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Smoking Aggravates the Impaired Pulmonary Function of Officially Acknowledged Female Victims of Air Pollution of 40 Years Ago

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Air pollution due to industrial waste and tobacco smoke is detrimental to pulmonary function. However, the combined effects of air pollution and smoking on pulmonary function have not been investigated. We examined the combined effect of air pollution of 40 years ago and concurrent smoking on the pulmonary function of officially acknowledged female victims in Japan, because females are more susceptible to the adverse effects of both irritants than males. The subjects comprised 655 female victims living in one of two areas with air pollution of 40 years ago and 572 females living in an area without air pollution. All victims have been prescribed standard respiratory medications. Pulmonary function was measured in 2000 for air-pollution groups (130 smokers and 525 non-smokers; mean age, 68.4 years) and during the period of 2004 to 2013 for non-air-pollution groups (113 smokers and 459 non-smokers; mean age, 69.0 years). The smokers included both current smokers and ex-smokers. The victims with a history of smoking had significantly lower forced expiratory volume in 1 second (FEV_1 % predicted) (mean, 74%) and significantly lower FEV_1/forced vital capacity (FVC) (mean, 70%) than the other groups ($P < 0.001$). Thus, smoking aggravates the pulmonary function in officially acknowledged female victims, despite the improved air pollution and the continuous medical care provided by the government. In conclusion, exposure to air pollution of 40 years ago and cigarette smoking are associated with reduced pulmonary function. These results highlight the importance of measures aimed at smoking cessation and limiting air pollution.

Keywords: air pollution; female; officially acknowledged victims of pollution-related illness; pulmonary function; smoking
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Introduction

Problems associated with air pollution, such as particulate matter up to 2.5 μm in size ($PM_{2.5}$), have become serious in developing countries such as China. The risk of health problems related to air pollution has been previously reported (Li et al. 2013; Wang et al. 2013). Air pollution has a substantial influence on health, including reduced pulmonary function and increased mortality and hospital admissions (Dockery et al. 1993; Anderson et al. 1997; Abbey et al. 1999; Peters et al. 1999; Linn et al. 2000; Galan et al. 2003; Tsai et al. 2003; Nafstad et al. 2004; Fung et al. 2005; Peacock et al. 2011). For example, a previous study reported that the mortality rate for all diseases increased by 0.55% and the mortality rate associated with pulmonary disease increased by 1.91% secondary to exposure of 10 $\mu g/m^3$ of $PM_{2.5}$ (Samoli et al. 2013).

The Japanese economy underwent significant development and achieved high economic growth in the 1950s and 1960s. In conjunction with industrial development, air pollution became a serious problem. A government environmental program began in the 1960s, and the Pollution Countermeasures Basic Law, the Law Concerning Pollution-Related Health Damage Compensation, and other measures were enacted in Japan in 1973. Individuals who are officially acknowledged to be victims of pollution-related ill-

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ness qualify for treatment and compensation. However, even if air quality improves, there is evidence that respiratory function remains impaired (Tanaka et al. 2013; Yanagita et al. 2013).

The observed concentrations that are associated with eye, nasal, and throat irritation correspond to an estimated smoking concentration ($PM_{2.5}$) of about 4.4 $\mu g/m^3$ (Junker et al. 2001). Smoking is a major factor that causes impairment in pulmonary function (Schroeder 2013), and mortality increases with the inhalation of passive smoke from only one smoker in a home (Hill et al. 2007). Thus, there is a need to investigate the influence of air pollution and smoking on pulmonary function from the viewpoint of preventing global health and socioeconomic problems. Furthermore, previous studies reported the influence of sex on the effects of air pollution (Kan et al. 2008) or smoking (Risch et al. 1993; Ben-Zaken Cohen et al. 2007; de Torres et al. 2009) and showed that females are more likely to be adversely affected than males. Thus, the health impairment caused by air pollution and smoking among females is a significant problem.

Tanaka et al. (2013) and Yanagita et al. (2013), in a longitudinal study, investigated respiratory function in nonsmoking, long-term, officially acknowledged victims of pollution-related illness. Normal lung function was not restored even after improvement in air quality. To date, the combined effects of air pollution of 40 years ago and smoking on pulmonary function has not been investigated. The objective of the present study was to investigate the detrimental effects of the combination of air pollution of 40 years ago and smoking history on the pulmonary function of officially acknowledged female victims of air pollution.

Methods

Study protocol and study population

The present study is a retrospective cross-sectional analysis of pulmonary function in smokers (smoking group) and non-smokers (non-smoking group) with air pollution of 40 years ago and smoking group and non-smoking group without air pollution. The group of smokers included both current smokers and ex-smokers, based on the data collected in 2000 for air-pollution group and those collected during the period between 2004 and 2013 for non-air-pollution group. The subjects' ages ranged from 55 to 85 years at the time of data collection. The subjects with air pollution were officially acknowledged female victims living in Kurashiki and Kitakyushu areas, as detailed below. This study was conducted following approval by the Ethics Committee of the Graduate School of Biomedical Sciences at Nagasaki University.

Air-pollution group

The air pollution group comprised 655 females working or living in one of the following areas with air pollution in Japan: the Mizushima area of Kurashiki, Okayama Prefecture, and the Kitakyushu area of Fukuoka Prefecture. The number of individuals in the smoking group was 130, and the number in the non-smoking group was 525. Fig. 1a shows a flow chart of the study subjects in the air-pollution group. The subjects were official victims of pollution-related illnesses from Mizushima and Kitakyushu areas that have a research partnership with Nagasaki University.

This study was conducted in 2009 using the records from medical examinations performed on the officially acknowledged victims of pollution-related illness in Kurashiki and Kitakyushu. All registered victims met the following conditions as determined by the Public Relief System of Kurashiki and Kitakyushu in accordance with the Pollution-Related Health Damage Special Measures Law (1969) and the Pollution-Related Health Damage Compensation Law (1973): (1) they resided or had spent time carrying out activities in an area specified as having significant air pollution (Table 1) and (2) they had been diagnosed with chronic bronchitis, asthma, or pulmonary emphysema by a respiratory physician from 1963 to 1988. In accordance with the Public Nuisance Countermeasures Law (1967), the registered victims were entitled to various forms of compensation, including a monthly consultation with a respiratory physician and annual assessment of respiratory symptoms by means of a detailed questionnaire and lung function testing. All victims were prescribed standard respiratory medications such as expectorants and bronchodilators.

Non-air-pollution group

This group served as the control group. The non-air-pollution group comprised 572 females who, from 2004 to 2013, participated in an epidemiological investigation and Festival of Health in Nagasaki Prefecture, which is an area of Japan without air pollution. Fig. 1b shows a flow chart of the study subjects in the non-air-pollution group. The number of individuals in the smoking group was 113, and the number in the non-smoking group was 459. None of these individuals were receiving respiratory medication or undergoing consultations with a respiratory physician.

Measurements

We evaluated age, height, weight, body mass index, and smoking status. Vital capacity (VC), forced vital capacity (FVC), and forced expiratory volume in 1 second (FEV_1) were measured, and the FEV_1/FVC ratio was calculated. These measurements were performed for the air-pollution groups in 2000 and for the non-air-pollution groups during the period of 2004 to 2013.

Spirometry measurements

Pulmonary function of the air-pollution group was measured using an electronic spirometer (FUDAC 70; Fukuda Sangyo Inc., Chiba, Japan), and pulmonary function of the non-air-pollution group was measured using a different electronic spirometer (Autospiro AS-407/507; Minato Medical Science Co., Osaka, Japan). Quality control and calibration of all spirometry measurements were performed according to the recommendations using a Japanese industrial standard-certified spirometer. VC, FVC, and FEV_1 were measured in accordance with the guidelines of the American Thoracic Society (American Thoracic Society 1995). Measurements were repeated until at least three reproducible forced expiratory curves had been obtained.

Air monitoring

Air pollution in Mizushima, Kitakyushu, and Nagasaki was measured according to the levels of three important pollutants: sulfur dioxide (SO_2), nitrogen dioxide (NO_2), and suspended particulate matter (SPM). SPM is particulate matter with a diameter of 10 m or less that is suspended in the atmosphere. Levels of air pollutants have

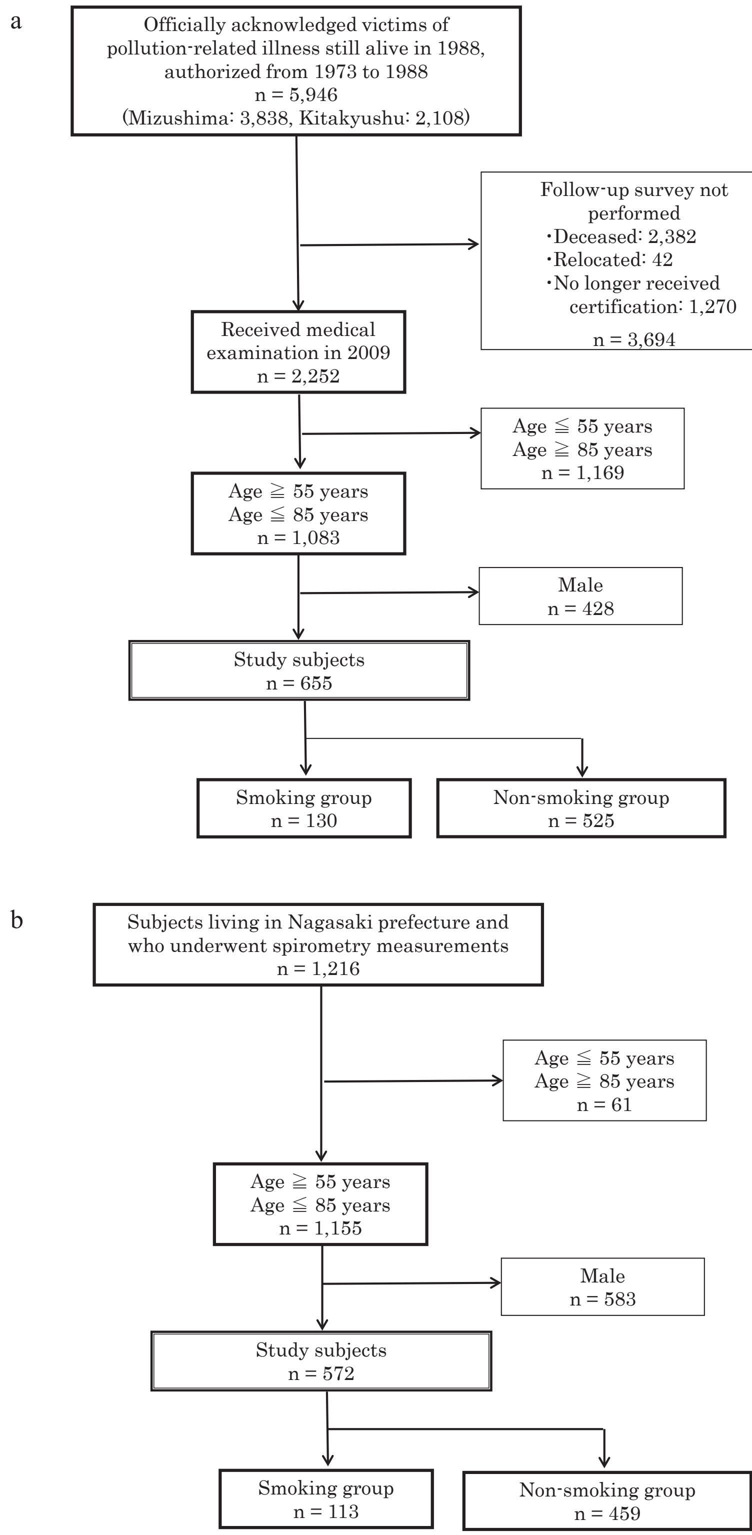

Fig. 1. Schematic representation of the study design.

a. Flow chart of the study subjects in the air-pollution group.

Overall 5,946 victims were considered for inclusion in this study. Those who were not able to undergo a follow-up survey, those who were younger than 65 years, and those with missing data were excluded. In total, 655 victims of pollution-related illness were included in this study.

b. Flow chart of the study subjects in the non-air-pollution group.

Overall 1,216 subjects were considered for inclusion in this study. Those who were younger than 55 years, those who were older than 85 years, and those with missing data were excluded. In total, 572 subjects living in Nagasaki prefecture were included in this study.

Table 1. Time required for certification of exposure to air pollution.

Illness	a)	b)	c)
Chronic bronchitis	24 months	48 months	36 months
Asthma	12 months	30 months	18 months
Pulmonary emphysema	36 months	66 months	52 months

a) Individual who resided in a designated area prior to 1973.
b) Individual who did not reside in a designated area, but spent at least 8 hours per day in a designated area.
c) Individual who resided in a designated area, then relocated, but continued to work in a designated area for at least 8 hours per day.

Table 2. Baseline characteristics of participants.

	From air-polluted area		From non-air-polluted area	
	Smoking (*n* = 130)	Non-smoking (*n* = 525)	Smoking (*n* = 113)	Non-smoking (*n* = 459)
Age (years)	68.4 ± 7.7	68.3 ± 7.2	66.8 ± 7.5**	69.3 ± 6.9
Height (m)	1.49 ± 0.06	1.49 ± 0.07	1.53 ± 0.07*	1.50 ± 0.06*
Weight (kg)	54.0 ± 10.9	53.3 ± 9.5	54.1 ± 9.8	52.3 ± 8.3
BMI (kg/m^2)	24.4 ± 4.5	24.0 ± 3.7	23.0 ± 3.7*	23.1 ± 3.2*
Diagnosed disease				
CB	66 (50.8%)	282 (53.7%)		
Asthma	62 (47.7%)	240 (46%)		
PE	2 (1.5%)	3 (0.3%)		

Values are presented as mean ± standard deviation or numbers and percentages of subjects.
BMI, body mass index; CB, chronic bronchitis; PE, pulmonary emphysema.
*$P < 0.05$ compared with subjects from air-polluted area.
**$P < 0.05$ compared with non-smoking from non-air-polluted area.

been subject to environmental standards in Japan since 1972. The data were obtained from the air pollution office (comprising a general environmental air measurement office and a motor exhaust measurement office), which is part of the public supervision system, in each district. The level of air pollution in Mizushima was measured at 22 sites (http://kurashiki-taiki.jp/index.pl), in Kitakyushu at 19 sites (http://soramame.taiki.go.jp/MstItiranFrame.php?Pref=40), and in Nagasaki pollution levels were measured at 24 sites (http://gissv02.pref.nagasaki.jp/TaikiWeb/MainController). These measurements reflect the average annual value for air pollution in each area.

Statistical analysis

The Kruskal-Wallis test was used after normality was determined using the Kolmogorov-Smirnov test. Bonferroni's multiple comparison method was performed as the post-hoc test. To evaluate the effects of concurrent air pollution and smoking, a two-way repeated analysis of variance was conducted for the existence of air pollution and smoking, respectively. We analyzed the scatter plots of age vs. FEV_1. Spearman correlations were used to determine the relationship between age and FEV_1 in the air-pollution and non-air-pollution groups. Moreover, adjusted differences in $\%FEV_1$ between the air-pollution and non-air-pollution groups were analyzed using analysis of covariance (ANCOVA) with age as the covariate. All analyses were performed using the IBM SPSS Statistics package version 20.0, and differences were considered to be statistically significant at $P < 0.05$.

Results

The clinical characteristics of the participants in this study are shown in Table 2. Data regarding the levels of SO_2, NO_2, and SPM in the air from 1969 to 2000 are shown in Figs. 2, 3 and 4. In 1968, the Air Pollution Control Law was enacted. In Mizushima, the NO_2 levels exceeded the acceptable level in 1970 and 1973. In Kitakyushu, the SO_2 level exceeded the acceptable level in 1969. The NO_2 levels were above the acceptable level for all years from 1970 to 1974. The environmental level of SO_2, NO_2, and SPM in Nagasaki prefecture was lower than the acceptable level.

Pulmonary function data were compared among the smoking group with pollution, non-smoking group with pollution, smoking group without pollution, and non-smoking group without pollution (Table 3). Significant differences were observed in the pulmonary functions among the four groups.

The smoking group with pollution had lower $\%FEV_1$ than the other groups ($P < 0.001$). The non-smoking group with pollution had lower $\%FEV_1$ than both the smoking group and non-smoking group without pollution ($P < 0.001$) (Fig. 5). The smoking group and non-smoking group with pollution had lower FEV_1/FVC than the smoking group and non-smoking group without pollution ($P < 0.001$). The smoking group without pollution had lower FEV_1/FVC than

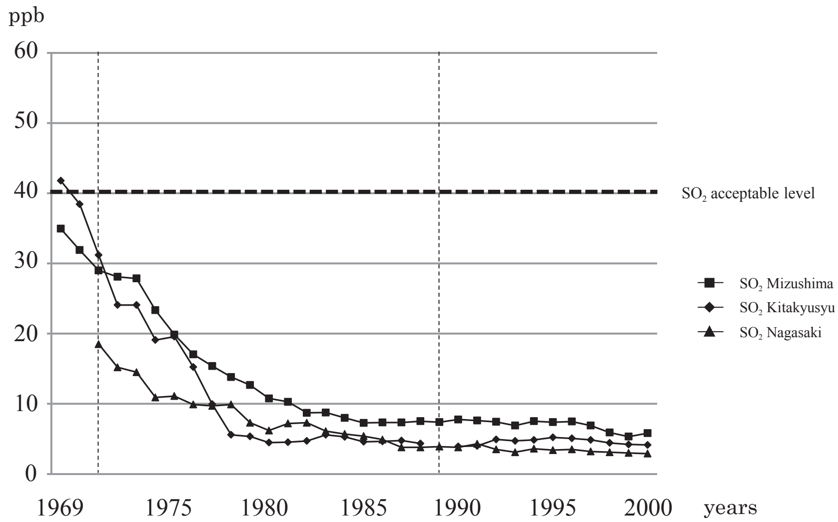

Fig. 2. Annual variations in air pollutant (sulfur dioxide) levels.
The air pollutant was sulfur dioxide (SO_2). The values of air pollution were measured at 21 sites in the Mizushima area, 19 sites in the Kitakyushu area, and 24 sites in the Nagasaki area. The horizontal line indicates the Environmental Quality Standards Regarding Air Pollution [40 parts per billion (ppb)]. Data at Kitakyushu in 1989 were not available. The measurement of SO_2 started in 1971 in Nagasaki.

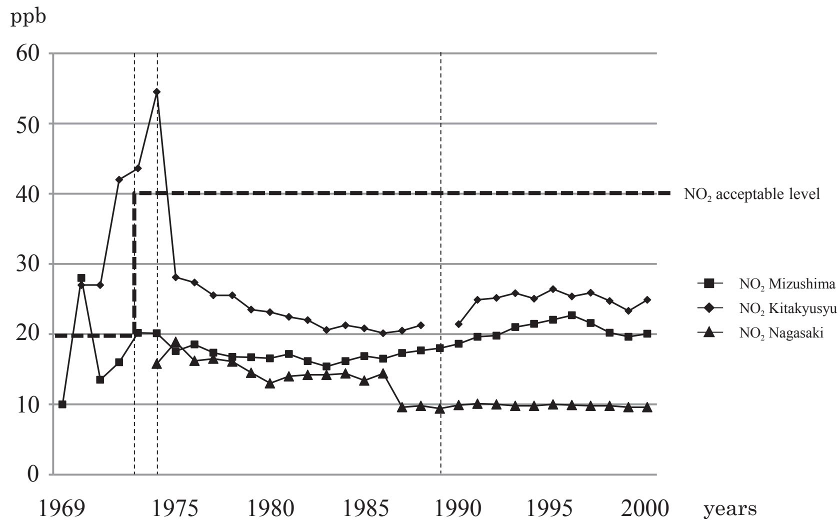

Fig. 3. Annual variations in air pollutant (nitrogen dioxide) levels.
The air pollutant was nitrogen dioxide (NO_2). The values of air pollution were measured at 21 sites in the Mizushima area, 19 sites in the Kitakyushu area, and 24 sites in the Nagasaki area. The horizontal line indicates the Environmental Quality Standards Regarding Air Pollution. In 1973, the acceptable level was changed by the Air Pollution Control Law from 20 to 40 ppb. Data at Kitakyushu in 1989 were not available. The measurement of NO_2 started in 1974 in Nagasaki.

the non-smoking group without pollution ($P < 0.01$). Furthermore, no significant difference in FEV_1/FVC was observed between the smoking group and non-smoking group with pollution (Fig. 6). The smoking group with pollution had lower %VC than the other groups ($P < 0.01$). Furthermore, no significant difference in %VC was observed in the non-smoking group with pollution and in the smoking and non-smoking groups without pollution (Fig. 7).

With respect to the interaction of air pollution and smoking, the combination of exposure to air pollution of 40 years ago and smoking showed significantly synergistic effects on %VC and %FEV_1 ($P < 0.001$). However, this same combination did not significantly affect FEV_1/FVC.

The results of the correlation analysis are given in Fig. 8a, b. FEV_1 was negatively associated with age in the air-pollution group (unstandardized regression coefficient = −20 ml/year, $P < 0.01$) and in the non-air-pollution group (unstandardized regression coefficient = −23 ml/year, $P < 0.01$). The ANCOVA results showed that exposure to air pollution was significantly related to %FEV_1 ($P < 0.001$), with statistically significant differences between the air-pol-

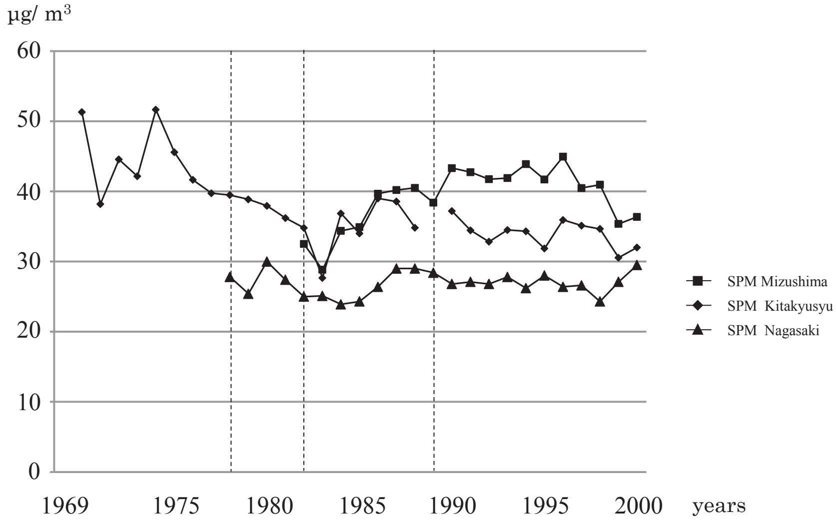

Fig. 4. Annual variations in air pollutant (suspended particulate matter) levels.
SPM, suspended particulate matter. Data at Kitakyushu in 1989 were not available. The Environmental Quality Standards Regarding Air Pollution defined an appropriate environmental level of SPM as ≤ 100 μg/m^3. The environmental level of SPM in all areas was lower than the Environmental Quality Standards Regarding Air Pollution. The measurement of SPM started in 1982 in Mizushima and in 1978 in Nagasaki.

Table 3. Pulmonary function of participants.

	From air-polluted area		From non-air-polluted area		P value
	Smoking (n = 130)	Non-smoking (n = 525)	Smoking (n = 113)	Non-smoking (n = 459)	
FEV_1 (mL)	1,382 ± 465*	1,501 ± 465*	1,863 ± 464	1,779 ± 383	< 0.001
%FEV_1 (% pred)	74 ± 24*	85 ± 25*	95 ± 19	99 ± 17	< 0.001
FEV_1/FVC (%)	70 ± 11**	71 ± 11**	77 ± 8	80 ± 7*	< 0.001
%VC (% pred)	91 ± 23*	99 ± 22	101 ± 15	99 ± 16	< 0.001
%FVC (% pred)	93 ± 23	96 ± 23	97 ± 16	98 ± 17	n.s.

Values are presented as mean ± standard deviation.
FEV_1, forced expiratory volume in 1 second; %FEV_1, FEV_1 % predicted; %FVC, forced vital capacity % predicted; FEV_1/FVC, forced expiratory volume % in 1 second; %VC, vital capacity % predicted.
*P < 0.05 compared with other groups.
**P < 0.05 compared with subjects from non-air-polluted area.

lution and non-air-pollution groups.

Discussion

We found that exposure to long-term air pollution remarkably reduced pulmonary function by the synergistic effect of the combination of exposure to air pollution and smoking, despite the fact that air pollution has improved and continuous medical care has been provided by the national government for 40 years.

The exposure to air pollution reduced the %FEV_1 in this study. The non-smoking group with pollution had lower %FEV_1 than did the smoking group without pollution (P < 0.001). Thus, exposure to air pollution appears to reduce the %FEV_1 to a greater extent than does a history of smoking. In this connection, exposure to SO_2, NO_2, and PM_{10} was significantly correlated with a decrease in FEV_1 (Schikowski et al. 2005; Forbes et al. 2009). Furthermore, despite the improvement in the air pollution, the lung function did not recover in officially acknowledged victims of pollution-related illness (Yanagita et al. 2013). The present study supports the findings of previous studies.

Furthermore, the combination of exposure to smoking and air pollution was associated with lower %FEV_1 than was exposure to only air pollution, and a synergistic effect of air pollution and smoking was shown. Taylor (2010) reported that exposure to tobacco smoke was the factor with the strongest influence on the development of chronic obstructive pulmonary disease. Lung inflammation and symptoms of disease became increasingly severe with higher amounts of exposure (Taylor 2010). Some reports have indicated that smoking with air pollution is significantly more closely correlated with decreased FEV_1 than not smoking with air pollution (Schindler et al. 2001; Qian et al. 2005). It is thought that the %FEV_1 is reduced to a

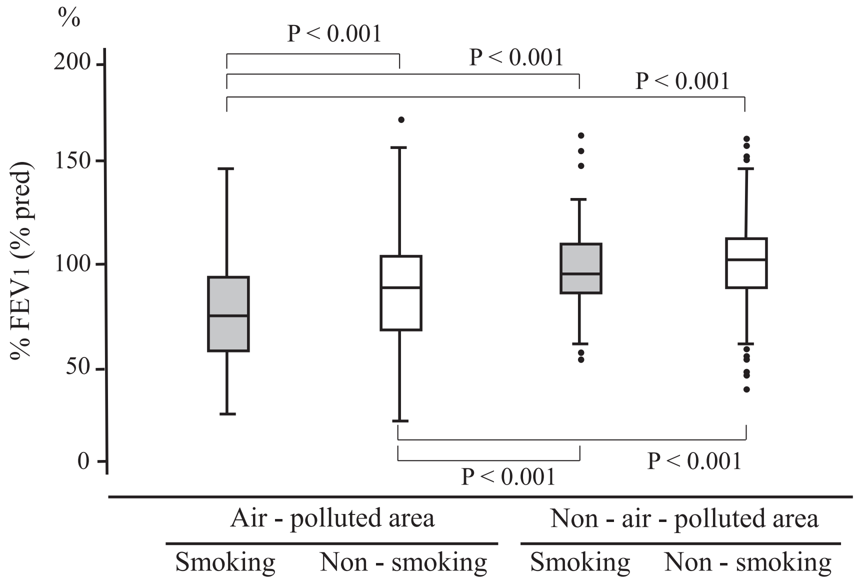

Fig. 5. Data grouped according to smoking status with or without exposure to air pollution.
The Kruskal-Wallis test was conducted to evaluate the difference in $\%FEV_1$. Bonferroni's multiple-comparison method was performed as the post-hoc test. The smoking group with pollution had a lower $\%FEV_1$ than did the other groups ($P < 0.001$). The non-smoking group with pollution had a lower $\%FEV_1$ than did both the smoking and non-smoking groups without pollution ($P < 0.001$). FEV_1, forced expiratory volume in 1 second; $\%FEV_1$, FEV_1 % predicted.

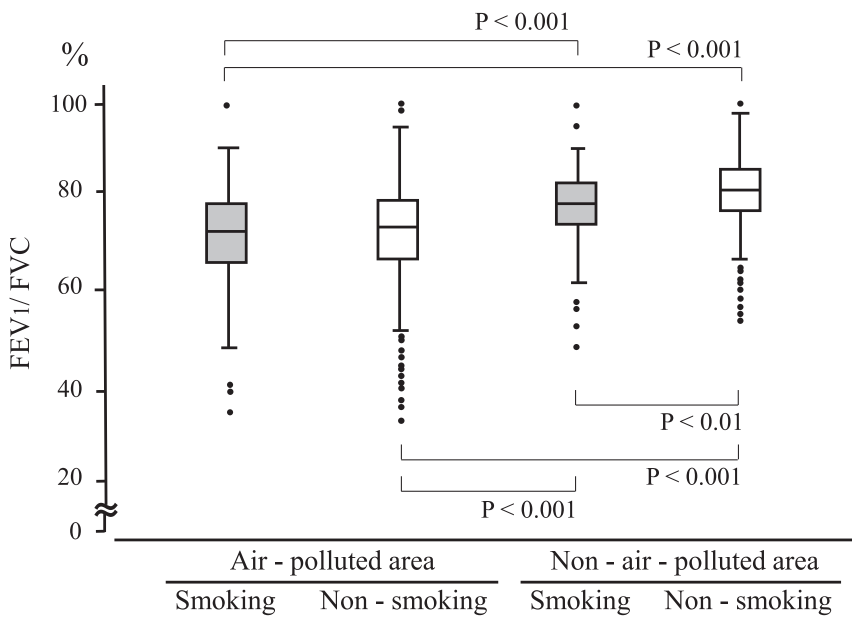

Fig. 6. FEV_1/FVC data grouped according to smoking status with or without exposure to air pollution.
The Kruskal-Wallis test was conducted to evaluate the difference in FEV_1/FVC. Bonferroni's multiple-comparison method was performed as the post-hoc test. The smoking and non-smoking groups with pollution had a lower FEV_1/FVC than did the smoking and non-smoking groups without pollution ($P < 0.001$). The smoking group without pollution had a lower FEV_1/FVC than did the non-smoking group without pollution ($P < 0.01$). FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; FEV_1/FVC, forced expiratory volume % in 1 second.

greater extent with the combination of exposure to air pollution and smoking than with exposure to only air pollution because the influence of the combination of exposure to air pollution of 40 years ago and smoking showed significantly synergistic effects.

The exposure to air pollution reduced the FEV_1/FVC ratio in this study. Exposure to air pollution was associated with a lower FEV_1/FVC than was exposure to smoking ($P < 0.001$). Forbes et al. (2009) indicated that exposure to SO_2, NO_2, and SPM is significantly correlated with decreased

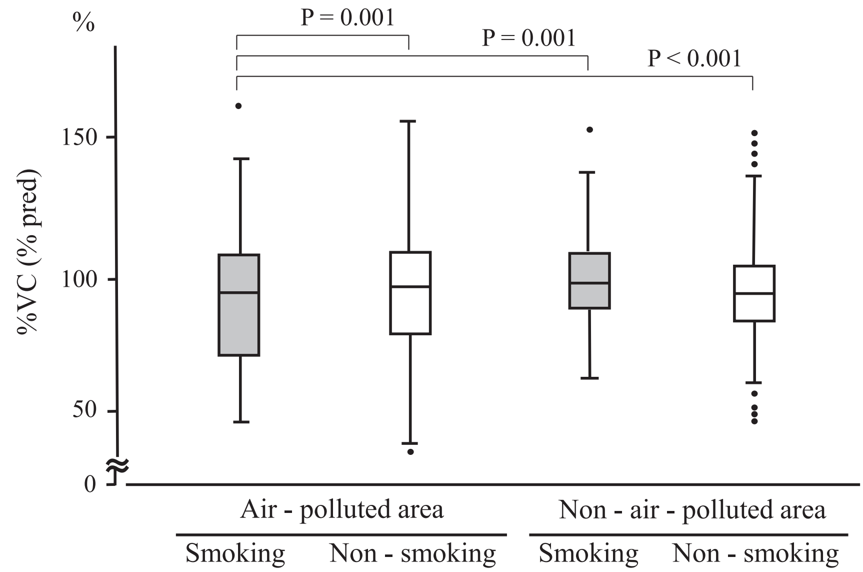

Fig. 7. %VC data grouped according to smoking status with or without exposure to air pollution.
The Kruskal-Wallis test was conducted to evaluate the difference in %FEV_1. Bonferroni's multiple-comparison method was performed as the post-hoc test. The smoking group with pollution had a lower %VC than did the other groups ($P < 0.01$). VC, vital capacity; %VC, VC % predicted.

FEV_1/FVC. Schikowski et al. (2005) also reported that long-term exposure to air pollution decreased FEV_1/FVC, FEV_1, and FVC. Furthermore, larger decreases in pulmonary function occur with higher amounts of exposure (Schikowski et al. 2005). These findings suggest that the influence of air pollution on FEV_1/FVC is stronger than smoking alone without pollution. However, the precise amount of smoking could not be determined in this study.

The combination of exposure to smoking and air pollution was associated with a lower %VC, and a synergistic effect of air pollution and smoking was shown in this study. Our findings suggest that %VC does not decrease in non-smoking group exposed to air pollution. Our findings also suggest that %VC decreases to a greater degree with the combination of exposure to air pollution and smoking. Moreover, among previous studies on the influence of air pollution, many have evaluated FVC, but none have evaluated VC. However, the present study suggests that %VC may also decrease by the synergistic effect of air pollution and smoking.

The combination of exposure to smoking and air pollution was not associated with lower %FVC in this study. Some reports have indicated that smoking with pollution is more significantly correlated with decreased FVC compared to non-smoking with pollution (Qian et al. 2005; Forbes et al. 2009). Our findings suggest a negative influence of the synergistic effect of smoking after air pollution exposure on the %FVC.

However, subjects in the air pollution groups exhibited lower %FEV_1, FEV_1/FVC, and FVC than did subjects who had not been exposed to air pollution. We consider that the lower %FEV_1, FEV_1/FVC, and FVC in the air pollution groups may have been caused by the high environmental levels of SO_2 and NO_2 from 1970 to 1975 in Kitakyushu and Mizushima.

The smoking group exhibited lower FEV_1/FVC than did the non-smoking group in the non-air-polluted area ($P < 0.01$). Taylor (2010) reported that exposure to tobacco smoke was the factor with the strongest influence on FEV_1/FVC. The present study also suggests that exposure to smoking negatively affects lung function.

Air pollution caused by rapid economic development is an international problem among the developing countries within Asia today. A very important finding of this study is the harmful effects sustained by continuing to smoke in such an environment. Moreover, 40 years after air pollution had improved, it was shown that pulmonary function was not restored even when regular medical treatment was administered. Smoking is a factor that further worsens respiratory function, and our findings further support the recommendation against smoking. Limitations of this study include the fact that only the subjects' smoking history was examined and that the precise amount of smoking could not be determined. Furthermore, exposure to passive smoking and the presence of symptoms could not be determined.

In conclusion, exposure to air pollution of 40 years ago and cigarette smoking are associated with reduced pulmonary function, in spite of continuous medical care guaranteed by the national government for 40 years. This study demonstrates that concurrent smoking enhances the detrimental effect of air pollution on pulmonary function and highlights the importance of measures aimed at smoking cessation and limiting exposure to air pollution.

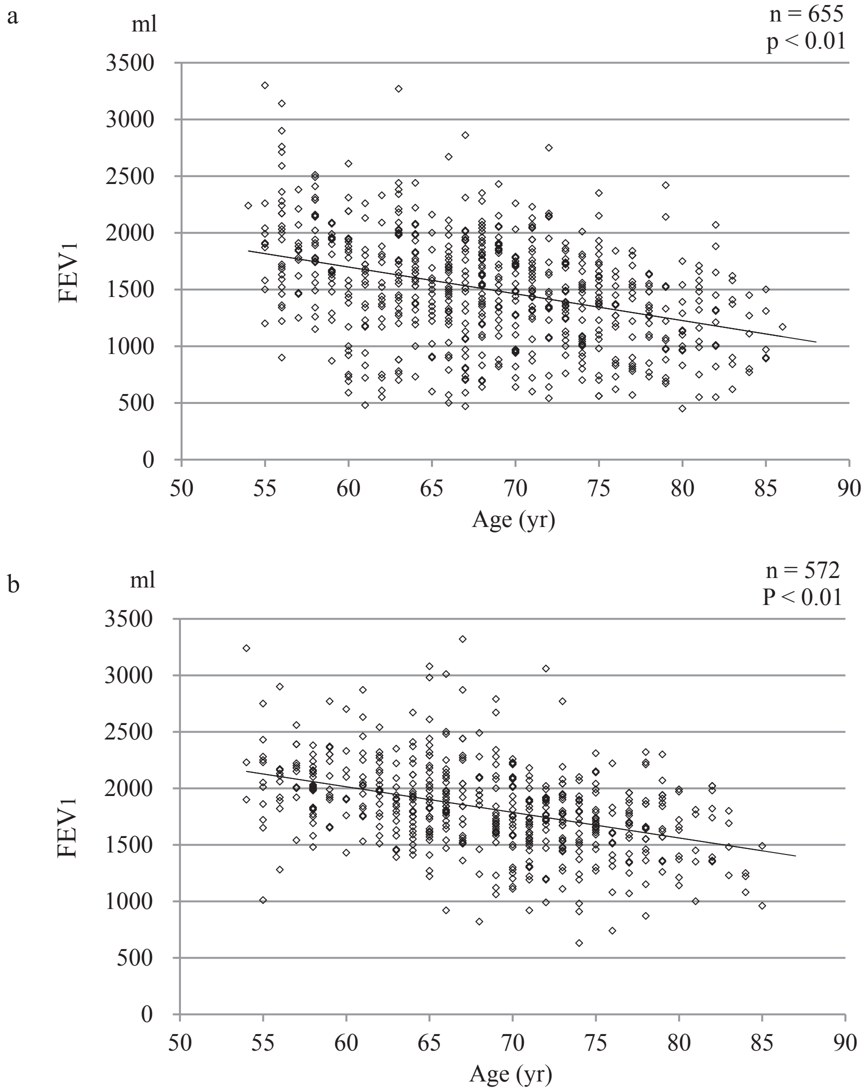

Fig. 8. Age-dependent decrease in FEV_1.
(a) Scatter plots of age vs. FEV_1 in the air-pollution group. (b) Scatter plots of age vs. FEV_1 in the non-air-pollution group.

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Conflict of Interest

The authors declare no conflict of interest.

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