Original Article

Impact of airflow obstruction on long-term mortality in patients with asthma in Japan

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ABSTRACT

Background: The long-term prognosis of asthma with airflow obstruction is poorly understood in Japan. The aim of this retrospective 26-year study was to investigate the long-term mortality risk of airflow obstruction in asthmatics.
Methods: Using data from the Omuta City Air Pollution-related Health Damage Cohort Program, mortality risk ratios of airflow obstruction in Japanese Individuals were analyzed by Cox proportional hazards models. Airflow obstruction was considered to be present when the forced expiratory volume in 1 sec (FEV$_1$)/forced vital capacity ratio was <0.7 and FEV$_1$ predicted was <80% based on spirometry.
Results: Among the 3146 victims with chronic respiratory diseases, 697 with adult asthma were selected. Median follow-up period was 26.3 (range 0.9—40.9) years. The airflow obstruction group (n = 193) showed significantly higher rates of mortality related to respiratory problems (risk ratio [95% confidence interval] 1.51 [1.86—1.93], P = 0.0017) and asthma attacks (1.86 [1.30—2.66], P = 0.0011) than the without airflow obstruction group (n = 504). Airflow obstruction was an independent risk factor for both respiratory-related (1.84 [1.36—2.49], P = 0.0001) and all-cause (1.44 [1.17—1.76], P = 0.0008) mortality after adjustment for age, sex, body mass index, and smoking status. More severe airflow obstruction was significantly associated with poorer prognosis.
Conclusions: This long-term cohort program revealed the impacts of asthma with airflow obstruction as an independent mortality risk. Findings suggest that intervention and prevention of airflow obstruction can reduce long-term mortality in patients with asthma.

Introduction

During the 1960s, Japan was severely affected by air pollution that accompanied its booming economic recovery. Exposure to air pollution is now known to be strongly linked to the development of chronic pulmonary diseases such as asthma, chronic bronchitis, pulmonary emphysema, chronic obstructive pulmonary disease (COPD), and asthma-COPD overlap (ACO) with characteristics of both asthma and COPD.[1,2] Today, many victims of air pollution in Japan still have chronic pulmonary diseases and long-term respiratory symptoms, necessitating regular medical attention.[3] According to a 2014 Japanese survey, the number of patients with asthma, including victims of air pollution, is still increasing; 1,177,000 (515,000 men and 662,000 women) regularly visit hospitals with this complaint. An updated survey report has indicated that the number of asthma-related and all-cause mortalities among patients with asthma as a comorbidity has been decreasing in the last few decades, from 5926 in 1996 to 1511 in 2015.[3,4] However, Japan still has the highest asthma-related mortality among developed nations; the age-standardized asthma mortality rate was 9.34 per million for all ages in the period 2001—2010.[5,6] The number of victims with air pollution-related asthma may be partly responsible for the higher asthma mortality in Japan.[3]

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Between the 1950s and 1970s, Omuta City (Fukuoka, Japan) was an industrial city with very severe air pollution. After the enactment of a national bill to offer compensation for pollution-related health damage by An Act in 1973, Omuta City was designated as a type I air pollution area in 1974.[3] This Act designated chronic bronchitis, asthma, and pulmonary emphysema as air pollution-related chronic respiratory diseases qualifying for compensation. Each resident receiving certification as a victim was followed-up prospectively by the Omuta City Air Pollution-related Health Damage Cohort Program.

Fixed airflow obstruction is known to be a risk factor for poor prognosis in asthma.[7] It may develop through several causes and mechanisms. Airway remodeling and loss of lung elastic attachments may lead to airflow obstruction.[8–11] Risk factors for airway obstruction include adult onset, frequent exacerbations, smoking, occupational exposure, ongoing eosinophilic airway inflammation, and airway hyperresponsiveness in asthma.[12,13] Air pollution is also a risk factor for airway obstruction.[14–17] Airflow obstruction and ACO-like features may account for the higher prevalence of mortality among Japanese adults with asthma, regardless of smoking status.

The level of mortality among Japanese individuals with asthma needs to be reduced to that observed in other developed countries. Investigations of respiratory-related and all-cause mortality among asthmatic patients would help reduce the level of asthma-related mortality in Japan. The long-term mortality statistics for patients with asthma are still unclear, despite several previous population-based cohort studies.[18,19] The present study utilized data from the Omuta City Air Pollution-related Health Damage Cohort Program. However, the program was not confirmed that development of asthma were associated with air-pollution by any medical tests or validated questionnaires in all enrolled patients. The patients with multifactor-related asthma may be enrolled in our study. Thus, we here accept a term of "asthma", not but "air pollution-related asthma" to distinguish between the legal and medial term strictly. The primary objective was to investigate differences in the causes of mortality between asthma victims with and without airflow obstruction and whether airflow obstruction was an independent factor related to respiratory-related and all-cause mortality in victims with asthma. The secondary objective was to compare the characteristics of asthma victims with and without airflow obstruction using data from the cohort program.

Methods

Cohort program and study design

The Omuta City Air Pollution-related Health Damage Cohort Program (Omuta, Fukuoka, Japan) by the Act was conducted between 1974 and 1988. During this period, 3146 victims with air pollution-related respiratory diseases were registered (Fig. 1). Each victim was required to complete a self-report questionnaire inquiring about respiratory symptoms and smoking status, and to undergo chest roentgenography, electrocardiography, and spirometry once a year after providing written consent for the cohort program. In case of a victim's death, bereaved families were required to submit a death certificate to Omuta City. Regarding smoking status, the questionnaire had two questions: "Question 1, Do you smoke now?," and "Question 2, Have you ever smoked before, if your answer to Question 1 was no." The non-smokers, ex-smokers, and current smokers were identified as those who gave negative answers to Questions 1 and 2, a negative answer to Question 1 and a positive answer to Question 2, and a positive answer to Question 1, respectively. However, the number of cigarettes smoked per day, duration of smoking, data on blood eosinophils, levels of serum total immunoglobulin E, and spirometry data after bronchodilators were not essential for this cohort program.

All information on adult victims (certified age $\geq$ 20 years) were obtained from the Department of Health and Welfare, Omuta City (Fig. 1). Baseline characteristics including age, gender, height, weight, smoking status, diagnosis of chronic respiratory diseases, and spirometry data were collected at the time of certification. Although the term "air pollution-related asthma" was used in the database, the enrolled patients in this study considered multifactor-related asthma because the interaction between asthma and air-pollution was not confirmed by any medical tests. The data for victims with other chronic respiratory diseases such as pulmonary tuberculosis, bronchiectasis, pneumoconiosis, and interstitial pneumonia confirmed by chest roentgenography were not included in the analyses. The date and age at death and the cause of mortality were obtained from the death certificate. The main cause and classification of mortality were selected in accordance with the code for International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10 Version 2016)[20] (Supplementary Methods).

Ethical approval

The study was conducted in accordance with the Good Clinical Practice guidelines and was approved by the local ethics board of Kurume University (No. 15—135, September 11, 2015). The study protocol was registered in the University Hospital Medical Information Network (UMIN) Center (UMIN No. 000031509) on February 28, 2018. Participation of patients with asthma was obtained through an opt-out methodology between the date of certification and August 31, 2015. The investigators signed a contract with Omuta City with regard to permission to use the data on August 27, 2015 (updated on August 19, 2016).

Quality control of spirometry data

To obtain adequate data for forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) for quality control of spirometry, the shape of the maximal expiratory flow—volume curve was re-evaluated in accordance with recommendations for standardization of lung function testing[21] (Supplementary Methods).
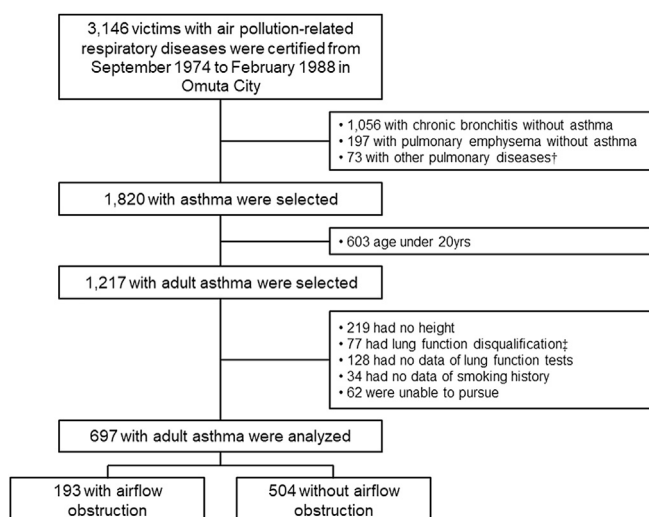
Fig. 1. Study design. † The 73 patients with other pulmonary diseases including old pulmonary tuberculosis (n = 39), pneumoconiosis (n = 19), bronchiectasis (n = 11), and interstitial pneumonitis (n = 4) were excluded on the basis of chest radiograms at certification. ‡ Eligibility criteria for flow—volume curves were based on the ATS/ERS task force.[21]

Diagnosis of asthma

Diagnosis of asthma was based on the criteria stipulated in the Act, i.e., in accordance with symptoms such as occasional spasmodic repeated and fluctuating wheezing and dyspnea. Other respiratory diseases were excluded on the basis of chest roentgenograms by each physician. However, diagnosis of asthmatic bronchitis was included as asthma.

Definition of airflow obstruction

Two Cox proportional hazards models were used to compare the criteria of airflow obstruction. One was a FEV_1/FVC ratio of <0.7 and %FEV_1 predicted <80% based on a previous study (model 1) (Supplementary Fig. 1A)[18] and the other was a FEV_1/FVC ratio of <0.7 based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria (model 2) (Supplementary Fig. 1B).[22] We accepted model 1. Following this, victims with a FEV_1/FVC ratio of ≥0.7 or %FEV_1 predicted ≥80% were defined as the control group. With regard to the severity of airflow obstruction,[21] victims with % FEV_1 predicted ≥50% and <80%, ≥30% and <50%, and <30% among the airflow obstruction group were defined as categories 1, 2, and 3, respectively. However, patients with ACO-like features were recognized as victims aged >40 years, with a FEV_1/FVC ratio <0.7, and who were current or ex-smokers, as done in a previous study[23] (Supplementary Fig. 2, Supplementary Table 1).

Statistical analyses

All data for baseline characteristics are expressed as the mean ± standard deviation and number (%) of victims. The baseline characteristics and frequency of causes (%) of mortality were compared between the airflow obstruction group and control group using Student's t test and chi-squared test or Fisher's exact test. In these models, the starting date was the date of certification of the cohort and the cut-off date was the date of death (for decedents) or August 31, 2015 (for subjects surviving until that date). The time to survival probability of respiratory-related and all-cause mortality was expressed as Kaplan-Meier curves, which were compared between victims with and without airflow obstruction and among categories for the total population, non-and ex-smokers, and current smokers using log-rank test (model 1). The effects of sex, age, and body mass index (BMI) on respiratory-related and all-cause mortality were also examined (Supplementary Fig. 3). Cox proportional hazards model analysis was conducted using the control group as a reference to examine the relationship between airflow obstruction and the time to survival probability of respiratory-related and all-cause mortality. The relative risk ratio (95% confidence interval [CI]) of airflow obstruction in relation to respiratory-related and all-cause mortality was calculated and adjusted for age and BMI as continuous variables and for sex (male/female) and smoking status (non-, ex-, or current) as nominal variables, whereas other covariates such as interaction terms were tested and considered significant if P values were less than 0.05. Statistical analyses were performed using the JMP version 9.0 software package (SAS Institute Japan Inc., Tokyo, Japan).

Results

Study population

Among 3146 adult victims with chronic respiratory diseases, a final total of 697 victims with adult asthma were analyzed, and the median (25th and 75th percentile [range]) observation period was 26.3 years (17.4–30.2 years [0.9–40.9 years]). Among 697 victims with adult asthma, 193 (27.7%, with airflow obstruction group) and 504 (72.3%, without airflow obstruction/control group) met the criteria at the time of certification (Fig. 1).

Table 1 shows that, in comparison with the control group, the airflow obstruction group had a significantly higher proportion of male ($P = 0.0378$), lower BMI ($P = 0.0049$), higher population of ex- and current smokers ($P = 0.0313$), and poorer pulmonary function (FEV_1, %FEV_1, and FEV_1/FVC, all $P < 0.0001$). Both all-cause mortality and respiratory-related morality in the airflow obstruction group were significantly higher than those in the control group between the date of certification and the cut-off date (August 31, 2015). Age at death due to respiratory-related disease was significantly ($P = 0.0010$) lower in the airflow obstruction group than in the control group. However, there was no inter-group difference in age at death due to all causes.

As shown in Table 2, the airflow obstruction group (risk ratio [95% CI]) had a significantly higher incidence of mortality due to asthma attack (1.86 [1.30–2.66], $P = 0.0011$) and heart failure (2.26 [1.10–4.67], $P = 0.0307$) than the control group. Among the total population, respiratory-related mortality accounted for the highest proportion, followed in descending order by mortality due to neoplasms, cardiovascular disease, cerebrovascular disease, digestive disease, renal failure, accidents, and senility (Supplementary Table 2).

Figure 2 shows the Kaplan-Meier curve of survival probability for respiratory-related and all-cause mortality between the airflow obstruction and control groups in terms of the total population, non- and ex-smokers, and current smokers. Among the total population, both respiratory-related and all-cause mortality were significantly shorter in the airflow obstruction group than in the control group ($P = 0.0013$ and $P = 0.0190$, respectively). Non- and ex-smokers and current smokers in the airflow obstruction group had a significantly shorter survival time in terms of respiratory-related mortality ($P = 0.0227$ and $P = 0.0117$, respectively), but not all-cause ($P = 0.0692$ and $P = 0.1391$, respectively) mortality than those in the control group.

As shown in Figure 3, airflow obstruction was an independent risk factor for respiratory-related (adjusted relative risk ratio 1.85 [95% CI 1.36 to 2.50], $P = 0.0001$) and all-cause mortality (1.44 [1.17 to 1.77], $P = 0.0006$) in the total population. Airflow obstruction was also an independent risk factor for respiratory-related and all-cause mortality in non- and ex-smokers (1.70 [1.17 to 2.43], $P = 0.0058$ and 1.41 [1.10 to 1.80], $P = 0.0071$, respectively) and current smokers (2.33 [1.34 to 4.02], $P = 0.0033$ and 1.54 [1.04 to 2.23], $P = 0.0316$, respectively) (data not shown).

Figure 4 shows the Kaplan-Meier curves of survival probability for respiratory-related and all-cause mortality among the control group and categories in the total population (Fig. 4A, D), non- and ex-smokers (Fig. 4B, E), and current smokers (Fig. 4C, F) (Supplementary Table 3A, B). In terms of respiratory-related mortality, survival probability was significantly shorter for category 3 than for categories 1 and 2 and the control group among the total population ($P = 0.0032$). It was also significantly shorter for category 3 than for categories 1 and 2 and the control group among non- and ex-smokers ($P = 0.0294$). However, there was no significant difference among the four groups for current smokers ($P = 0.0829$). In terms of all-cause mortality, the survival probability was shorter in category 2 for the total population ($P = 0.0041$) and for non-smokers and ex-smokers ($P = 0.0307$). In current smokers, however, there was no significant difference among the four categories ($P = 0.0858$).

Table 1
Characteristics of victims with asthma.

Characteristic[†]	Airflow obstruction group	Control group	P value
Number (% of total)	193 (27.7)	504 (72.3)	
Age, years, mean ± SD	54.4 ± 12.4	53.1 ± 0.6	0.2
Male, n (%)	88 (45.6)	186 (36.9)	0.0378*
BMI, kg/m^2	22.1 ± 3.4	22.9 ± 3.6	0.0049*
Smoking status, n (%)			
Non-/Ex-/Current	85/54/54 (44.0/28.0/28.0)	277/107/120 (55.0/21.2/23.8)	0.0313*
Lung function[‡], mean ± SD			
FEV$_1$, L	1.31 ± 0.47	1.97 ± 0.71	<0.0001*
%FEV$_1$ predicted, %	51.1 ± 13.1	78.7 ± 17.9	<0.0001*
a FEV$_1$/FVC ratio	0.59 ± 0.09	0.83 ± 0.09	<0.0001*
Mortality between the date of certification and the cut-off date (August 31st, 2015), n (%)			
All-cause mortality	138 (71.5)	301 (59.7)	0.0039*
Respiratory-related mortality	70 (36.3)	121 (24.0)	0.0017*
Age at death, years, mean ± SD			
All-cause mortality	79.6 ± 10.5	78.0 ± 8.3	0.1
Respiratory-related mortality	78.1 ± 8.6	82.4 ± 8.4	0.0010

BMI, body mass index; SD, standard deviation.
*$P < 0.05$ between groups.
[†] Patients with a FEV$_1$/FVC ratio of <0.7 and %FEV$_1$ predicted <80% and a FEV$_1$/FVC ratio of ≥0.7 or %FEV$_1$ predicted ≥80% are considered as the airflow obstruction group and the control group, respectively. Data are expressed as mean ± SD and number (%) of patients, and comparisons between groups are made using standard t test and chi-squared test. However, data for age, BMI, smoking status, and lung function are those used at the time of victim certification.
[‡] Spirometry values were not assessed after administration of bronchodilators.

Table 2
Risk ratio of mortality for each cause of death among patients with airflow obstruction relative to the control group.

Causes of death	Total	Airflow obstruction group	Control group	Risk ratio (95% CI)	P value
Number, n (%)	697 (100)	193 (100)	504 (100)		
Respiratory-related	191 (27.4)	70 (36.3)	121 (24.0)	1.51 (1.86–1.93)	0.0017*
Asthma attacks	101 (14.5)	42 (21.8)	59 (11.7)	1.86 (1.30–2.66)	0.0011*
Respiratory tract infections	88 (12.6)	27 (14.0)	61 (12.1)	1.16 (0.76–1.76)	0.5
Interstitial pneumonia	2 (0.3)	1 (0.5)	1 (0.2)	2.61 (0.16–41.6)	0.5
Neoplasm-related	89 (12.8)	27 (14.0)	62 (12.3)	1.14 (0.75–1.73)	0.5
Lung cancer	27 (3.9)	4 (2.1)	23 (4.6)	0.45 (0.16–1.30)	0.2
Hepatocellular carcinoma	16 (2.3)	5 (2.6)	11 (2.2)	1.19 (0.42–3.37)	0.8
Colon or rectum cancer	12 (1.7)	5 (2.6)	7 (1.4)	1.87 (0.60–5.81)	0.3
Gastric cancer	9 (1.3)	5 (2.6)	4 (0.8)	3.26 (0.89–12.0)	0.1
Minor causes[†]	25 (3.6)	8 (4.1)	17 (3.4)	n/a	
Cardiovascular-related	53 (7.6)	18 (9.3)	35 (6.9)	1.34 (0.78–2.31)	0.3
Heart failure	28 (4.0)	13 (6.7)	15 (3.0)	2.26 (1.10–4.67)	0.0307*
Acute coronary disease	14 (2.0)	3 (1.6)	11 (2.2)	0.71 (0.20–2.53)	0.8
Minor causes[†]	11 (1.6)	2 (1.0)	9 (1.8)	n/a	
Cerebrovascular-related	20 (2.9)	6 (3.1)	14 (2.8)	1.12 (0.44–2.87)	0.8
Digestive disease-related	20 (2.9)	1 (0.5)	19 (3.8)	0.14 (0.02–1.02)	0.0205*
Liver cirrhosis	12 (1.7)	0 (0)	12 (2.4)	0.00 (n/a)	0.0438*
Minor causes[†]	8 (1.6)	1 (0.5)	7 (1.4)	n/a	
Renal failure-related	4 (0.6)	2 (1.0)	2 (0.4)	2.61 (0.37–18.4)	0.3
Accident-related	20 (2.9)	4 (2.1)	16 (3.2)	0.65 (0.22–1.93)	0.6
Suffocation	11 (1.6)	3 (1.6)	8 (1.6)	0.98 (0.26–3.65)	1.0
Trauma	9 (1.3)	1 (0.5)	8 (1.6)	0.33 (0.04–2.59)	0.5
Senility-related	2 (0.3)	0 (0)	2 (0.4)	0.00 (n/a)	1.0
Others*	10 (1.4)	2 (1.0)	8 (1.6)	n/a	
Unknown	30 (4.3)	8 (4.1)	22 (4.4)	0.95 (0.43–2.10)	1.0

All data are expressed as the number of deaths (% of total deaths). The risk ratio (95% CI and P values) of mortality for each cause of death among patients with airflow obstruction relative to the control group was calculated by chi-squared test.
CI, confidence interval; n/a = not available.
*$P < 0.05$ between groups.
[†] Rare causes of death accounting for <1% of total deaths were included as minor causes or others. The odds ratios for minor causes and others were not analyzed.

Discussion

This study presents the results of long-term respiratory-related and all-cause mortality among certificated victims of asthma with and without airflow obstruction based on data from the Omuta City Air Pollution-related Health Damage Cohort Program. Few previous studies have examined the long-term prognosis of patients with asthma.[15–17] In this study, we found that airflow obstruction was an independent predictive risk factor for long-term respiratory-related and all-cause mortality among victims with asthma, even after adjustment for smoking status, sex, and BMI. In addition, the severity of airflow obstruction was associated with long-term respiratory-related and all-cause mortality. Airflow obstruction was strongly associated with respiratory-related mortality, but not all-cause mortality, regardless of smoking status. Our results support those of previous studies.[12–14,18,19,24] Patients with asthma who have airflow obstruction may show a natural course similar to that of the general population with asthma and airflow obstruction.

A Danish study[25] demonstrated that outpatients with asthma with %FEV$_1$ predicted <70% had a higher risk of mortality than
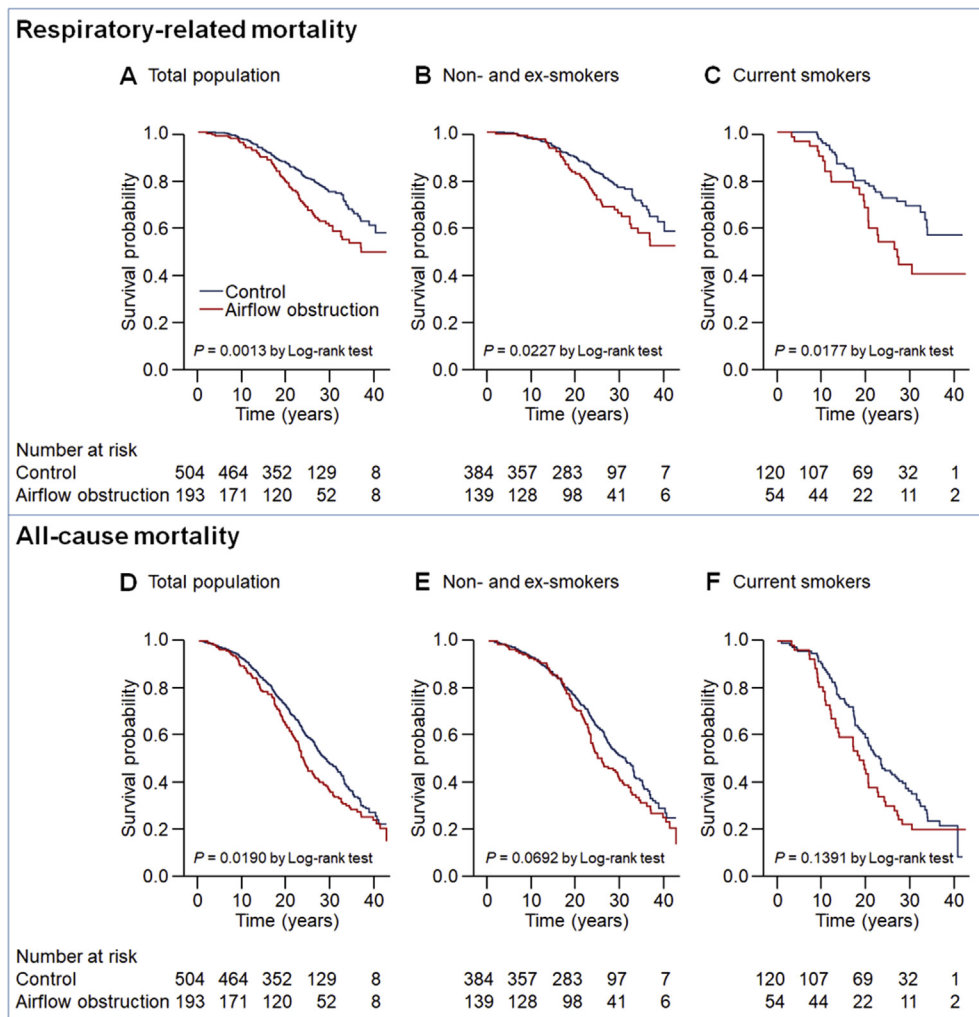
Fig. 2. Kaplan-Meier curves of survival probability for respiratory-related and all-cause mortality in the airflow obstruction and control groups for the total population, non- and ex-smokers, and current smokers.

those with %FEV$_1$ predicted ≥70% during the study period. Huang et al.[19] showed that a FEV$_1$/FVC ratio of <0.7 and %FEV$_1$ predicted of <80% resulted in a higher risk of mortality among both patients with asthma and the general population. Our criteria for airflow obstruction were a FEV$_1$/FVC ratio of <0.7 and %FEV$_1$ predicted <80% in accordance with the GOLD statement.[22] In terms of survival probability, we found no significant difference in risk for both respiratory-related and all-cause mortality between patients with a FEV$_1$/FVC ≥0.7 and FEV$_1$/FVC <0.7 and %FEV$_1$ predicted >80%. Therefore, lung function within the range of a FEV$_1$/FVC <0.7 and %FEV$_1$ ≥ 80% may not pose any risk for long-term mortality. In addition, individuals with FEV$_1$/FVC <0.7 and %FEV$_1$ predicted >80% accounted for only approximately 0.7% (n = 5) of the 697 included victims.

Several ACO diagnostic criteria have been proposed worldwide.[18,22,23,26–29] Age at onset is an important factor for diagnosis of ACO. Previous studies[18,30] divided ACO into two types using an age cut-off of 40 years. In general, episodes of asthma, onset at age >40 years, presence of a smoking history, and fixed airflow obstruction with a FEV$_1$/FVC ratio of <0.7 post-bronchodilation seem to be necessary for ACO diagnosis.[18,22,23,26–29] Our study classified victims aged ≥40 years based on the presence of a smoking history and a FEV$_1$/FVC ratio of <0.7 pre-bronchodilation at certification as having ACO-like feature[23] because the Act did not

require the onset of airway diseases, smoking index, and lung function based on post-bronchodilation spirometry data (Supplementary Fig. 2, Supplementary Table 1). The victims with ACO showed significantly worse respiratory-related and all-cause mortality than those who were smokers and aged ≥40 years without airflow obstruction. Among the victims aged ≥40 years, smokers (current and ex-smokers) had a significantly worse prognosis than non-smokers (Supplementary Fig. 2). Among those aged <40 years, only two non-smokers with airflow obstruction died due to asthma attacks, whereas none died in the other subgroups based on respiratory-related mortality (Supplementary Fig. 2, Supplementary Table 1). For younger patients with asthma, airflow obstruction may have an adverse effect on prognosis, although the resulting mortality may be low.

Our study demonstrated that respiratory-related mortality was the leading cause of death, followed in descending order by neoplasm- and cardiovascular-related mortality, among long-term causes of mortality, and that the proportion of mortality due to asthma attacks was 14.5% in the total study population. When causes of mortality were compared between victims with and without airflow obstruction, the former had a higher proportion of respiratory-related and heart failure-related mortality than the latter. The proportion of asthma attack-related mortality in the victims with and without airflow obstruction was 21.8% and 11.7%,
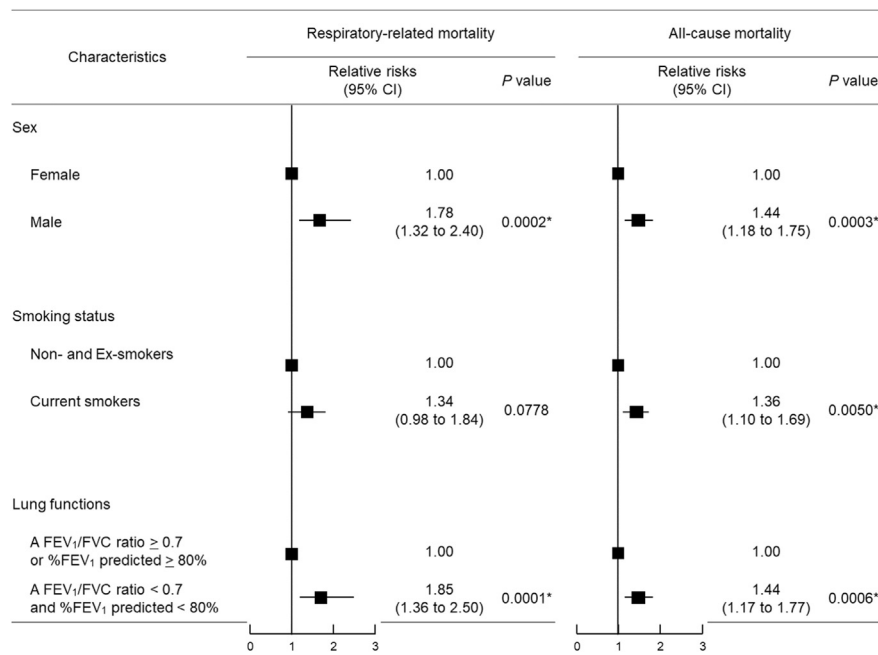
Fig. 3. Adjusted relative risks of sex, smoking status, and lung function parameters in relation to respiratory-related and all-cause mortality. Female, smoking status, and lung function in terms of a FEV_1/FVC ratio of ≥ 0.7 or $\%FEV_1$ predicted $\geq 80\%$ are used as a reference for the Cox proportional hazards analysis, which is adjusted for age and BMI as continuous variables. The adjusted relative risks and range of 95% CI are shown as boxes and bars, respectively. *$P < 0.05$. CI, confidence interval; FEV_1, forced expiratory volume in 1 s; FVC, forced volume capacity; BMI, body mass index.

respectively. The long-term decreasing trend in asthma mortality is real and is not attributable to a trend in transferring certification from an underlying to a contributory cause.[31] A study of the United States Multiple Cause-of-Death Files between 1990 and 2001 demonstrated that asthma was the underlying cause of 45% of asthma-related deaths.[32] A recent Japanese study reported that the proportion of asthma attack-related mortality was only 1% among patients with asthma and that no deaths occurred among patients with ACO during a 2-year period.[33] In the present study, the mean age at death was ≥ 75 years for both respiratory-related and all-cause mortality. Only 8 (4%) of 191 respiratory-related deaths occurred in victims aged < 65 years in the period 1983—2014, and there was respiratory-related mortality in this age range after 2003 (Supplementary Fig. 4, Supplementary Table 4). Taken together with the present results, these data indicate that malignancies and cardiovascular diseases may play a more important role than asthma attacks as the main causes of mortality among patients with asthma in the future.[34]

Relationships between the development of airflow obstruction and smoking status have often been controversial in patients with asthma.[10—13,35—39] Some studies have demonstrated that the development of airflow obstruction is associated with asthma, but not smoking status, in patients with asthma.[11,29,36] Conversely, others have reported that active or current smoking may be an important risk factor for development of airflow obstruction.[10,12,13,37—39] Active smokers may develop bronchial hyperresponsiveness.[40,41] Even current and former smokers with preserved lung function develop exacerbations and activity limitation and present evidence of airway disease.[42] The present study demonstrated that current, not but ex-smokers, had significantly poorer prognosis than non-smokers. Comparison of airflow obstruction levels between current and ex-smokers and patients with asthma who quit smoking has revealed reduced airway obstruction, suggesting that smoking cessation is crucial for the management of asthma.[43] Giving up smoking may improve airway inflammation and small airway function in patients with asthma.[44,45] Taken together, the data suggest that quitting smoking is important for improving the prognosis of patients with asthma, regardless of exposure to air pollution.[46]

Our study had several limitations. First, the definition of asthma was based on the physician's diagnosis. Therefore, airway inflammation, hyperresponsiveness, and reversibility were not assessed by the Act. Furthermore, airflow obstruction was evaluated without bronchodilation, and only once at the time of certification. Therefore, we were unable to evaluate whether airflow obstruction was fixed or not. Second, we did not assess the criteria for a lower normal limit of airflow obstruction because a healthy reference population was not employed in this study.[18,47] Third, the prognosis of patients with asthma might have been better if adequate inhaled medicines had been provided, especially in individuals with greater airway reversibility and airflow obstruction before bronchodilation. However, our study did not include any information about the medication administered to each victim. Fourth, the symptoms,[48,49] disease control levels,[50] history of exacerbations,[36] and duration of disease,[51] are important risk factors that affect prognosis and the development and severity of airflow obstruction. However, our study could not evaluate these risk factors as confounders for the association between airflow obstruction and mortality. In COPD, the correlation between the severity of airflow obstruction in terms of $\%FEV_1$ predicted and mortality is weak, although the severity of airway obstruction is an independent risk factor related to mortality.[22] Mortality is associated with symptoms such as dyspnea and daily life activity, rather than airflow obstruction, in patients with COPD.[52,53] Fifth, our study demonstrated that current smoking was associated with prognosis. Heavy smoking may lead to fixed airflow obstruction. However, neither the smoking index nor change in smoking status was assessed during follow-up. Further studies are required to evaluate important risk factors affecting the prognosis, development, and severity of airflow obstruction.
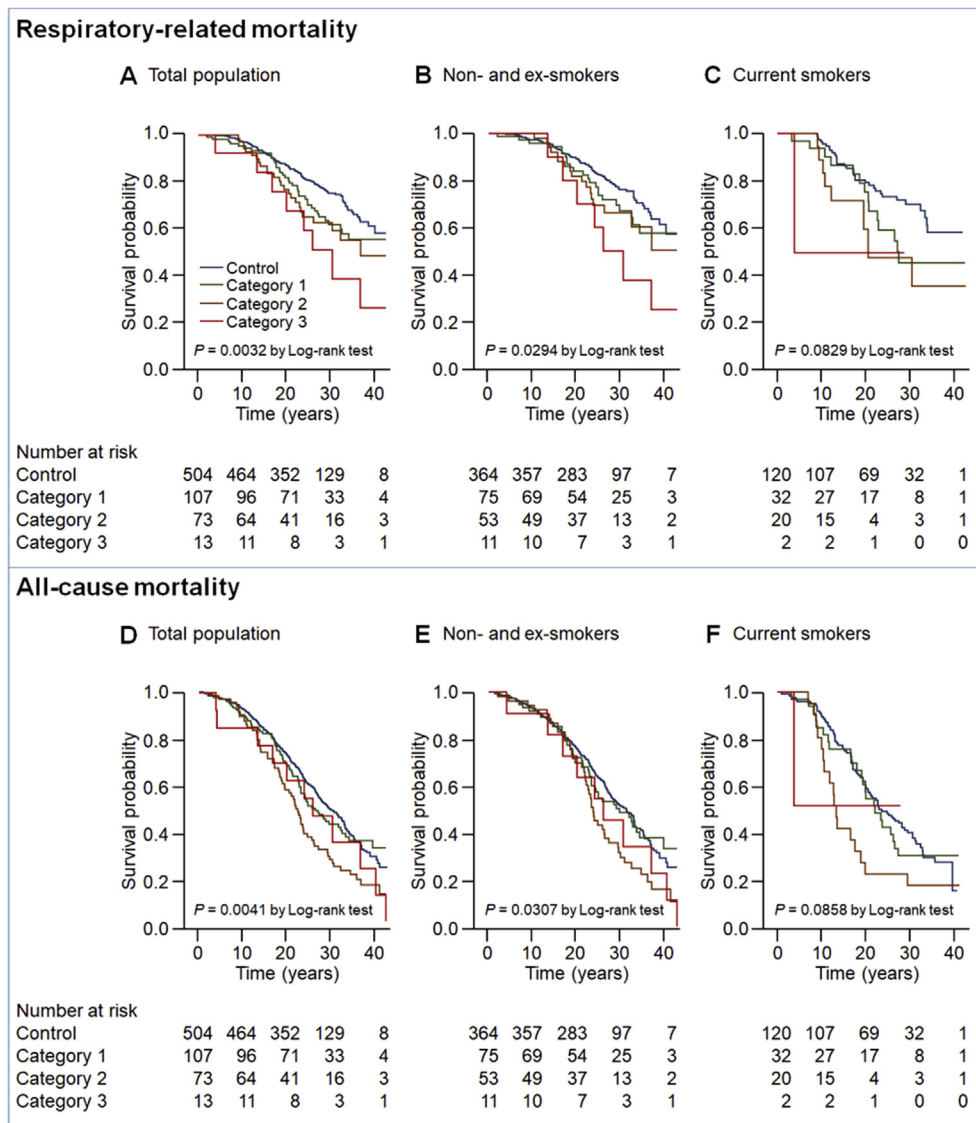
Fig. 4. Kaplan-Meier curve of survival probability for respiratory-related and all-cause mortality among three categories of airflow obstruction severity and control groups among the total population, non- and ex-smokers, and current smokers. Victims in the total population with a FEV_1/FVC ratio of >0.7 or $\%FEV_1$ predicted >80%, a FEV_1/FVC ratio of <0.7 and $\%FEV_1$ predicted >50% - ≤ 80%, a FEV_1/FVC ratio of <0.7 or $\%FEV_1$ predicted >30% - ≤ 50%, and a FEV_1/FVC ratio of <0.7 or $\%FEV_1$ predicted ≤30% are classified as controls (n = 504), category 1 (n = 107), category 2 (n = 73), and category 3 (n = 13), respectively. FEV_1, forced expiratory volume in 1 s; FVC, forced volume capacity.

In conclusion, we investigated long-term respiratory-related and all-cause mortality among patients with asthma with and without airflow obstruction. Individuals with airflow obstruction showed significantly higher long-term respiratory-related and all-cause mortality than those without airflow obstruction. Current smoking appeared to be associated with airflow obstruction and poor prognosis. Respiratory-related conditions, especially asthma attacks, were the main causes of mortality among victims with airflow obstruction. Smoking cessation and airflow obstruction intervention and prevention may help reduce respiratory-related and all-cause mortality among patients with asthma.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.alit.2019.04.009.

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