart disease.

Keywords Air pollution · $PM_{2.5}$ · Short-term exposure · Cardiovascular · HRV

Introduction

Air pollution is one of the most serious global concerns, given the adverse effects on human health and the environment. An association between air pollution and human health outcomes has been reported by numerous epidemiological studies conducted over the past decade. Many of these studies have emphasized the effects of particulate matter (PM) air pollution on mortality and morbidity for cardiovascular disease (CVD) (Brook et al. 2010; Gold & Mittleman 2013; Pope et al., 2004a; Taneepanichskul et al. 2018). Proposed mechanisms to explain the association between PM air pollution inhalation and CVD include oxidative stress, endothelial dysfunction, systemic inflammation (Araujo 2011; Brook et al. 2004, 2010; Pope et al., 2004b), insulin resistance (Rajagopalan & Brook 2012), epigenetic modification (Peng et al. 2016; Wang et al. 2016), and changes in cardiac autonomic function and the autonomic nervous system (Brook et al. 2010; Rajagopalan & Brook 2012).

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Heart rate variability (HRV) is the physiological phenomenon of variation occurring in the time interval between heartbeats and is measured by variation in the beat-to-beat interval. Analysis of HRV provides insight into autonomic function and has broad applications in human physiology (Stein & Kleiger 1999). HRV is widely used to estimate cardiac autonomic function and can be assessed over short-term (usually 5–15 min) or long-term (24 h) timeframes (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996). Although short-term records of HRV are used more widely due to high practicality and reproducibility, the 24-h measurement has been used as an alternative method to assess patient mortality and adverse prognoses (Min et al., 2008b). Moreover, 24-h HRV was found to be a stronger predictor of death from chronic heart failure relative to other conventional clinical measurements (Nolan et al. 1998). Fei et al. (1994) showed that short-term HRV values are related to long-term values, but the correlations were not strong enough for short-term HRV to replace 24-h HRV altogether. Additionally, short-term HRV has lower prognostic power than 24-h measurements, specifically with regard to morbidity and mortality (Shaffer & Ginsberg 2017).

A reduction in HRV has been associated with a higher risk of mortality among adult and elderly subjects (Huikuri & Stein 2013; Stein et al. 1994; Thayer et al. 2010), for example, as observed in several studies targeting cardiovascular diseases such as myocardial infarction (Buccelletti et al. 2009) and coronary artery disease (Carney et al. 1995; Huikuri 1995). Recent studies have consistently found that higher particles with diameters ≤ 2.5 μm ($PM_{2.5}$) and particles with diameters ≤ 10 μm (PM_{10}) concentrations were associated with lower HRV in elderly subjects (Creason et al. 2001; Gold et al. 2000; Holguín et al. 2003; Liao et al. 1999, 2004; Pope et al. 1999, Pope et al., 2004b). Exposure to ozone (O_3), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2) in adult and elderly subjects was also associated with lower HRV (Min et al., 2008a; Park et al. 2005), which may increase the risk of cardiovascular mortality and morbidity. However, several previous studies were performed in relatively small study populations (Creason et al. 2001; Gold et al. 2000; Holguín et al. 2003; Liao et al. 1999, 2004), and nearly all of these used short-term HRV rates and included only elderly subjects. In this study, we aimed to examine the association between short-term exposure to $PM_{2.5}$ and 24-h HRV in a large study population in Japan.

Methods

Study design and subjects

We conducted a cross-sectional study using the data of ambulatory electrocardiogram (ECG) data from the Allostatic State Mapping by Ambulatory ECG Repository (ALLSTAR) project (Hayano et al. 2018). This project was launched in 2009 and collected the 24-h ambulatory ECG data of the patients who visited the medical institutes and underwent 24-h ambulatory ECG monitoring to diagnose heart diseases. The goals of the ALLSTAR project are to establish a new method to evaluate the health impact of environmental factors, to increase the value of the Holter ECG in medical treatment, and to contribute to the promotion of predictive and preventive medicine in the longevity society (http://www.med.nagoya-cu.ac.jp/mededu.dir/allstar/). The ALLSTAR project was approved by the Institutional Review Board of Nagoya City University Graduate School of Medical Sciences and Nagoya City University Hospital (No. 709). As shown in the Appendix (Fig. S1), we extracted the data of the patients living in Aichi from April 2010 through March 2012; in Tokyo, Kanagawa, and Hokkaido from April 2011 through March 2013; and in Saitama, Chiba, and Osaka from April 2010 through March 2013. Patients who met the following criteria were included: (1) 20 years $\leq$ age $\leq$ 89 years; (2) ECG data with sinus node rhythm (SNR). Those who had chronic atrial fibrillation (CAF) or an implanted pacemaker or those with paroxysmal atrial fibrillation (PAF) or atrial flutter (AFL) were excluded.

HRV measurement

Ambulatory ECG was measured by a 24-h ECG recorder (Cardy 303 series, Suzuken Co. Ltd., Nagoya, Japan), a continuous medical test device used to measure heart rate, rhythm, and other abnormalities that may affect normal heart function, following a standard procedure (Hayano et al. 2018; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996). Another term used for HRV is "RR variability," for which R is the point corresponding to the peak of the QRS complex of the ECG wave. The term "NN" is used in place of "RR" to emphasize when the processed beats are "normal" beats (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996).

As shown in Fig. 1, QRS complex is the combination of three of the graphical deflections seen on a typical ECG. It corresponds to the depolarization of the right and left ventricles of the human heart and contraction of the large ventricular muscles. The instantaneous heart rate (R-R interval) can be calculated from the time between any two QRS complexes. The P wave indicates atrial depolarization. It occurs when the sinus node creates an action potential that depolarizes the atria. The T wave occurs after the QRS complex and is a result of ventricular repolarization (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996).

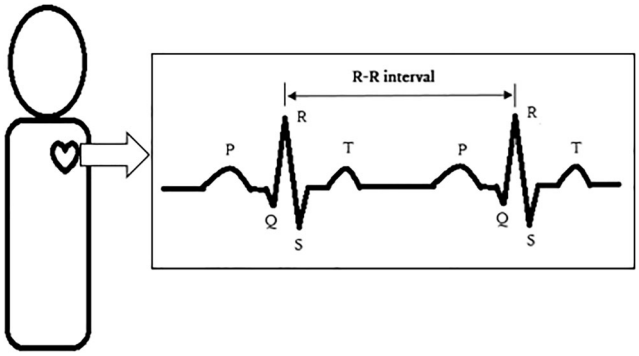

Fig. 1 QRS complex

In this study, we excluded the subjects with less than 18 h (821 subjects) or more than 26 h (25 subjects), in accordance with previous studies (Pieters et al. 2012; Winkler et al. 2013). We assessed the following HRV indices: mean of normal-to-normal (NN) intervals (MEANNN), standard deviation of NN (SDNN) intervals, standard deviation of the average NN intervals calculated over short periods (typically 5 min; (SDANN)), high frequency (HF, 0.15–0.40 Hz), low frequency (LF, 0.04–0.15 Hz), very low frequency (VLF, 0.003–0.04 Hz), and ultra-low frequency (ULF, ≤ 0.003 Hz). We also calculated the LF/HF ratio to express the relative balance between sympathetic-vagal nervous activity (Stein et al. 1994). HRV was only analyzed when NN intervals were ≥ 90% of all R-R intervals (Hayano et al. 1999) and R-R intervals ranged from 350 to 1300 ms (Franz 1994; Suzuki et al. 2012) to avoid the adverse effects of exclusion of frequent ectopic beats or noises (Hayano et al. 1999).

Exposure assessment

Daily 24-h measurements of $PM_{2.5}$, photochemical oxidants (O_x), NO_2, and SO_2 from 2010 to 2013 were obtained from the National Institute for Environmental Studies (NIES). These data were hourly measurements from background monitoring stations. The 24-h means were averaged to obtain the daily mean (24-h mean) concentration value. If there were more than 4 h of missing values, the data were considered missing data for the day. We used air pollution data from one background monitoring station from each prefecture that collected $PM_{2.5}$ data during the study period. For Tokyo, there were 5 monitoring stations and the correlation between $PM_{2.5}$ in each station in Tokyo in the study period (Apr. 2011 to Mar. 2013) was higher than 0.9 (Table S1; in the Appendix). We chose a station located at the center of the 23 wards of Tokyo that has a large population. The study period for each prefecture was determined according to the availability of $PM_{2.5}$ data. For other 6 prefectures, there was only one ambient monitoring station in each prefecture that had complete data of $PM_{2.5}$ in this study period (Apr. 2010 to Mar. 2013). Weather data, including daily average temperature and relative humidity, were obtained from the Japan Meteorological Agency.

Statistical analysis

Regression models were used to analyze the association of short-term exposure to $PM_{2.5}$ with 24-h HRV indices. Measures of HRV and age were $\log_{10}$-transformed to improve normality and stabilize variances for suitability to analyze data by linear regression (Park et al. 2005). A linear term of each HRV measure was included in the model. The model was adjusted for $\log_{10}$(age), sex, temperature (averaged from the current day to 1 day before), and relative humidity (the current day). We examined lagged effects up to the previous 3 days (lag3) and the moving average of the current day and previous 3 day (lag03) (Min et al., 2008a; Park et al. 2005) for single and moving average lag structures, respectively.

Statistical analyses comprised two stages: (1) analysis of prefecture-specific associations between short-term exposure to ambient $PM_{2.5}$ and HRV indices; and (2) a random-effects meta-analysis to obtain pooled effect estimates of ambient $PM_{2.5}$ on HRV indices. An I^2 statistic was used to describe the proportion of heterogeneity not due to chance, while Cochran's Q statistic was used to test for heterogeneity (Higgins & Thompson 2002).

We also included the co-pollutants (O_x, NO_2, and SO_2) one by one into the model (two-pollutant models) to evaluate the robustness of the single-pollutant model. The associations were presented as percentage change in HRV indices per 10 μg/m^3 increase in $PM_{2.5}$, with 95% confidence intervals (CIs).

All statistical analyses were conducted using R statistical project (version 3.5.3). $P < 0.05$ was considered statistically significant.

Results

Table 1 shows the general characteristics and HRV measurements of subjects from 7 prefectures in Japan. We categorized patients by sex and seven age groups: 20–29 years, 30–39 years, 40–49 years, 50–59 years, 60–69 years, 70–79 years, and 80–89 years. In general, there were more elderly subjects (age 60 to 89) than adults (age 20 to 59), and more females than males. The population from age group 70–79 was the largest among the age groups across all 7 prefectures. Additionally, mean subject age in Hokkaido was slightly higher than that of other prefectures.

Table 2 shows daily summary values of the environmental variables. Mean concentrations of ambient $PM_{2.5}$ throughout these prefectures in Japan ranged from 12.4 to 19.0 μg/m^3. The lowest mean concentration of ambient $PM_{2.5}$ was observed in Hokkaido, whereas the highest ambient $PM_{2.5}$ was

Table 1 Basic characteristics of study subjects in each prefecture during the study period

	Hokkaido	Saitama	Chiba	Tokyo	Kanagawa	Aichi	Osaka
Study subjects	13,247	8458	5816	13,228	8239	4464	6041
Sex, *n* (%)							
Male	5797 (43.7)	3503 (41.4)	2309 (39.7)	6418 (48.5)	3846 (46.7)	1952 (43.7)	2521 (41.7)
Female	7472 (56.3)	4936 (58.4)	3505 (60.3)	6806 (51.5)	4391 (53.3)	2502 (56.1)	3511 (58.1)
Age (years), mean (SD)	68.2 (13.7)	65.0 (14.5)	64.9 (14.8)	63.2 (15.7)	63.3 (15.4)	63.2 (15.1)	65.6 (15.0)
Age category, *n* (%)							
20–29	184 (1.4)	170 (2.0)	115 (2.0)	441 (3.3)	209 (2.5)	132 (3.0)	172 (2.9)
30–39	412 (3.1)	448 (5.3)	336 (5.8)	893 (6.8)	506 (6.1)	276 (6.2)	291 (4.8)
40–49	776 (5.9)	797 (9.4)	547 (9.4)	1404 (10.6)	1030 (12.5)	470 (10.5)	515 (8.5)
50–59	1488 (11.2)	1015 (12.0)	736 (12.7)	1813 (13.7)	1125 (13.7)	609 (13.6)	653 (10.8)
60–69	3317 (25.0)	2197 (26.0)	1475 (25.4)	3156 (23.9)	1884 (22.9)	1172 (26.3)	1438 (23.8)
70–79	4270 (32.2)	2632 (31.1)	1683 (28.9)	3732 (28.2)	2352 (28.6)	1251 (28.0)	2022 (33.5)
80–89	2827 (21.3)	1199 (14.2)	924 (15.9)	1789 (13.5)	1133 (13.8)	554 (12.4)	950 (15.7)
HRV, mean (SD)							
Log(MEANNN)	2.92 (0.06)	2.92 (0.05)	2.92 (0.05)	2.91 (0.05)	2.91 (0.05)	2.91 (0.05)	2.91 (0.05)
Log(SDNN)	2.06 (0.14)	2.10 (0.12)	2.10 (0.12)	2.09 (0.14)	2.10 (0.12)	2.10 (0.12)	2.10 (0.12)
Log(SDANN)	2.01 (0.16)	2.06 (0.13)	2.06 (0.14)	2.05 (0.15)	2.06 (0.14)	2.06 (0.14)	2.05 (0.14)
Log(HF)	2.54 (0.62)	2.62 (0.57)	2.64 (0.57)	2.58 (0.60)	2.61 (0.57)	2.63 (0.58)	2.60 (0.58)
Log(LF)	2.70 (0.51)	2.81 (0.45)	2.83 (0.46)	2.78 (0.49)	2.82 (0.46)	2.83 (0.46)	2.79 (0.47)
Log(LF/HF)	0.16 (0.34)	0.19 (0.33)	0.19 (0.32)	0.20 (0.34)	0.21 (0.33)	0.19 (0.32)	0.18 (0.33)
Log(VLF)	3.27 (0.38)	3.35 (0.33)	3.36 (0.34)	3.33 (0.37)	3.36 (0.34)	3.36 (0.34)	3.32 (0.35)
Log(ULF)	4.00 (0.31)	4.09 (0.26)	4.09 (0.27)	4.06 (0.30)	4.09 (0.27)	4.09 (0.27)	4.08 (0.27)

recorded in Osaka. Mean temperatures ranged from 9.2 °C in Hokkaido to 16.9 °C in Osaka, while mean relative humidity ranged from 60.5% in Tokyo to 70.0% in Hokkaido (Table 2).

According to single lag structure (Table S2; in the Appendix), significant associations between HRV indices and $PM_{2.5}$ were mostly observed in the current day (lag0) and previous 1 day (lag1). Table 3 presents the estimated percent changes in HRV indices for 10 μg/m^3 increments in $PM_{2.5}$ after adjusting for age, sex, temperature, and relative humidity. We observed significant decreases in SDNN, SDANN, and ULF associated with $PM_{2.5}$ at lag01, lag02, and lag03 in Hokkaido. A significant decrease in VLF was also associated with $PM_{2.5}$ at lag02 in Hokkaido. Significant decreases in MEANNN, SDNN, SDANN, VLF, and ULF were associated with $PM_{2.5}$ at lag01 in Kanagawa. Moreover, we also found decreases in SDNN, SDANN, and ULF in Chiba and Tokyo related to $PM_{2.5}$ at lag02 and lag03, respectively. Although not statistically significant, we detected an inverse relationship between $PM_{2.5}$ with SDNN, SDANN, and VLF at lag01 in Osaka. However, we found no significant association between HRV and $PM_{2.5}$ for any of moving average lags in Aichi and Saitama.

Pooled results for lag01 are shown in Table 4. Significant decreases in SDNN, SDANN, and ULF were associated with $PM_{2.5}$. A decrease in VLF was also associated with $PM_{2.5}$. The association of $PM_{2.5}$ with HRV indices in moving average lags from two-pollutant models in a random-effects meta-analysis showed no marked change when O_x, NO_2, and SO_2

Table 2 Daily average concentration of each environmental variable examined in each prefecture during the study period

	Hokkaido	Saitama	Chiba	Tokyo	Kanagawa	Aichi	Osaka
$PM_{2.5}$ (μg/m^3)	12.4 (5.7)	15.9 (9.1)	14.8 (4.4)	14.7 (8.0)	17.1 (9.7)	16.6 (8.7)	19.0 (9.4)
SO_2 (ppb)	0.8 (0.9)	1.1 (0.9)	3.1 (2.0)	1.5 (0.8)	4.7 (2.7)	1.4 (0.8)	3.0 (2.1)
NO_2 (ppb)	10.7 (7.8)	20.8 (9.1)	17.1 (7.5)	17.9 (8.5)	20.7 (9.4)	20.1 (7.6)	21.7 (8.5)
O_x (ppb)	26.4 (10.6)	23.8 (12.1)	26.7 (12.0)	26.8 (12.9)	19.8 (12.2)	23.3 (11.5)	25.7 (12.1)
Temperature (°C)	9.2 (10.3)	15.5 (9.1)	16.3 (8.3)	16.6 (8.4)	16.2 (8.1)	16.2 (9.1)	16.9 (8.7)
Relative humidity (%)	70.0 (9.9)	64.2 (14.9)	66.0 (15.3)	60.5 (15.7)	66.5 (16.1)	66.0 (12.8)	62.6 (11.3)

Values shown as daily means (standard deviation)

Table 3 Prefecture-specific percent change (95% CI) in HRV indices in moving average $PM_{2.5}$ lags

	Hokkaido	Saitama	Chiba	Tokyo	Kanagawa	Aichi	Osaka
Log(MEANNN)							
Lag01	− 0.43 (− 0.88, 0.02)	− 0.16 (− 0.49, 0.16)	− 0.18 (− 0.59, 0.23)	− 0.21 (− 0.53, 0.12)	− 0.25 (− 0.56, 0.07)	− 0.28 (− 0.73, 0.17)	− 0.26 (− 0.62, 0.09)
Lag02	− 0.46 (− 0.96, 0.04)	− 0.24 (− 0.59, 0.12)	− 0.19 (− 0.64, 0.26)	− 0.04 (− 0.4, 0.31)	− 0.1 (− 0.45, 0.25)	− 0.27 (− 0.77, 0.22)	− 0.27 (− 0.66, 0.12)
Lag03	− 0.51 (− 1.05, 0.03)	− 0.16 (− 0.55, 0.23)	− 0.15 (− 0.64, 0.34)	0.06 (− 0.33, 0.46)	− 0.14 (− 0.53, 0.25)	− 0.28 (− 0.81, 0.26)	− 0.2 (− 0.62, 0.23)
Log(SDNN)							
Lag01	− 1.79 (− 2.93, − 0.65)*	0.08 (− 0.68, 0.85)	− 0.74 (− 1.73, 0.25)	− 0.5 (− 1.3, 0.31)	− 0.89 (− 1.65, − 0.12)*	0.62 (− 0.48, 1.72)	− 0.46 (− 1.32, 0.41)
Lag02	− 2.4 (− 3.65, − 1.13)*	0.11 (− 0.73, 0.95)	− 1.04 (− 2.12, 0.06)	− 0.64 (− 1.53, 0.24)	− 0.49 (− 1.33, 0.36)	0.73 (− 0.47, 1.95)	− 0.32 (− 1.27, 0.64)
Lag03	− 2.44 (− 3.78, − 1.08)*	− 0.03 (− 0.93, 0.88)	− 0.85 (− 2.02, 0.34)	− 1.07 (− 2.05, − 0.08)*	− 0.55 (− 1.48, 0.4)	0.8 (− 0.49, 2.12)	− 0.29 (− 1.31, 0.75)
Log(SDANN)							
Lag01	− 2.37 (− 3.62, − 1.1)*	0.13 (− 0.73, 1.0)	− 0.66 (− 1.77, 0.47)	− 0.68 (− 1.58, 0.23)	− 1.07 (− 1.92, − 0.21)*	0.53 (− 0.7, 1.78)	− 0.54 (− 1.5, 0.43)
Lag02	− 3.02 (− 4.4, − 1.62)*	0.13 (− 0.81, 1.08)	− 1.03 (− 2.25, 0.21)	− 0.81 (− 1.81, 0.19)	− 0.78 (− 1.72, 0.17)	0.51 (− 0.85, 1.88)	− 0.33 (− 1.4, 0.74)
Lag03	− 2.91 (− 4.4, − 1.4)*	− 0.17 (− 1.19, 0.85)	− 0.82 (− 2.14, 0.82)	− 1.33 (− 2.43, − 0.22)*	− 0.96 (− 2.0, 0.09)	0.74 (− 0.72, 2.22)	− 0.3 (− 1.45, 0.86)
Log(HF)							
Lag01	− 3.1 (− 7.92, 1.97)	− 0.82 (− 4.52, 3.02)	− 0.91 (− 5.53, 3.93)	1.06 (− 2.56, 4.82)	− 1.93 (− 5.44, 1.71)	− 1.01 (− 6.19, 4.45)	1.4 (− 2.75, 5.73)
Lag02	− 2.19 (− 7.59, 3.52)	− 1.62 (− 5.62, 2.56)	− 1.99 (− 7.02, 3.31)	0.31 (− 3.67, 4.44)	0.5 (− 3.47, 4.63)	1.43 (− 4.38, 7.6)	1.95 (− 2.64, 6.75)
Lag03	− 0.39 (− 6.28, 5.88)	− 1.92 (− 6.24, 2.6)	− 1.29 (− 6.76, 4.5)	0.21 (− 4.2, 4.82)	1.55 (− 2.88, 6.18)	1.73 (− 4.54, 8.41)	1.16 (− 3.74, 6.31)
Log(LF)							
Lag01	− 2.6 (− 6.57, 1.53)	0.59 (− 2.3, 3.57)	− 2.2 (− 5.8, 1.53)	− 0.13 (− 3.0, 2.82)	− 1.56 (− 4.31, 1.28)	1.48 (− 2.65, 5.8)	− 0.44 (− 3.63, 2.85)
Lag02	− 2.83 (− 7.23, 1.77)	1.08 (− 2.09, 4.36)	− 3.25 (− 7.16, 0.83)	− 0.14 (− 3.31, 3.13)	0.35 (− 2.75, 3.55)	2.55 (–2.04, 7.35)	− 0.11 (− 3.63, 3.55)
Lag03	− 2.18 (− 6.93, 2.81)	0.51 (− 2.9, 4.04)	− 2.29 (− 6.55, 2.18)	− 0.79 (− 4.29, 2.84)	0.22 (− 3.2, 3.77)	2.56 (− 2.37, 7.75)	− 0.56 (− 4.34, 3.36)
Log(LF/HF)							
Lag01	0.51 (− 2.14, 3.24)	1.42 (− 0.66, 3.54)	− 1.3 (− 3.76, 1.22)	− 1.18 (− 3.12, 0.8)	0.38 (− 1.59, 2.38)	2.52 (− 0.36, 5.49)	− 1.82 (− 3.98, 0.39)
Lag02	− 0.66 (− 3.57, 2.34)	2.74 (0.44, 5.1)*	− 1.29 (− 3.99, 1.5)	− 0.45 (− 2.61, 1.75)	− 0.14 (− 2.3, 2.06)	1.1 (− 2.02, 4.32)	− 2.01 (− 4.38, 0.42)
Lag03	− 1.8 (− 4.89, 1.38)	2.48 (− 0.01, 5.02)	− 1.01 (− 3.94, 2.01)	− 1.0 (− 3.38, 1.44)	− 1.31 (− 3.67, 1.11)	0.82 (− 2.53, 4.28)	− 1.7 (− 4.26, 0.93)
Log(VLF)							
Lag01	− 2.59 (− 5.56, 0.47)	0.45 (− 1.64, 2.59)	− 0.61 (− 3.27, 2.12)	− 0.33 (− 2.48, 1.87)	− 1.98 (− 3.98, 0.05)	1.05 (− 1.97, 4.16)	− 1.33 (− 3.67, 1.06)
Lag02	− 3.49 (− 6.75, − 0.12)*	0.8 (− 1.49, 3.15)	− 1.16 (− 4.07, 1.84)	− 0.25 (− 2.63, 2.19)	− 0.27 (− 2.51, 2.02)	1.03 (− 2.28, 4.46)	− 1.02 (− 3.61, 1.64)
Lag03	− 3.36 (− 6.87, 0.28)	0.01 (− 2.45, 2.54)	− 0.73 (− 3.89, 2.53)	− 0.65 (− 3.29, 2.05)	− 0.26 (− 2.74, 2.28)	1.39 (− 2.19, 5.09)	− 1.29 (− 4.06, 1.57)
Log(ULF)							
Lag01	− 4.86 (− 7.21, − 2.45)*	0.21 (− 1.46, 1.9)	− 1.65 (− 3.79, 0.53)	− 1.45 (− 3.18, 0.31)	− 1.78 (− 3.42, − 0.11)*	0.77 (− 1.64, 3.24)	− 0.63 (− 2.5, 1.28)
Lag02	− 6.3 (− 8.87, − 3.66)*	0.09 (− 1.72, 1.94)	− 2.35 (− 4.68, 0.05)	− 1.84 (− 3.74, 0.09)	− 1.22 (− 3.04, 0.63)	0.8 (− 1.84, 3.52)	− 0.1 (− 2.17, 2.01)
Lag03	− 6.27 (− 9.03, − 3.42)*	− 0.42 (− 2.38, 1.57)	− 1.91 (− 4.45, 0.69)	− 2.9 (− 4.99, − 0.77)*	− 1.69 (− 3.7, 0.36)	1.37 (− 1.49, 4.31)	− 0.01 (− 2.24, 2.28)

Coefficients expressed as percent change per 10 μg/m^3 . Significance indicated by *$P < 0.05$

Lag01, the moving average of the current day and previous 1 day

Table 4 Estimated percent change (95% CI) in HRV indices (pooled effect) for $PM_{2.5}$ levels (lag01)

	Percent change (%)	I^2 (%)	Cochran's Q test	
			Q	P value
Log(MEANNN)	− 0.24 (− 0.38, − 0.1)*	0.0	1.1	0.98
Log(SDNN)	− 0.51 (− 1.01, − 0.01)*	53.6	12.4	0.05
Log(SDANN)	− 0.64 (− 1.26, − 0.02)*	62.2	14.7	0.02
Log(HF)	− 0.61 (− 2.18, 0.99)	0.0	3.2	0.78
Log(LF)	− 0.64 (− 1.87, 0.61)	0.0	3.79	0.71
Log(LF/HF)	− 0.02 (− 1.13, 1.09)	39.4	10.0	0.12
Log(VLF)	− 0.78 (− 1.67, 0.15)	0.75	5.82	0.44
Log(ULF)	− 1.29 (− 2.51, − 0.05)*	63.4	15.1	0.02

Coefficients expressed as percent change per 10 μg/m^3. Significance indicated by *$P < 0.05$

were added to the models as shown in the Appendix (Table S3). In addition, these associations still remained after including 846 subjects with less than 18 h (821 subjects) or more than 26 h (25 subjects) in the analysis.

Sex- and age-group specific results are shown in the Appendix. The associations between HRV indices and $PM_{2.5}$ did not differ between males and females (Fig. S2; in the Appendix). Similarly, no significant age group–dependent differences were observed (Fig. S3; in the Appendix).

Discussion

In this study, we investigated the association between short-term $PM_{2.5}$ and 24-h HRV in 7 prefectures in Japan. Decreases in HRV indices, especially for SDNN, SDANN, VLF, and ULF, were associated with $PM_{2.5}$ in Hokkaido, Chiba, Tokyo, and Kanagawa. Although the results in Osaka were not significant, the findings in this prefecture followed the same pattern as that observed in the other four prefectures. In contrast, we found no clear association between $PM_{2.5}$ and HRV indices in Saitama and Aichi. When the results were pooled, decreases in SDNN, SDANN, VLF, and ULF were found to be associated with $PM_{2.5}$.

Previous studies have consistently found that ambient $PM_{2.5}$ was associated with reduced short-term HRV in elderly subjects (Creason et al. 2001; Holguín et al. 2003; Liao et al. 1999). Some previous studies that examined high average ambient PM concentrations (> 50 μg/m^3) found that $PM_{2.5}$ and PM_{10} were associated with decreased 24-h HRV (Chuang et al. 2007; Pope et al. 1999). In contrast, other studies of lower average ambient PM concentrations (< 20 μg/m^3) did not find a significant association between $PM_{2.5}$ and 24-h HRV (Lipsett et al. 2006) or short-term HRV (Sullivan et al. 2005). In the present study, short-term exposure to $PM_{2.5}$ was associated with lower 24-h HRV, particularly for SDNN, SDANN, VLF, and ULF. These associations remained even after adjusting for co-pollutants. However, we found no clear association between 24-h HRV and $PM_{2.5}$ in Saitama and Aichi. The absence of an association in some cities may be due to the low mean concentration of ambient $PM_{2.5}$ (< 20 μg/m^3) in our study and may also reflect the differences in sources and specific composition of $PM_{2.5}$ between study sites (Lipsett et al. 2006; Sullivan et al. 2005).

Although several mechanistic hypotheses have been proposed regarding the acute adverse effects of $PM_{2.5}$ on cardiac autonomic regulation, studies pinpointing the pathophysiologic mechanisms that connect ambient levels of $PM_{2.5}$ exposure to changes in autonomic nervous system are still few in number. One plausible mechanism is that when $PM_{2.5}$ is inhaled into the lungs and then passed from the lungs to the heart, changes in the vasculature and blood stream may induce changes in autonomic nervous function and lead to an imbalance in cardiac autonomic control (Creason et al. 2001; Gold et al. 2000; Liao et al. 1999, 2004; Magari et al. 2001; Pope et al. 1999). A reduction in HRV could also occur through an inflammatory response. This hypothesis is supported by previous studies that found a relationship between changes in physiology mediated by the autonomic nervous system and air pollution (Lipsett et al. 2006; Peters et al. 1997; Tan et al. 2000).

The reasons for the heterogeneity of the association among the prefectures might be due to many factors such as the difference between pollution mixture and concentration, weather conditions, demographic characteristics, and lifestyle (Strak et al. 2017) of the residents. For example, Hokkaido is located in northern of Japan and the climate in Hokkaido prefecture is different from that in the other 6 prefectures (Table 2). The lifestyle of people in colder regions like Hokkaido might differ from that in the other 6 prefectures in this study, that is, longer period of house's and car's heater usage which produces more indoor air pollution. On the other hand, staying indoors for longer hours during winter time may prevent the residents from exposure to outdoor air pollution. All of these factors might affect the association between HRV and $PM_{2.5}$. This study examined the association of daily variation of $PM_{2.5}$ and HRV; it is possible that time-variant factors, such as temperature and relative humidity, may confound the association. Indeed, many studies indicated that temperature and humidity influence cardiovascular disease. There is also a study suggesting the association between ambient temperature and HRV by Ren et al. (2011). Besides, many previous studies examining the association between air pollution and HRV adjusted for temperature and relative humidity in the model (Min et al., 2008a; Park et al. 2010; Zanobetti et al. 2010).

We examined the association between $PM_{2.5}$ and HRV indices up to lag3, as the percent changes after this point were fairly small in magnitude. According to single lag structure

(Table S2; in the Appendix), the magnitude of many HRV indices became lower after lag3 in many prefectures and some of them were close to zero. Other previous studies that applied a cross-sectional analysis to examine the association between short-term ambient PM exposure and HRV also found that the association between PM exposure and HRV was the strongest when the 2-day (48-h) average of $PM_{2.5}$ (Park et al. 2010; Park et al. 2005) was applied.

In this study, only HRV data with a recording duration of 18 to 26 h were used, in accordance with previous studies (Pieters et al. 2012; Winkler et al. 2013). We tried to include the subjects with less than 18 h or more than 26 h in the analysis, but they did not affect the estimation.

Short-term measurement of HRV is widely used due to practical advantages and reproducibility (Min et al., 2008b). While Fei et al. (1994) found that short-term HRV was noticeably associated with long-term HRV, the correlation was not strong enough to warrant replacing the long-term HRV measurement with short-term HRV measurement (Fei et al. 1994). Since slower regulatory mechanisms contribute to HRV metrics recorded over a 24-h time period, short-term HRV values are not be able to represent long-term HRV values (Shaffer & Ginsberg 2017). Nunan et al. (2010) indicated that time-domain HRV indices were strongly influenced by the length of the recording period. Short-term measurement of HRV was poorly estimated in 24-h values (Nunan et al. 2010). For instance, in one study, 24-h SDNN values were found to predict future heart attack risk, whereas 5-min SDNN values did not (Shaffer et al. 2014). Nolan et al. (1998) also demonstrated that 24-h HRV was a stronger predictor of death due to chronic heart failure, in comparison with other conventional clinical measurements. Frequency-domain HRV indices, including ULF and VLF, are recommended for measurement periods longer than 24 h (Shaffer & Ginsberg 2017). In addition, Shaffer and Ginsberg (2017) suggested that short-term HRV lacks the prognostic power of 24-h measurements with regard to morbidity and mortality.

Our findings suggest that higher levels of $PM_{2.5}$ are associated with a decrease in VLF and ULF. $PM_{2.5}$ could lead to a higher risk of mortality because the combination of decreased VLF and ULF could be used to identify a subgroup of patients with a higher mortality risk (Bigger et al. 1992). Additionally, VLF power is more strongly associated with all-cause mortality than LF or HF power (Hadase et al. 2004; Schmidt et al. 2005; Tsuji et al. 1996, Tsuji et al., 1994).

The LF/HF ratio was calculated to express the relative balance between sympathetic-vagal nervous activity (Stein et al. 1994). Previous studies observed the association between increased LF/HF with cardiovascular risk (Jia et al. 2011; Lombardi et al. 2000). Additionally, recent studies also observed the positive association between LF/HF with $PM_{2.5}$ (Park et al. 2005) and O_3 (Jia et al. 2011). However, we found no clear association between $PM_{2.5}$ and LF/HF in this study.

This study has several limitations. First, our ECG records were obtained from patients who visited the clinic complaining of symptoms or who had heart disease. Therefore, our study subjects did not represent the general population. Second, air pollution data were obtained from an environmental monitoring station and might not accurately represent the exact exposure levels experienced by each individual. Third, we did not obtain information on subjects that could have confound the association between $PM_{2.5}$ and HRV, such as smoking status, alcohol consumption, body mass index (BMI), hypertension, diabetes, and respiratory and cardiovascular disease history.

Conclusions

Increased exposure to $PM_{2.5}$ was associated with lower 24-h HRV in patients with symptoms/signs suggestive of heart disease. Further epidemiological studies are needed to understand and identify plausible mechanisms underlying the association, as well as longitudinal studies to confirm the causal relationship between HRV and $PM_{2.5}$ exposure.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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