Fine particulate matter and out-of-hospital cardiac arrest of respiratory origin

To the Editor:

Exposure to ambient air pollution increases mortality and is a leading contributor to the global disease burden [1]. Epidemiological studies have elucidated a relationship between out-of-hospital cardiac arrests (OHCAs) and air pollutants, especially particulate matter (diameter ⩽2.5 µm; $PM_{2.5}$) [2, 3]. The causes of OHCA are broadly categorised as cardiac and non-cardiac [4]. A 10 µg·m^{-3} increase in $PM_{2.5}$ exposure yielded a 1.6% increase in the incidence of cardiac origin OHCA [3, 5]. However, few studies on OHCAs of non-cardiac origin, including intrinsic respiratory diseases (COPD/pneumonia/asthma) are available. We examined the association between short-term exposure to $PM_{2.5}$ and bystander-witnessed respiratory origin OHCAs, including eventual prognosis. We also investigated differences between $PM_{2.5}$ exposure-related cardiac and respiratory origin OHCAs.

The All-Japan Utstein Registry, a prospective, nationwide, population-based registry that undertook Utstein-style data collection [6], was established (Fire and Disaster Management Agency). OHCAs registered between 1 January 2005 and 31 December 2016 were assessed and were presumed to be of cardiac origin unless a non-cardiac cause was evident. Measurements of ozone, nitrogen dioxide and sulfur dioxide in addition to $PM_{2.5}$ concentrations in each air pollution monitoring station located in a distinct prefectural capital were obtained from the atmospheric environment database (National Institute for Environmental Studies). Data published by the Japan Meteorological Agency were used to evaluate the daily mean ambient temperature and relative humidity levels. Periods of influenza epidemic were defined as weeks in which the number of recorded cases were greater than the 90th percentile of the distribution during the study period.

The study design has been reported previously [5]. Briefly, a case-crossover design was used to examine the association between short-term $PM_{2.5}$ exposure and OHCAs. The "case day" was defined as the day of OHCA occurrence; "control days" were selected using a time-stratified method [7]. We applied a conditional logistic regression model to estimate the odds ratios (with 95% confidence intervals) for every 10 µg·m^{-3} increase in $PM_{2.5}$ concentrations at lag0–1 (mean $PM_{2.5}$ concentrations on the case day and 1 day before). All analyses were performed using STATA 15.1 (Stata Corporation, College Station, TX, USA). A $p<0.05$ was considered statistically significant. This study was approved by the ethics committee of Kawasaki Medical School.

During 2005–2016 in Japan, 1 423 338 OHCAs were documented: 594 791 were of non-cardiac origin; 243 338 occurred during the $PM_{2.5}$-monitoring period (April 2011–December 2016), of which, 72 124 were bystander-witnessed. Of these, 21 383 had a respiratory aetiology. The mean±SD age was 80.6±13.8 years (16 598 were ⩾75 years, 10 905 were men, and 12 142 had OHCAs during cold seasons, *i.e.* November to April). Initial non-shockable rhythms (pulseless electrical activity/asystole) were detected in 20 450 patients; 13 271 patients received bystander resuscitation. The time from collapse to initial electrocardiogram (ECG) was <10 min in 14 125 respiratory origin OHCAs. The mean daily $PM_{2.5}$ concentration was 13.9 µg·m^{-3} by nationwide analysis. The prefecture-specific results for environmental factors were presented previously [5].

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Particulate matter is a potential risk factor for out-of-hospital cardiac arrests (OHCAs) of respiratory origin. The percent increase in incidence of OHCA of respiratory origin is equivalent to that of $PM_{2.5}$ exposure-related OHCAs of cardiac origin. http://bit.ly/3tDXym0

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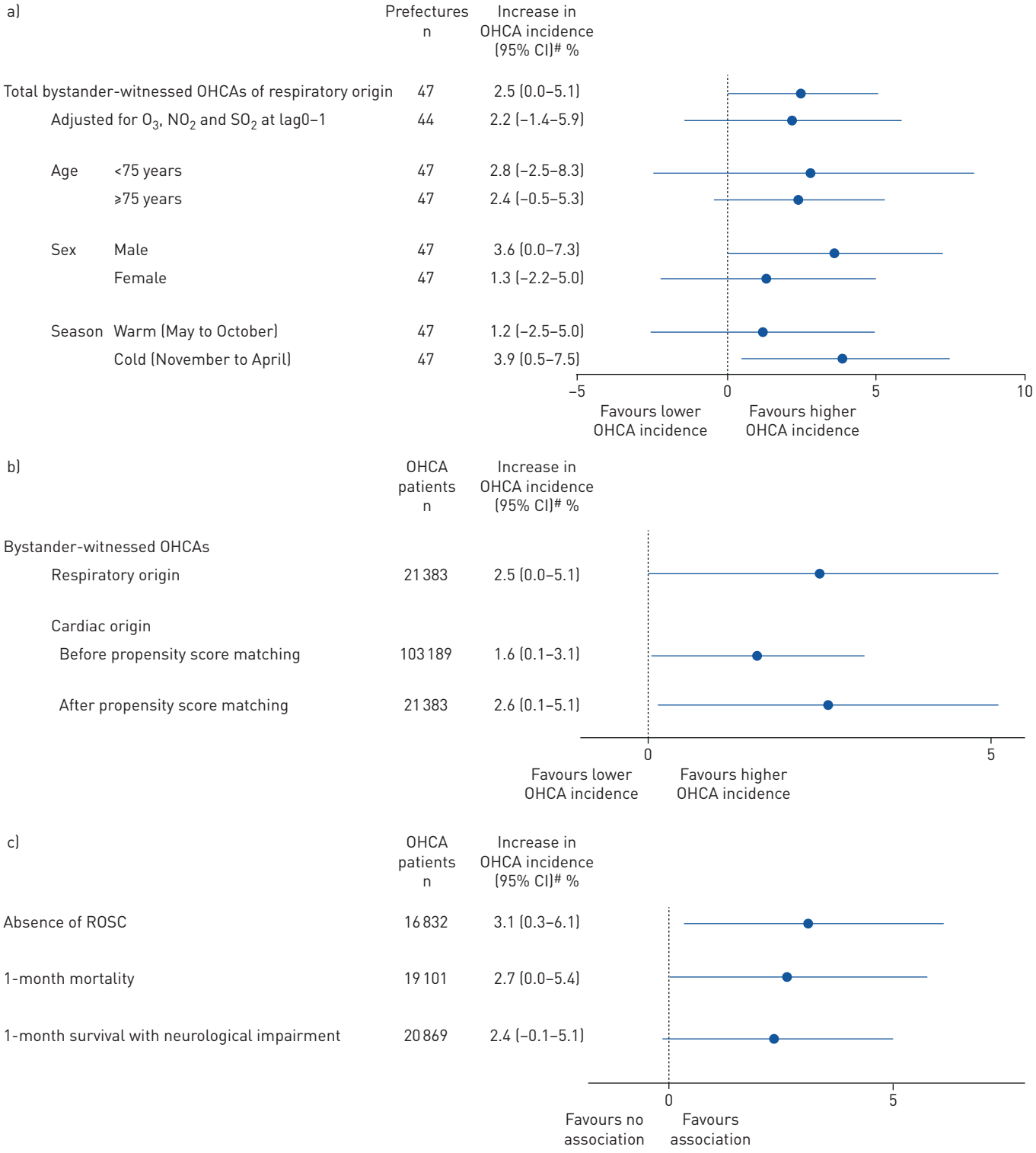

FIGURE 1 a) $PM_{2.5}$ (particulate matter with diameter ⩽2.5 µm) exposure and total bystander-witnessed out-of-hospital cardiac arrests (OHCAs) of respiratory origin. OHCAs adjusted for ambient temperature/relative humidity at lag0—1 (mean $PM_{2.5}$ concentrations on the case day and 1 day before) and incidence of influenza. b) Bystander-witnessed OHCAs of respiratory/cardiac origin affected by $PM_{2.5}$ exposure before and after propensity score matching. The model included ambient temperature/relative humidity at lag0—1 (mean $PM_{2.5}$ concentrations on the case day and 1 day before) and incidence of influenza. c) $PM_{2.5}$ exposure and poor outcomes following bystander-witnessed OHCAs of respiratory origin. #: odds ratio: percentage increase for every 10 µg·m^{-3} increase in $PM_{2.5}$ at lag0–1. ROSC: return of spontaneous circulation.

Figure 1a demonstrates a stratified analysis of the sensitivity of the association between $PM_{2.5}$ exposure and bystander-witnessed respiratory origin OHCAs (increase: 2.5%, 95% CI 0.0–5.1%). Point estimates of percentage increases were higher in men (3.6%, 95% CI 0.0–7.3%) and cold seasons (3.9%, 95% CI 0.5–7.5%).

When the analysis was limited to patients with bystander-witnessed cardiac origin OHCAs during the same $PM_{2.5}$ exposure period (n=103 189), there was a significant association between $PM_{2.5}$ exposure and OHCA incidence (1.6%, 95% CI 0.1–3.1%). On comparing respiratory and cardiac origin OHCA incidences as related to $PM_{2.5}$ exposure, heterogeneous patient backgrounds were observed. Following propensity score matching, 21 383 (100%) and 21 383 (21%) of respiratory and cardiac origin OHCAs were included in the analysis. For the date (month/year) and location (prefecture) of onset, we extracted the details of patients with cardiac origin OHCAs matched to those with respiratory origin OHCAs. Baseline covariates were well-balanced between the groups (absolute standardised difference <10%). The percent increase in cardiac origin OHCAs associated with increased $PM_{2.5}$ concentrations was 2.6% (95% CI 0.1–5.1%), which was equivalent to the percent increase in respiratory origin OHCAs associated with increased $PM_{2.5}$ concentrations (figure 1b).

An initial shockable rhythm (ventricular fibrillation/pulseless ventricular tachycardia) was not significantly correlated with $PM_{2.5}$ exposure and had a wide confidence interval because the rate of patients was only 1.8%. However, there was a trend of an association between $PM_{2.5}$ exposure and a non-shockable rhythm (2.4%, 95% CI −0.2–5.1%). A time-stratified analysis was performed and the non-shockable rhythm detected $\geq$10 (2.8%, 95% CI −1.6–7.5%) or <10 min (2.2%, 95% CI −1.0–5.4%) after the period from collapse to initial ECG did not correlate with $PM_{2.5}$ exposure (p=0.90).

We examined the association of $PM_{2.5}$ exposure with poor prognosis in patients with respiratory origin OHCAs (figure 1c). Increased $PM_{2.5}$ concentrations were detected in patients who experienced an absence of return of spontaneous circulation (3.1%, 95% CI 0.3–6.1%), 1-month mortality (2.7%, 95% CI 0.0–5.4%), or 1-month survival with neurological impairment (2.4%, 95% CI −0.1–5.1%).

Our findings suggest that short-term $PM_{2.5}$ exposure is associated with bystander-witnessed respiratory origin OHCAs in Japan. We had a large sample size (nationwide data of >20 000 bystander-witnessed respiratory origin OHCAs) for point estimates of a $PM_{2.5}$-OHCA association, which may increase accuracy.

A previous meta-analysis reported that mortality was higher due to respiratory rather than cardiac causes related to $PM_{2.5}$ exposure [8]. However, this association cannot be simply accepted, given the differences in patient background between respiratory *versus* cardiac origin OHCAs. Propensity score matching demonstrated the percent increase in incidence of respiratory origin OHCA associated with increased $PM_{2.5}$ concentrations was equivalent to that of cardiac origin OHCA associated with increased $PM_{2.5}$ concentrations, suggesting that the initial $PM_{2.5}$-induced mechanism associated with the underlying respiratory or cardiac disease may be identical, followed by cardiopulmonary deterioration and OHCA. $PM_{2.5}$ can be inhaled deeply into the small airways/alveoli of the lungs and may increase and sustain oxidative stress throughout the respiratory tract and at a systemic level to induce inflammation [9, 10]. In the lungs, particulate matter may induce alveolar inflammation, thereby activating cellular and molecular events, aggravating pre-existing pulmonary diseases and generating ischaemic/anoxic insults [11]. In the heart, particulate matter-induced inflammation may increase the vulnerability of pre-existing coronary arterial plaques, leading to acute coronary syndrome [12]. Previous findings have suggested that respiratory viral infections may interact with particulate matter, thereby causing additional oxidative stress and expediting inflammation, resulting in cardiac arrest following the exacerbation of respiratory failure/cardiac complications [10, 13]. $PM_{2.5}$ may have a common effect on the occurrence of respiratory/cardiac origin OHCA in patients with underlying cardiopulmonary diseases.

Most patients with respiratory origin OHCA developed non-shockable rhythms as the initial cardiac rhythm. The incremental severity of COPD is associated with an increasing prevalence of non-shockable rhythms [14], indicating that we may have included patients with severe respiratory diseases. We previously reported that the occurrence of an initial non-shockable rhythm was associated with an increase in $PM_{2.5}$ concentration in cardiac origin OHCAs [5]. Most non-$PM_{2.5}$ cardiac origin OHCAs are due to ischaemic heart disease accompanied by an initial shockable rhythm [4]. More than 20% of cardiac origin OHCA patients are thought to have comorbid COPD [14], which may be influenced by $PM_{2.5}$ exposure, thus contributing to the manifestation of an initial non-shockable rhythm. Taken together, increased $PM_{2.5}$ concentrations are associated with respiratory/cardiac origin OHCAs that commonly present with a non-shockable rhythm, which remains a strong predictor of poor outcomes [15].

In conclusion, increased $PM_{2.5}$ concentration is associated with bystander-witnessed respiratory origin OHCAs. $PM_{2.5}$-related deterioration of respiratory function and cardiac complications may promote

OHCA in individuals with pre-existing cardiopulmonary conditions. Our findings emphasise the need to improve air quality, which is one of the sustainable development goals.

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