

Coarse particulate matter and emergency ambulance dispatches in Fukuoka, Japan: a time-stratified case-crossover study

Takehiro Michikawa, Kayo Ueda, Ayano Takeuchi, Kenji Tamura, Makoto Kinoshita, Takamichi Ichinose & Hiroshi Nitta

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Coarse particulate matter and emergency ambulance dispatches in Fukuoka, Japan: a time-stratified case-crossover study

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Abstract

Objectives There is no conclusive evidence of adverse health effects caused by short-term exposure to coarse particulate matter, so in this case-crossover study we looked for an association between exposure and emergency ambulance dispatches (as a proxy of acute health outcomes).

Methods We used data on emergency ambulance dispatches in Fukuoka City, Japan between 2005 and 2010. After excluding ambulance dispatches related to external injuries and pregnancy/childbirth, we analyzed data on 176,123 dispatches. Citywide daily mean concentrations of suspended particulate matter (SPM) and fine particulate matter (PM_{2.5}) were calculated from ambient monitoring data, and the differences between concentrations of SPM and PM_{2.5} were used as an exposure surrogate of coarse particulate matter. Using a conditional logistic regression model, we estimated the ambient temperature and relative

humidity adjusted odds ratios (ORs) per 10 µg/m³ increase in coarse particulate matter.

Results The average daily concentration of coarse particulate matter over the study period was 9.9 µg/m³, representing 33 % of the total concentration of SPM. Elevated concentrations of coarse particulate matter were associated with an increase in respiratory disease-related emergency ambulance dispatches for adults aged 65 years or older (9,716 dispatches, OR for lag0–1 = 1.065, 95 % confidence interval = 1.023–1.109). After additional adjustment for exposure to PM_{2.5}, we observed a statistically non-significant increased risk (OR = 1.035, 0.986–1.086).

Conclusions We found weak evidence of adverse effects of short-term exposure to coarse particulate matter on human health.

Keywords Particulate matter · Coarse particle · Short-term exposure · Emergency ambulance dispatches · Case-crossover design

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Introduction

Accumulating evidence leaves no doubt that particulate matter has adverse effects on human health [1]. The adverse effects of fine particulate matter (PM_{2.5}, i.e., particles that pass through a size-selective inlet with a 50 % cut-off level of 2.5 µm in aerodynamic diameter) have received particular attention in recent years. In 2009, the US Environmental Protection Agency reported a causal relationship between short-term exposure to PM_{2.5} and mortality and cardiovascular diseases [2]. However, several research questions regarding particulate matter remain unanswered. One concerns the associations between coarse particulate matter and mortality and

morbidity. Coarse particulate matter is typically classified as particulate matter measuring between 2.5 and 10 μm ($\text{PM}_{10-2.5}$) in diameter. Unlike fine particles, coarse particles do not reach the alveoli of the lungs [3] but are deposited along the bronchial tubes; they have been associated with pulmonary toxicity [4, 5]. Although exposure to coarse particulate matter is also thought to adversely affect human health, there is no conclusive evidence of causal associations between short-term exposure to coarse particulate matter and mortality and morbidity [2].

Japanese Air Quality Standards [6] apply to suspended particulate matter (SPM that passes through a size-selective inlet with a 100 % cut-off level of 10 μm in aerodynamic diameter) and $\text{PM}_{2.5}$, so PM_{10} (particles that pass through a size-selective inlet with a 50 % cut-off level of 10 μm in aerodynamic diameter) is not monitored in Japan. In the present study, therefore, we defined the difference between concentrations of SPM and $\text{PM}_{2.5}$ as an exposure surrogate of coarse particulate matter. Our hypothesis was that coarse particulate matter would cause acute health effects. To examine this hypothesis, we conducted time-stratified case-crossover analyses to investigate any association between short-term exposure to coarse particulate matter and emergency ambulance dispatches, which were used as a proxy marker of acute health events. We have previously reported that exposure to $\text{PM}_{2.5}$ was positively associated with ambulance dispatches in Fukuoka City, Japan, where $\text{PM}_{2.5}$ concentrations had measured before Air Quality Standards for $\text{PM}_{2.5}$ were established in 2009 [7]. We used the same dataset in this study.

Materials and methods

Information on emergency ambulance dispatches

The present study was carried out in Fukuoka City, which is on the island of Kyushu in western Japan (130°24'E, 33°35'N); it is the closest part of Japan to the Asian continent. Fukuoka's population is approximately 1.5 million, and the climate is moderate (average annual temperature: c. 17 °C).

In Japan, local governmental fire defense headquarters provide emergency medical services in accordance with the Local Autonomy Law and Firefighting Acts, with costs covered from tax revenues [8, 9]; ambulance services are thus provided free of charge. We obtained data on all emergency ambulance dispatches covering the entire city of Fukuoka between January 1, 2005 and December 31, 2010 ($n = 307,711$). After excluding dispatches related to external injuries and pregnancy/childbirth, we were left with data on 176,123 dispatches (57.2 %) for analysis.

Records of the initial diagnoses made at the emergency departments where the transported patients were treated were used to code the causes of the dispatches according to the International Classification of Diseases, 10th revision (ICD-10); one medical doctor (TM) masked to exposure information performed all coding. We defined ambulance dispatches related to respiratory diseases (ICD-10: J00-99, 15,857 dispatches) and cardiovascular diseases (ICD-10: I00-99, 31,837 dispatches) as cause specific.

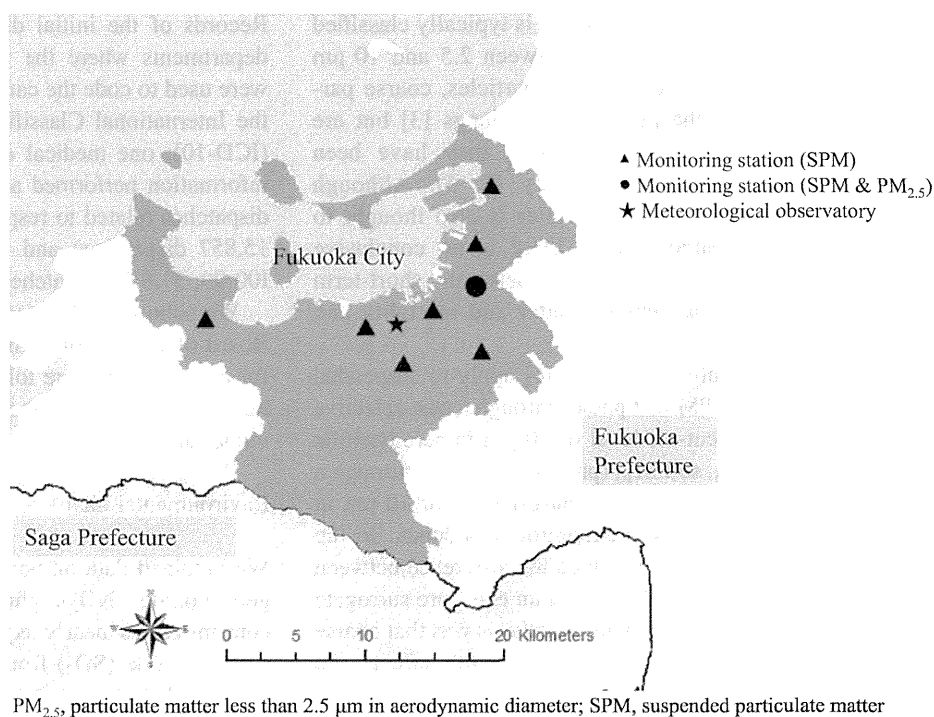
We submitted the study protocol to the Ethical Review Board of the National Institute for Environmental Studies for approval but were told by the Board that approval was not required because the study data did not include individual identifiers.

Environmental data

We obtained data on hourly measurements of SPM, nitrogen dioxide (NO_2), photochemical oxidants (Ox) with concentrations nearly equivalent to those of ozone, and sulfur dioxide (SO_2) from the National Institute for Environmental Studies' atmospheric environment database; we obtained data on $\text{PM}_{2.5}$ from Fukuoka City records. The mass concentrations of SPM were measured by β -ray absorption. The 8 ambient pollution monitoring stations representing urban background concentrations in Fukuoka provided data on concentrations of pollutants in the city (Fig. 1), and citywide daily mean concentrations of SPM, NO_2 , and SO_2 and daily maximum 8-h mean concentrations of Ox were calculated by averaging the measurements made by the 8 monitoring stations. In one of these stations, $\text{PM}_{2.5}$ was measured by the tapered element oscillating microbalance method.

In the present study, we calculated daily mean concentrations of coarse particulate matter by subtracting daily mean concentrations of $\text{PM}_{2.5}$ from those of SPM. Under Japanese Air Quality Standards [6], SPM is defined as airborne particles with a 100 % cut-off point of 10 μm in aerodynamic diameter. Overseas, PM_{10} and $\text{PM}_{2.5}$ are usually defined as particles with a 50 % cut-off point of 10 and 2.5 μm , respectively, in aerodynamic diameter. Although the SPM definition does not specify the size of particles collected with a 50 % cut-off point, measurements by the 8 stations in Fukuoka showed a 50 % cut-off point of approximately 7 μm . Therefore, we deduced that SPM concentrations correspond more or less to PM_7 concentrations and defined SPM as particles with a 50 % cut-off level of 7 μm in aerodynamic diameter. Thus, coarse particulate matter as defined in this study was taken as $\text{PM}_{7-2.5}$, in the same way as $\text{PM}_{10-2.5}$ was calculated by subtracting $\text{PM}_{2.5}$ from PM_{10} . In Fukuoka, coarse particles consisted mainly of natural particles such as sea-salt and soil particles [10]. During the study period of 2,191 days,

Fig. 1 Location of monitoring stations and meteorological observatory in Fukuoka City



SPM measurements were available on all days, and PM_{2.5} measurements on 2,162 days. On 8 days, there were negative concentrations of coarse particulate matter, so these were excluded, leaving 2,154 days of coarse particulate matter measurements for our analyses.

Meteorological data collected by the Fukuoka District Meteorological Observatory were obtained from the Japan Meteorological Agency: hourly measurements were used to calculate daily mean ambient temperatures and relative humidity. Data on weekly influenza incidence were obtained from the Japan National Institute of Infectious Diseases. Influenza epidemic weeks were defined as those when the weekly number of influenza cases was above the 90th percentile of distribution during the study period [11], and influenza epidemics were used as a dichotomized variable.

Statistical analyses

To assess the association between short-term exposure to coarse particulate matter and emergency ambulance dispatches, we used a time-stratified case-crossover approach. We defined case periods as the days of ambulance dispatches and selected control periods (3–4 per case) on corresponding days of the week within the same calendar month of the same year. For instance, if an outcome occurred on August 14, 2008, we assigned August 7, 21,

and 28, 2008 as the 3 control days. With this approach, we were able to adjust for time-invariant characteristics such as age and sex, and time-dependent confounding within strata time by methods [12].

Conditional logistic regression models were used to examine the association between coarse particulate matter and emergency ambulance dispatches. Then, to examine lag pattern of coarse particulate matter and control for confounding by it, we applied a lag-stratified distributed lag model [13] and included the average concentrations of coarse particulate matter during the case day (lag0) to 1 day preceding it (lag1) (lag0–1), during lag2–lag3 (lag2–3), and during lag4–lag6 (lag4–6) [14]. Odds ratios (ORs) for a 10 μg/m³ increase in coarse particulate matter concentrations with 95 % confidence intervals (CIs) were calculated after adjustment for the mean ambient temperature (a natural spline with 4 degrees of freedom) and relative humidity from the case day (lag0) to 3 days before (lag3). We performed stratified analyses by age strata (0–19 years, 20–64 years, and 65 years or older), and using likelihood ratio tests to check whether the effects of coarse particulate matter concentrations on ambulance dispatches were modified by age strata. In addition, we conducted several sensitivity analyses. First, to eliminate the possibility of bias in control selection, we excluded dispatches occurring on national holidays. Second, we excluded dispatches occurring on “Asian dust” days (lag0–3) (Asian dust is mineral dust blown from deserts in China and

Mongolia to western Pacific regions [15]). Because exposure to Asian dust is reportedly associated with emergency ambulance dispatches [16], it was important to look for associations between coarse particulate matter concentrations and ambulance dispatches after excluding days of extra-high exposure to this natural coarse particulate matter. Third, we additionally included influenza epidemics in the model. Finally, to evaluate the independent effects of coarse particulate matter, we constructed two-pollutant models adjusted for co-pollutants, namely $PM_{2.5}$, NO_2 , Ox , and SO_2 . Although we took into consideration the effects of season (spring, summer, autumn, and winter) in terms of the association between coarse particulate matter and ambulance dispatches, statistical evidence of effect modification by season was not observed (p for effect modification = 0.31).

Statistical analyses were conducted with Stata11 (Stata Corporation, College Station, TX, USA). All p values are two-sided with significance levels set at $p < 0.05$.

Results

Of the 176,123 emergency ambulance dispatches, 16,415 (9.3 %) were for the 0- to 19-year-old age group, 79,734 (45.3 %) for the 20- to 64-year-old age group, and 79,974 (45.4 %) for the 65-year or older age group; 86,127 (48.9 %) of the dispatches were for men. Descriptive statistics of exposure data are shown in Table 1. The average daily concentration of coarse particulate matter over the study period was $9.9 \mu\text{g}/\text{m}^3$, representing 33 % of the total concentrations of SPM. Coarse particulate matter concentration correlated moderately with that of $PM_{2.5}$ (Pearson's

correlation coefficient = 0.49), but not with concentrations of the other pollutants (correlation coefficients = 0.02 for NO_2 , 0.02 for Ox , and 0.18 for SO_2).

We examined the association between exposure and coarse particulate matter and emergency ambulance dispatches (Table 2). All-cause ambulance dispatches were not associated with coarse particulate matter (OR for lag0-1 = 1.006 per $10 \mu\text{g}/\text{m}^3$ increase in coarse particulate matter, 95 % CI = 0.996-1.016). Although a statistically significant association was found in the 65-year or older age group (OR for lag0-1 = 1.020, 95 % CI = 1.005-1.035), there was no evidence of effect modification by age strata ($p = 0.65$). However, coarse particulate matter was clearly associated with an elevated risk of respiratory disease-related ambulance dispatches for those aged 65 years or older (OR for lag0-1 = 1.065, 95 % CI = 1.023-1.109), and effect modification of exposure to coarse particulate matter across age strata was demonstrated ($p = 0.02$). Null association was observed for cardiovascular-related ambulance dispatches.

We attempted to confirm the robustness of the positive association we observed with regard to respiratory disease-related ambulance dispatches (Fig. 2). When dispatches occurring on national holidays were excluded (OR for lag0-1 per $10 \mu\text{g}/\text{m}^3$ increase in coarse particulate matter = 1.075, 95 % CI = 1.031-1.122) and additional adjustments were made for influenza epidemics (OR = 1.067, 95 % CI = 1.025-1.111), the results did not change substantially. Although the OR point estimate was slightly higher when ambulance dispatches on Asian dust days were excluded (OR = 1.111, 95 % CI = 1.039-1.189), no significant difference in point estimates on days with or without Asian dust was observed (p for effect modification = 0.31). In the two-

Table 1 Summary of daily mean concentrations of coarse particulate matter (PM) and other air pollutants from January 2005 to December 2010 in Fukuoka, Japan

Pollutant	Number of days	Mean (SD)	Percentile		
			25	50	75
Coarse PM ($\mu\text{g}/\text{m}^3$) ^a	2,154 ^b	9.9 (7.3)	5.8	8.4	12.1
SPM ($\mu\text{g}/\text{m}^3$)	2,191	30.3 (16.1)	19.5	26.5	37.1
$PM_{2.5}$ ($\mu\text{g}/\text{m}^3$)	2,162	20.3 (11.2)	12.2	17.8	25.5
$PM_{2.5}/\text{SPM}$	2,154 ^b	0.67 (0.13)	0.58	0.68	0.76
NO_2 (ppb)	2,191	14.0 (6.4)	9.2	12.8	17.6
Ox (ppb) ^c	2,191	44.1 (15.5)	33.8	42.3	53.6
SO_2 (ppb)	2,191	3.5 (1.6)	2.3	3.2	4.3

NO_2 nitrogen dioxide, Ox photochemical oxidants, $PM_{2.5}$ particulate matter less than $2.5 \mu\text{m}$ in aerodynamic diameter, SD standard deviation, SO_2 sulfur dioxide, SPM suspended particulate matter

^a Concentrations of coarse particulate matter were defined as concentrations that were calculated by subtracting $PM_{2.5}$ from SPM

^b On 8 days, we observed negative concentrations of coarse particulate matter and excluded those days in the analyses

^c Daily maximum 8-h mean concentrations

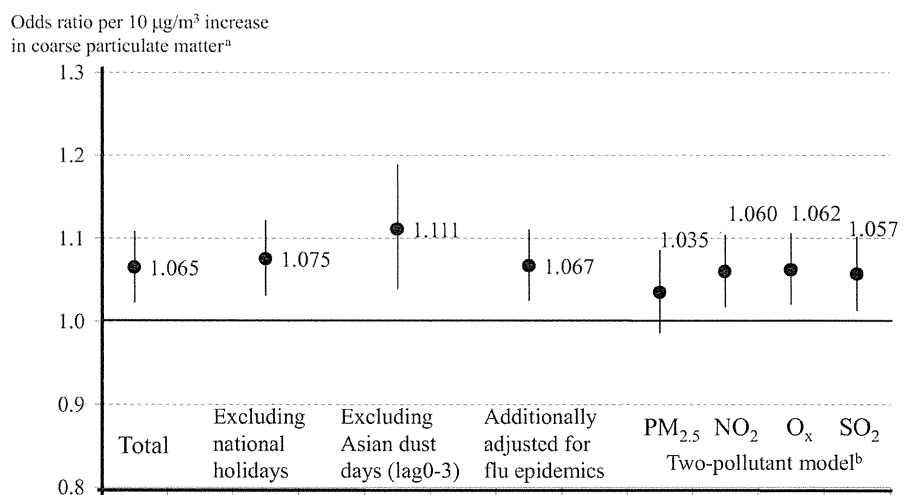
Table 2 Odds ratios (ORs) and 95 % confidence intervals (CIs) of emergency ambulance dispatches per 10 µg/m³ increase in coarse particulate matter according to age strata

	All-causes			Respiratory diseases			Cardiovascular diseases		
	<i>n</i>	OR ^a	95 % CI	<i>n</i>	OR ^a	95 % CI	<i>n</i>	OR ^a	95 % CI
Total									
Lag0–1	176,123	1.006	0.996–1.016	15,857	1.028	0.995–1.063	31,837	0.998	0.974–1.022
Lag2–3		0.999	0.988–1.009		1.010	0.975–1.046		1.000	0.976–1.024
Lag4–6		0.997	0.986–1.009		0.994	0.958–1.033		0.979	0.953–1.006
Age (years)									
< 20									
Lag0–1	16,415	0.998	0.966–1.031	1,816	0.983	0.887–1.089	196	0.952	0.684–1.323
Lag2–3		0.984	0.951–1.018		0.983	0.884–1.094		0.835	0.535–1.303
Lag4–6		0.994	0.958–1.032		0.943	0.836–1.064		0.917	0.674–1.247
20–64									
Lag0–1	79,734	0.994	0.979–1.009	4,325	0.952	0.888–1.021	10,001	0.986	0.945–1.029
Lag2–3		1.006	0.991–1.022		1.059	0.990–1.134		1.012	0.971–1.055
Lag4–6		1.004	0.986–1.021		1.000	0.933–1.072		0.999	0.951–1.048
≥ 65									
Lag0–1	79,974	1.020	1.005–1.035	9,716	1.065	1.023–1.109	21,640	1.004	0.975–1.034
Lag2–3		0.994	0.979–1.010		0.994	0.950–1.040		0.994	0.965–1.024
Lag4–6		0.991	0.974–1.008		0.999	0.952–1.049		0.972	0.940–1.005
<i>p</i> value ^b			0.65			0.02			0.54

^a We entered the averaged concentration of coarse particulate matter during lag0–lag1 (lag0-1), during lag2–lag3 (lag2-3) and during lag4–lag6 (lag4-6) simultaneously in the model, and also controlled for 4-day average daily mean ambient temperature and relative humidity

^b Effect modification by age strata was tested by the likelihood ratio test

Fig. 2 Sensitivity analyses of the association between coarse particulate matter (lag0–1) and emergency ambulance dispatches due to respiratory diseases (*n* = 9,716) in older adults (≥65 years or older). Error bars indicate 95 % confidence intervals



NO₂, nitrogen dioxide; O_x, photochemical oxidants; PM_{2.5}, particulate matter less than 2.5 µm in aerodynamic diameter; SO₂, sulfur dioxide

^aWe entered the averaged concentration of coarse particulate matter during lag0–lag1 (lag0-1), during lag2–lag3 (lag2-3) and during lag4–lag6 (lag4-6) simultaneously in the model, and also controlled for 4-day average daily mean ambient temperature and relative humidity

^bAdditionally adjusted for the averaged concentration of each pollutant during lag0-1, during lag2-3 and during lag4-6.

pollutant model, our finding was robust after adjustment for NO₂, O_x, and SO₂; however, the observed effects of coarse particulate matter concentration were not significant after

adjustment for PM_{2.5} (OR per 10 µg/m³ increase = 1.035, 95 % CI = 0.986–1.086) [OR per interquartile range increase (6.3 µg/m³) = 1.022, 95 % CI = 0.991–1.054]. In

this case, we found a significantly increased risk for exposure to $PM_{2.5}$ [OR per interquartile range increase ($13.3 \mu\text{g}/\text{m}^3$) for lag0–1 = 1.050, 95 % CI = 1.008–1.094].

Discussion

On the basis of our previous work [7], we are confident that ambulance dispatches are an adequate indicator of acute health effects of particulate matter exposure. An advantage of using data on emergency ambulance dispatches is that any selection bias was negligible, because we obtained information on all ambulance dispatches in Fukuoka City and covered the whole target population. In the present study, we found that elevated concentrations of coarse particulate matter were associated with an increase in respiratory disease-related emergency ambulance dispatches for adults aged 65 years or older. After adjustment for exposure to $PM_{2.5}$, however, the OR point estimate was attenuated and the statistical evidence weakened. Exposure to coarse particulate matter was not associated with cardiovascular-related ambulance dispatches.

Although we conclude that short-term exposure to coarse particulate matter might have adverse effects on human health, two possible methodological shortcomings should be noted. First, instead of directly measuring concentrations of coarse particulate matter, we estimated them from the differences between SPM and $PM_{2.5}$ concentrations. Daily mean concentrations of SPM were calculated by averaging the measurements made by the 8 monitoring stations, whereas those of $PM_{2.5}$ were estimated from the measurements at one monitoring station. Thus, the estimated concentrations might have been subject to measurement errors. Second, our cause-specific categorizations of ambulance dispatches were based on initial diagnoses made by emergency physicians, and the final diagnoses were probably different in some cases. However, such exposure and outcome misclassifications are generally non-differential, so they are likely to lead to null associations. Despite these possible shortcomings, increasing concentrations of coarse particulate matter resulted in a statistically significant increase in the risk of respiratory disease-related ambulance dispatches for older Japanese adults.

To the best of our knowledge, the present study is the first to investigate the acute health effects of coarse particulate matter (i.e., the difference between SPM and $PM_{2.5}$) in Japan. We found no evidence of an association between exposure and $PM_{10-2.5}$ and emergency ambulance dispatches. It is difficult to discuss epidemiological consistency with the past literature, but one study in 35 California counties reported that a $10 \mu\text{g}/\text{m}^3$ increase in $PM_{10-2.5}$ concentrations for lag1 was associated with a 0.7 % (95 % CI = 0.3–1.1) increase in respiratory emergency room

visits from 2005 to 2008 [17]. Another study in Helsinki also reported a positive association between exposure and $PM_{10-2.5}$ and asthma and chronic obstructive pulmonary disease emergency room visits from 1998 to 2004 (percent change per $7.2 \mu\text{g}/\text{m}^3$ increase for lag0 = 2.70 (95 % CI = 0.21–5.26) for adults (15–64 years) and 2.45 (0.18–4.76) for older adults (≥ 65 years) [18]. Earlier findings from mechanism studies have demonstrated pulmonary effects of $PM_{10-2.5}$. Exposure of cells to coarse particles led to increased levels of inflammatory biomarkers such as tumor necrosis factor alpha and interleukin-6 [19, 20]. In rats and mice, exposure to coarse particles contributed to increased pulmonary inflammation [21, 22]. In addition, an increase in inflammatory cells in sputum and bronchoalveolar lavage fluid was observed in healthy young volunteers exposed to coarse particles [4, 5]. Taken as a whole, our results are supported by both epidemiological and experimental evidence.

In the present study, we found a clear association between coarse particulate matter concentrations and respiratory effects only in older adults (aged ≥ 65 years), whereas other studies using $PM_{10-2.5}$ have also found associations in other age strata. A positive association with respiratory-related emergency visits was observed in children under 15 years of age who lived in Santiago, Chile [23], and associations with asthma and chronic obstructive pulmonary disease emergency room visits were found not only among adults aged 65 years or older but also among those aged 15–64 years old in Helsinki, Finland [18]. Adverse health effects of particulate matter on older adults are not surprising, because recent meta-analysis shows that older populations are more vulnerable to particulate matter than younger populations [24]. In our model including $PM_{2.5}$, exposure to coarse particulate matter was not statistically significantly associated with respiratory disease-related ambulance dispatches; however, the OR point estimate was still above unity, and there was an overlap 95 % CI with and without adjustment for $PM_{2.5}$. Therefore, the non-significance might have resulted from a lack of statistical power due to the relatively small number of cases in the stratified analysis, and we do not think that our finding after adjustment for $PM_{2.5}$ denies an independent association between coarse particulate matter concentrations and ambulance dispatches. Because the point estimate (interquartile range increase) for the association of coarse particulate matter with ambulance dispatches was slightly lower than that for the association of $PM_{2.5}$, it seemed likely that the health effects of coarse particulate matter were relatively smaller than those of $PM_{2.5}$.

Although we observed little effect of coarse particulate matter (the difference between concentrations of SPM and $PM_{2.5}$) on cardiovascular disease-related emergency

ambulance dispatches, several earlier studies in Western countries found the associations between coarse particulate matter defined as PM_{10-2.5} and mortality and morbidity, including hospital admissions for cardiovascular disease [25]. One possible explanation for the null association in this study is that the breakdown of cardiovascular diseases in Japan is different from that in Western countries. In Japan, the incidence of stroke is much higher than that of coronary heart disease [26]. Therefore, the association between particulate matter and cardiovascular diseases in Japan may also differ from that in Western countries, where coronary heart disease is the most common cardiovascular complaint. It should also be noted that our results lack generalizability, because our study was restricted to one city. The acute cardiovascular effects of coarse particulate matter exposure in Japan require further study.

In conclusion, our findings indicate that short-term exposure to coarse particulate matter (estimated by subtracting concentrations of PM_{2.5} from those of SPM) might have acute health effects. Japan's current Air Quality Standards include both SPM and PM_{2.5} [6], so further epidemiological studies are required to determine whether it is appropriate to regulate SPM and PM_{2.5} separately.

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Conflict of interest The authors declare no conflict of interest.

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The Role of Smoking Status on the Progression-Free Survival of Non-Small-Cell Lung Cancer Patients Harboring Activating Epidermal Growth Factor Receptor (*EGFR*) Mutations Receiving First-Line *EGFR* Tyrosine Kinase Inhibitor Versus Platinum Double Chemotherapy: A Meta-Analysis of Prospective Randomized Trials

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Key Words. Meta-analysis • *EGFR* TKIs • Smoking status • *EGFR* mutant non-small-cell lung cancer • Gefitinib • Erlotinib • Afatinib

ABSTRACT

Background. Univariate analyses from several randomized phase III trials seemed to suggest ever-smokers with advanced mutated epidermal growth factor receptor (*EGFRm*) non-small-cell lung cancer (NSCLC) did not seem to benefit from *EGFR* tyrosine kinase inhibitors (TKIs) as first-line treatment when compared with platinum-doublet chemotherapy as measured by progression-free survival (PFS).

Methods. A literature-based meta-analysis of PFS outcomes as measured by log-transformed pooled hazard ratio (HR) was performed using a random-effect model. Pooled HRs for smoking status, age, gender, ethnicity, type of *EGFR* mutation, and *EGFR* TKI were obtained. Comparison of the pooled HR was performed by metaregression analysis.

Results. Among the 1,649 *EGFRm* NSCLC patients analyzed from 7 prospective randomized trials (WJTOG3405, NEJ002, EURTAC, OPTIMAL, LUX Lung-3, LUX Lung-6, and ENSURE),

83.7% were Asians, and 30.0% were ever-smokers. An equal percentage of ever-smokers received doublet chemotherapy (30.2%) or *EGFR* TKI (30.0%). The pooled HR for PFS was 0.29 (95% confidence interval [CI]: 0.21–0.39) for never-smokers and 0.54 (95% CI: 0.38–0.76) for ever-smokers ($p < .007$ by metaregression). The pooled PFS HR for exon 19 deletion was 0.25 (95% CI: 0.19–0.31) and 0.44 for exon 21 substitution (95% CI: 0.34–0.57) ($p < .001$ by metaregression analysis). The pooled PFS HR was 0.33 (95% CI: 0.24–0.46) for Asians and 0.48 for non-Asians (95% CI: 0.28–0.84) ($p = .261$ by metaregression analysis).

Conclusion. *EGFRm* NSCLC patients derived significant PFS benefit from TKI over platinum-doublet chemotherapy as first-line treatment regardless of smoking status; however, PFS benefit is significantly better in never-smokers by metaregression analysis. *The Oncologist* 2015;20:1–9

Implications for Practice: The purpose of this meta-analysis was to ascertain the role of smoking status in influencing progression-free survival (PFS) outcomes in patients harboring the two common activating epidermal growth factor receptor mutations (*EGFRm*) who received first-line *EGFR* tyrosine kinase inhibitors (TKIs) in comparison with platinum-doublet chemotherapy. We found that *EGFRm* patients benefited from first-line *EGFR* TKIs regardless of smoking status, but *EGFRm* patients who were never-smokers benefited significantly more from *EGFR* TKIs than *EGFRm* patients with a history of smoking. Thus oncologists should be cognizant that the duration of PFS benefit from *EGFR* TKIs is likely to be shorter among ever-smokers with *EGFRm*, and close surveillance and alternative therapy should be formulated sooner.

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