Ⅲ. 研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書籍名	出版社名	出版地	出版年	ページ
Ebisawa M	Chapter 9 Food-induced Anaphylaxis and Food Associated Exercise-induced Anaphylaxis	editorial supervisor: Drs. John M. James, Wesley Burks, and Philippe Eigenmann	Food Allergy: Expert Consult Basic	Elsevier		2011	113-127

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Satoshi Konno[1], Nobuyuki Hizawa[2], Yuma Fukutomi[3,4], Masami Taniguchi[3], Yukio Kawagishi[5], Chiharu Okada[6,7],]Yasushi Tanimoto[8], Kiyoshi Takahashi[6], Akira Akasawa[9], Kazuo Akiyama[3], Masaharu Nishimura[1]:	The prevalence of rhinitis and its association with smoking and obesity in a nationwide survey of Japanese adults	Allergy	in press		2012
Fukutomi Y*, Taniguchi M, Watanabe J, Nakamura H, Komase Y, Ohta K, Akasawa A, Nakagawa T, Miyamoto T, Akiyama K	Time Trend in the Prevalence of Adult Asthma in Japan: Findings from Population-Based Surveys in Fujieda City in 1985, 1999, and 2006.	Allergol Int.	60(4)	443-8	2011.
Fukutomi Y*, Taniguchi M, Tsuburai T, Tanimoto H, Oshikata C, Ono E, Sekiya K, Higashi N, Mori A, Hasegawa M, Nakamura H and Akiyama K	Obesity and aspirin intolerance are risk factors for difficult-to-treat asthma in Japanese non-atopic women. Clinical & Experimental	Allergy:	in press		2012
Fukutomi Y, Taniguchi M,	Association betweenBody Mass Index and Asthma among Japanese Adults:	Int Arch Allergy	157(3)	281-287	2011

Nakamura H, Konno S, Nishimura M, Kawagishi Y, Okada C, Tanimoto Y, Takahashi K, Akasawa A, Akiyama K.	Risk within the Normal Weight Range.	Immunol			
Okabe Y, Adachi Y, Itazawa T, Yoshida K, Ohya Y, Odajima H, Akasawa A, Miyawaki T.	Association between obesity and asthma in Japanese preschool children.	Pediatr Asthma Immunol	In press		2012
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Futamura M, Ohya Y, Akashi M, Adachi Y, Odajima H, Akiyama K, Akasawa A.	Age-related prevalence of allergic diseases in Tokyo schoolchildren.	Allergol Int	60	509-515	2011
大矢幸弘	アトピー性皮膚炎 Q&A 食物アレルギーが関与する割合はどのくらいですか	小児科診療	74 巻	112-114	2011
下条直樹 河野陽一	アトピー性皮膚炎の疫学	日本医師会雑誌	140	960—962	2011
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Urisu A, Ebisawa M, Mukoyama T, Morikawa A, Kondo N	Japanese guideline for food allergy	Allergol Int.	60	221-36	2011
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Akiyama H, Imai T, Ebisawa M	Japan food allergen labeling regulation-history and evaluation	Adv Food Nutr Res.	62	139-71	2011

Ⅳ. 研究成果の刊行物・別刷

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The prevalence of rhinitis and its association with smoking and obesity in a nationwide survey of Japanese adults

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asthma; rhinitis; smoking; BMI.

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Abstract

Background Rhinitis is a common disease, and its prevalence is increasing worldwide. Several studies have provided evidence of a strong association between asthma and rhinitis. Although smoking and obesity have been extensively analyzed as risk factors of asthma, associations with rhinitis are less clear.
Objective The aims of our study were (i) to evaluate the prevalence of rhinitis using the European Community Respiratory Health Survey (ECRHS) questionnaire in Japanese adults and (ii) to evaluate the associations of smoking and body mass index (BMI) with rhinitis.
Methods Following our study conducted in 2006–2007 to determine the prevalence of asthma using the ECRHS questionnaire, our present analysis evaluates the prevalence of rhinitis and its association with smoking and BMI in Japanese adults 20–79 years of age (N = 22819). We classified the subjects (20–44 or 45–79 years) into four groups as having (i) neither rhinitis nor asthma; (ii) rhinitis without asthma; (iii) asthma without rhinitis; or (iv) rhinitis with asthma. We then evaluated associations with smoking and BMI in each group.
Results The overall age-adjusted prevalence of rhinitis was 35.1% in men and 39.3% in women. A higher prevalence was observed in the younger population than in the older population. Active smoking and obesity were positively associated with asthma without rhinitis. In contrast, particularly in the 20- to 44-year age-group, active smoking and obesity were negatively associated with rhinitis without asthma.
Conclusion The results of the present study suggest that smoking and obesity may have different effects on the development of rhinitis and asthma.

Rhinitis, particularly allergic rhinitis, is one of the most common respiratory disorders. Although rhinitis is not a life-threatening condition, it has a huge socioeconomic impact, as it affects people at the ages normally associated with active employment or attending school. Accordingly, epidemiologic studies for evaluating the prevalence of rhinitis and associated factors are required.

Several epidemiologic studies of the general population have provided evidence of a strong association between asthma and rhinitis (1–3). Practice guidelines for asthma care reinforce the importance of identifying and treating rhinitis in patients with asthma (4,5). Although it was initially believed that a common atopic background accounts for the increased risk of patients with rhinitis developing asthma,

recent studies have demonstrated that rhinitis is also a risk factor for asthma in nonatopic patients (2). These results suggest that rhinitis and asthma could be manifestations of the same disease, irrespective of atopic status, and that they represent a continuum, sharing common pathologic and physiologic characteristics. This phenomenon has been labeled 'one airway one disease' or 'united airways disease'.

Conversely, there also exist major differences between the upper and lower airways (6,7). Important differences between pulmonary and nasal responses include the residence time of inflammatory cells, chemical mediators, and the mechanisms regulating repair of the epithelium following an inflammatory event. Bronchi are characterized by the presence of smooth muscle, which is responsible for bronchoconstriction. The remodeling of the airways is less extensive in the nose than in the bronchial wall.

Both genetic and environmental factors play important roles in the etiology of rhinitis and asthma. Among various environmental factors, smoking and obesity have been extensively analyzed as risk factors of asthma (8–13). There is accumulating evidence that exposure to environmental tobacco smoke is associated with the development of asthma in children (8,9). Several studies have also suggested that active smoking is associated with the development of asthma in adults (10, 11). However, the association of rhinitis with smoking and obesity is less clear. Of note, recent studies have shown an inverse association of rhinitis with smoking and obesity (3,14,15).

In the present analysis, following our study conducted in 2006–2007 for evaluation of the prevalence of asthma and its risk factors (16,17), we evaluated the prevalence of rhinitis using the European Community Respiratory Health Survey (ECRHS) questionnaire, which has been used in several studies for the nationwide analysis of the prevalence of rhinitis (18–22). In addition, we evaluated the association of smoking and body mass index (BMI) with rhinitis, considering the coexistence of rhinitis and asthma. This study was approved by the Ethics Committee of Sagamihara National Hospital and Hokkaido University.

Methods

Study design and questionnaire

A population-based, cross-sectional study was conducted with Japanese subjects 20–79 years of age, living in ten different areas of Japan. Detailed methods for selecting areas, participants, questionnaire distribution, and response rates in each area were described in our previous reports (16,17). We classified subjects as having rhinitis if they responded affirmatively to the question, 'Do you have any nasal allergies including hay fever?' We classified subjects as having a wheeze if they responded affirmatively to the question, 'Have you had wheezing or whistling in your chest at any time in the last 12 months?' This question is used worldwide for the evaluation of the prevalence of asthma for subjects aged 20–44 years (23–26). We also classified patients as having asthma if they met following two criteria (17,25): (i) an affirmative response to the question, 'Have you ever had asthma?' followed by 'Was this confirmed by a doctor?' and (ii) having at least one asthma-related symptom in the last 12 months. A subject was considered to have asthma-related symptoms if he or she answered in the affirmative to at least one of the following four questions: (i) 'Have you had wheezing or whistling in your chest at any time in the last 12 months?', (ii) 'Have you woken up with a feeling of tightness in your chest at any time in the last 12 months?', (iii) 'Have you been woken up by an attack of shortness of breath at any time in the last 12 months?', and (iv) 'Have you been woken up by an attack of coughing at any time in the last 12 months?' We classified subjects according to their smoking habits as 'active smokers' if they were current smokers and had smoked at least one cigarette per day or one cigar a week for the past year, or 'past smokers' if they had smoked for at least 1 year (as defined above) but not during the last month. All other subjects were considered nonsmokers. Body mass index was categorized into four groups: <18.50, 18.50–24.99, 25.00–29.99, and ≥30.00 kg/m^2. This study was conducted from July to October 2006, except in Mitake Town, Gifu, where the study was conducted from January to February 2007.

Statistical analysis

A total of 22819 subjects who responded to all questions regarding gender, age, the presence of wheeze, asthma, and rhinitis, smoking habit, height, and body weight were analyzed. Statistical analyses were performed using the statistical software package SYSTAT for Windows, version 11 (SYSTAT, San Jose, CA, USA). Fisher's exact tests were carried out to assess the differences in prevalence between men and women. Univariate and multivariate logistic regression models were used to calculate adjusted odds ratios (OR) and 95% confidence intervals (CI). To assess the differences in prevalence between areas, the prevalence in each area was adjusted to a standard population with an equal distribution by age using age-groups 20–29, 30–39, 40–49, 50–59, 60–69, and 70–79 for men and women separately. Age-specific prevalence of rhinitis with 95% CI was also calculated to explore the effects of age. For all statistical analyses, a P value <0.05 was considered significant.

Results

Table 1 shows the age-standardized prevalence of rhinitis in ten areas, and Table 2 shows the prevalence of rhinitis by age and gender in all subjects. The overall age-adjusted prevalence of rhinitis was 35.1% (95%CI, 34.2–35.9) for men and 39.3% (38.4–40.2) for women. A gradual decrease in the prevalence of rhinitis in subjects >20 years of age in men and in subjects >50 years of age in women was observed (Table 2). The prevalence was lowest in Kamishihoro Town, Hokkaido, probably due to reduced levels of cedar pollen in Hokkaido (the north island of Japan), which is a major cause of pollinosis in Japan (Table 1). In the age-groups 30–39, 40–49, 50–59, and 60–69, the prevalence of rhinitis was significantly higher among women than among men (Table 2). To adjust for the effect of gender differences in smoking

Table 1 Age-standardized prevalence of rhinitis per area

Study area	Number of responders (*n*)	Prevalence of rhinitis (%)			
		Men (*N* = 11132)		Women (*N* = 11687)	
		No adjustment	Age-adjusted*	No adjustment	Age-adjusted *
Kamishihoro Town, Hokkaido	3016	17.7 (15.8–19.6)	18.8 (16.8–20.8)	23.1 (21.0–25.2)	24.0 (21.8–26.1)
Fuchu Town, Toyama	2814	30.0 (27.6–32.4)	29.1 (26.7–31.5)	29.0 (26.6–31.4)	28.7 (26.4–31.1)
Setagaya Ward, Tokyo	1774	48.9 (45.6–52.2)	47.3 (44.0–50.6)	49.3 (46.0–52.6)	48.3 (45.0–51.5)
Sagamihara City, Kanagawa	3523	43.3 (41.0–45.6)	44.3 (42.0–46.6)	50.3 (48.0–52.6)	50.4 (48.0–52.7)
Fujieda City, Shizuoka	2534	38.1 (40.8–45.4)	38.3 (35.6–41.0)	46.8 (44.1–49.5)	46.4 (43.7–49.1)
Mitake Town, Gifu	1490	40.7 (37.1–44.3)	40.0 (36.5–43.5)	43.7 (40.2–47.2)	41.5 (38.0–45.0)
Nagakute Town, Aichi	1232	41.7 (37.6–45.8)	41.3 (37.3–45.4)	47.4 (43.6–51.2)	44.9 (41.1–48.6)
Akiohta Town, Hiroshima	1959	31.2 (28.2–34.2)	32.6 (29.6–35.6)	34.0 (31.1–36.9)	40.2 (37.2–43.2)
Kurashiki Town, Okayama	2259	33.0 (30.2–35.8)	32.9 (30.1–35.7)	37.9 (35.1–40.7)	37.8 (35.0–40.6)
Nangoku City, Kochi	2218	31.2 (28.4–34.0)	31.0 (28.3–33.8)	34.0 (31.3–36.7)	34.7 (32.0–37.5)

Data are presented as percentage with 95% confidence interval in parentheses.
*Prevalence was adjusted to a standard population by age and gender, using the age-groups 20–29, 30–39, 40–49, 50–59, 60–69, and 70–79 years.

Table 2 Prevalence of rhinitis by gender and age

Age (years)	Prevalence of rhinitis (%)		
	Men	Women	*P*-value
All subjects (*N* = 22819)			
20–29	48.2 (45.7–50.7)	47.8 (45.2–50.4)	0.83
30–39	45.2 (42.9–47.4)	49.7 (47.5–51.9)	0.0050
40–49	40.9 (38.6–43.2)	50.0 (47.8–52.2)	<0.001
50–59	32.9 (31.0–34.9)	38.7 (36.8–40.6)	<0.001
60–69	25.2 (23.4–27.1)	29.6 (27.7–31.4)	0.0015
70–79	18.0 (16.1–19.9)	20.1 (18.2–22.0)	0.13
Nonsmokers (*N* = 13610)			
20–29	49.5 (45.9–53.1)	48.2 (45.2–51.2)	0.60
30–39	49.6 (45.6–53.6)	50.0 (47.5–52.6)	0.85
40–49	49.7 (45.4–54.0)	50.1 (47.6–52.6)	0.87
50–59	40.6 (36.8–44.3)	39.1 (37.0–41.1)	0.50
60–69	27.1 (23.9–30.3)	29.7 (27.7–31.7)	0.19
70–79	17.5 (14.5–20.5)	20.0 (18.0–22.0)	0.19

Data are presented as percentage with 95% confidence interval in parentheses.

Table 3 Association of rhinitis and the presence of wheeze or asthma*

	Rhinitis and wheeze		Rhinitis and asthma	
	OR	95%CI	OR	95%CI
20–44 years				
All subjects (*N*=8563)	2.29	1.96–2.67	2.90	2.38–3.55
Nonsmokers (*N*=4892)	2.74	2.16–3.47	3.14	2.34–4.20
45–79 years				
All subjects (*N*=14256)	2.05	1.83–2.29	3.36	3.04–4.37
Nonsmokers (*N*=8718)	2.50	2.14–2.92	4.43	3.48–5.62

The definition of 'wheeze' and 'asthma' is described in Methods.
*Odds ratios (OR) and 95% confidence intervals were calculated for the association of rhinitis with wheeze or asthma.
$P < 0.001$ for all analyses.

prevalence on prevalence of rhinitis (16), the prevalence of rhinitis was calculated after limiting the subjects to nonsmokers ($N = 13610$). The prevalence of rhinitis among nonsmokers was not significantly different between genders in all age-groups (Table 2).

As rhinitis and asthma have been reported to coexist (1–3), associations between rhinitis and the presence of wheeze/asthma were analyzed in this population of survey respondents. Positive associations between rhinitis and wheeze/asthma were shown among all respondents 20–44 years of age ($P < 0.001$) and 45–79 years of age ($P < 0.001$) (Table 3). A similar association was also observed in nonsmokers ($P < 0.001$) (Table 3).

Because significant coexistence of rhinitis and wheeze/asthma was observed, we classified all subjects into four groups and evaluated the pure association of rhinitis with smoking and obesity: (i) none of the conditions [Rhinitis(−) Wheeze(−); $N = 13267$], [Rhinitis(−) Asthma(−); $N = 14025$]; (ii) rhinitis without wheeze/asthma [Rhinitis(+) Wheeze(−); $N = 7263$], [Rhinitis(+) Asthma(−); $N = 7767$]; (iii) wheeze/asthma without rhinitis [Rhinitis(−) Wheeze(+); $N = 1126$], [Rhinitis(−) Asthma(+); $N = 368$]; (iv) rhinitis with wheeze/asthma [Rhinitis(+) Wheeze(+); $N = 1163$], [Rhinitis(+) Asthma(+); $N = 659$]. Table 4 shows the characteristics of the subjects in each group.

Tables 5, and 6, Tables S1 and S2 show the results of the multivariate logistic regression analysis for the association of smoking status and BMI using the outcome variables 'rhinitis without wheeze/asthma', 'wheeze/asthma without rhinitis', and 'rhinitis and wheeze/asthma' in the 20–44-year (Table 5, Table S1) and 45–79-year (Table 6, Table S2) age-groups. Active smoking was positively associated with wheeze

Table 4 Characteristics of subjects in the eight groups

	Rhinitis (−) Wheeze (−)	Rhinitis (+) Wheeze (−)	Rhinitis (−) Wheeze (+)	Rhinitis (+) Wheeze (+)	Rhinitis (−) Asthma (−)	Rhinitis (+) Asthma (−)	Rhinitis (−) Asthma (+)	Rhinitis (+) Asthma (+)
Number	13267	7263	1126	1163	14026	7767	368	659
Age (years) (median, range)	55 (20–79)	45 (20–79)	59 (20–79)	47 (20–79)	56 (20–79)	46 (20–79)	53 (20–79)	43 (20–79)
Men/women	6584/6683	3312/3951	682/444	554/609	7075/6951	3582/4185	191/177	284/375
Smoking status (*n*)								
Nonsmokers	7896	4614	473	627	8194	4854	176	387
Past smokers	1797	1061	219	198	1939	1142	77	117
Current smokers	3574	1588	433	338	3893	1771	115	155
BMI (kg/m^2)(*n*)								
<18.50	1045	622	95	91	1108	649	33	64
18.50–24.99	9420	5371	708	746	9892	5598	236	419
25.00–29.99	2469	1113	269	270	2659	1247	79	136
≥30.00	333	157	54	56	367	173	20	40

BMI, body mass index.
The definition of 'wheeze' and 'asthma' is described in Methods.

Table 5 Association of smoking status or BMI with the presence of rhinitis and/or asthma (20–44 years)

	Rhinitis (+) Wheeze(−)		Rhinitis (−) Wheeze(+)		Rhinitis (+) Wheeze(+)		Rhinitis (+) Asthma(−)		Rhinitis (−) Asthma(+)		Rhinitis (+) Asthma(+)	
	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
All subjects (*N* = 8563)												
Sex												
Male	1	Reference	1	Reference	1	Reference	1	Reference	1	Reference	1	Reference
Female	1.00	0.90–1.11	1.07	0.80–1.43	1.36**	1.09–1.68	1.01	0.91–1.12	1.30	0.88–1.93	1.57**	1.21–2.04
Smoking status												
Nonsmokers	1	Reference	1	Reference	1	Reference	1	Reference	1	Reference	1	Reference
Past smokers	1.24*	1.05–1.47	2.02**	1.30–3.16	1.92***	1.42–2.60	1.22*	1.04–1.44	1.78	1.00–3.19	2.02***	1.42–2.86
Current smokers	0.78***	0.69–0.87	2.36***	1.75–3.18	1.41*	1.12–1.77	0.78***	0.70–0.87	1.78**	1.19–2.67	1.24	0.94–1.64
BMI												
<18.50	0.92	0.80–1.07	0.92	0.60–1.42	0.72	0.52–1.01	0.90	0.78–1.04	0.74	0.40–1.38	0.81	0.55–1.18
18.50–24.99	1	Reference	1	Reference	1	Reference	1	Reference	1	Reference	1	Reference
25.00–29.99	0.80**	0.69–0.93	1.07	0.74–1.56	1.38*	1.06–1.81	0.83*	0.72–0.96	1.05	0.63–1.76	1.31	0.94–1.82
≥30.00	0.77	0.58–1.02	2.40***	1.43–4.02	1.85**	1.20–2.87	0.74*	0.56–0.97	2.01	0.98–4.10	2.40***	1.50–3.83
Nonsmokers (*N* = 4892)												
Sex												
Male	1	Reference	1	Reference	1	Reference	1	Reference	1	Reference	1	Reference
Female	0.92	0.80–1.06	0.72	0.46–1.12	1.06	0.78–1.43	0.92	0.80–1.05	0.88	0.50–1.57	1.44	1.00–2.09
BMI												
<18.50	0.86	0.71–1.03	1.25	0.70–2.26	0.53*	0.33–0.86	0.83*	0.70–1.00	0.73	0.30–1.75	0.53*	0.30–0.93
18.50–24.99	1	Reference	1	Reference	1	Reference	1	Reference	1	Reference	1	Reference
25.00–29.99	0.77*	0.63–0.95	1.47	0.82–2.63	1.31	0.88–1.94	0.79*	0.65–0.97	1.46	0.70–3.03	1.21	0.75–1.96
≥30.00	0.56**	0.38–0.83	1.93	0.80–4.68	1.66	0.89–3.10	0.58**	0.39–0.85	1.94	0.66–5.70	1.93	0.95–3.91

BMI, body mass index.
OR and 95% CI for rhinitis, wheeze(asthma), and comorbidity using none of the conditions as reference group.
Data are adjusted by age, sex, smoking status, BMI, pet ownership, and center.
*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$.

without rhinitis in both age-groups (20–44 years: OR = 2.36, $P < 0.001$; 45–79 years: OR = 2.12, $P < 0.001$). In contrast, being an active smoker was negatively associated with rhinitis without wheeze (20–44 years: OR = 0.78, $P < 0.001$; 45–79 years: OR = 0.57, $P < 0.001$). Being overweight (BMI, 25.00–29.99) or obese (BMI ≥ 30.00) was positively associated with

Table 6 Association of smoking status or BMI with the presence of rhinitis and/or asthma (45–79 years)

	Rhinitis (+) Wheeze(−)		Rhinitis (−) Wheeze(+)		Rhinitis (+) Wheeze(+)		Rhinitis (+) Asthma(−)		Rhinitis (−) Asthma(+)		Rhinitis (+) Asthma(+)	
	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
All subjects (N = 14256)												
Sex												
Male	1	Reference	1	Reference	1	Reference	1	Reference	1	Reference	1	Reference
Female	1.14*	1.03–1.27	0.90	0.75–1.09	1.33**	1.08–1.65	1.17**	1.05–1.28	1.23	0.87–1.74	1.44*	1.07–1.94
Smoking status												
Nonsmokers	1	Reference	1	Reference	1	Reference	1	Reference	1	Reference	1	Reference
Past smokers	1.14*	1.01–1.30	1.80***	1.44–2.25	1.53**	1.19–1.98	1.15*	1.02–1.30	2.30***	1.55–3.40	1.42	1.00–2.02
Current smokers	0.57***	0.50–0.64	2.12***	1.73–2.61	1.12	0.88–1.43	0.60***	0.53–0.67	1.38	0.92–2.06	0.54**	0.36–0.81
BMI												
<18.50	0.82*	0.69–1.00	1.50**	1.13–1.99	1.23	0.88–1.72	0.80*	0.67–0.95	1.70*	1.05–2.76	1.75**	1.16–2.63
18.50–24.99	1	Reference	1	Reference	1	Reference	1	Reference	1	Reference	1	Reference
25.00–29.99	0.97	0.87–1.07	1.53***	1.29–1.83	1.54***	1.26–1.87	0.98	0.89–1.09	1.44*	1.04–1.99	1.38*	1.04–1.84
≥30.00	0.99	0.74–1.35	2.32***	1.54–3.58	2.46***	1.58–3.81	1.02	0.77–1.35	2.31*	1.15–4.64	2.55**	1.42–4.60
Nonsmokers (N = 8718)												
Sex												
Male	1	Reference	1	Reference	1	Reference	1	Reference	1	Reference	1	Reference
Female	1.00	0.89–1.13	0.69**	0.55–0.88	1.25	0.95–1.64	1.04	0.92–1.17	1.11	0.70–1.75	1.28	0.89–1.83
BMI												
<18.50	0.91	0.73–1.13	1.72*	1.14–2.60	1.29	0.83–2.00	0.89	0.72–1.10	1.40	0.66–2.96	1.50	0.89–2.55
18.50–24.99	1	Reference	1	Reference	1	Reference	1	Reference	1	Reference	1	Reference
25.00–29.99	0.89	0.78–1.03	1.67***	1.29–2.16	1.48**	1.14–1.93	0.91	0.80–1.04	1.77*	1.14–2.75	1.34	0.94–1.91
≥30.00	0.88	0.59–1.30	3.01***	1.78–5.09	2.73***	1.60–4.68	0.89	0.62–1.28	1.98	0.71–5.56	2.65**	1.34–5.22

BMI, body mass index.
OR and 95% CI for rhinitis, wheeze(asthma), and comorbidity using none of the conditions as reference group.
Data are adjusted by age, sex, smoking status, BMI, pet ownership, and center.
*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$.

wheeze without rhinitis (obesity: OR = 2.40, $P < 0.001$), but negatively associated with rhinitis without wheeze (overweight: OR = 0.80, $P = 0.0028$) in the 20–44-year age-group. When the same analysis was performed after limiting subjects to lifetime nonsmokers, a similar association of high BMI and rhinitis without wheeze (overweight: OR = 0.77, $P = 0.015$; obesity: OR = 0.56, $P = 0.0043$) was observed. When asthma was used instead of wheeze, similar results were obtained regarding the positive association between smoking and asthma without rhinitis, and the negative association between obesity and rhinitis without asthma in subjects 20–44 years of age (Table 5, Table S1).

Discussion

Consistent with the results from a number of earlier studies (1–3), a strong association between rhinitis and the presence of wheeze/asthma was observed in this study, supporting the hypothesis that rhinitis and asthma represent a continuum of the same disease. Of note, significant association between two conditions was observed even in elderly subjects (45–79 years). Although it was initially believed that a common atopic background accounts for the increased risk of asthma development in patients with rhinitis, recent studies have demonstrated that rhinitis is also a risk factor for asthma in nonatopic patients (2). Moreover, recent studies report a higher prevalence of sinonasal symptoms even in chronic obstructive pulmonary disease (COPD) (27–29). Collectively, the co-occurrence of rhinitis and the presence of wheeze/asthma observed both in younger (20–44 years) and older (45–79 years) adults in this study could be explained not only by the underlying common allergic components of rhinitis and asthma, but also by the common pathogenesis of upper and lower airway inflammation unrelated to atopy and allergy.

Although this study revealed the coexistence of rhinitis and wheeze/asthma, their association with the potential risk factors of active smoking and obesity opposed one another. In contrast to the results from several studies showing positive association between smoking and asthma (10, 11), the present study demonstrates that active smoking has a negative correlation with rhinitis. Consistent with our results, the protective effect of smoking on the development of cedar allergy has been reported in the Japanese population (14). Tobacco smoke has been shown to suppress human

immunity, including inhibition of cytokine production and T-cell responsiveness (30,31). Accordingly, the immunosuppressive effect of smoking might result in the low prevalence of rhinitis in active smokers.

Several *in vivo* studies have shown that short-term smoking or administration of nicotine attenuated allergic airway inflammation in mice (32,33), whereas smoking enhanced airway hyperresponsiveness in other reports (34,35). Botelho et al. have recently shown that smoking attenuated eosinophilic airway inflammation, while enhancing airway remodeling in a house dust mite (HDM)-induced asthma model in mice (35). Taken together, factors other than allergic responses, such as the induction of airway hyperreactivity or remodeling, which could directly influence the airways, might account for the effect of smoking on asthma.

In the present study, the presence of rhinitis was higher among women than in men in all subjects. However, when subjects were limited to lifetime nonsmokers, no significant difference was observed between genders (Table 2), suggesting that the higher prevalence of rhinitis among women in all subjects was influenced by the lower smoking rate among women. Therefore, when the prevalence of rhinitis is evaluated in epidemiologic surveys, smoking status needs to be considered.

Another interesting and unexpected finding of this study is that obesity had a negative association with rhinitis in subjects 20–44 years of age. Although the association between obesity and asthma has been gaining more attention, few studies have been conducted concerning the relationship between obesity and other allergic diseases. Of note, a recent large survey of school children in Japan showed that the obesity was negatively associated with the prevalence of rhinitis (15), which is consistent with our results. A recent report by Johnston et al. (36) showed enhanced airway responsiveness with attenuation of airway inflammation in obese mice. These results may support our findings of opposing effects of obesity on asthma and rhinitis, similar to the opposite effects of smoking on both disease conditions.

Several previous reports have shown results contradicting those in our study regarding the association between smoking status/obesity and rhinitis (37–39). The exact reasons for this inconsistency are unclear; however, unlike the current study, most previous studies did not consider the coexistence of rhinitis and asthma. One previous study that did consider the coexistence of rhinitis and asthma was conducted in Italy using the ECRHS questionnaire and, similar to our study, found a negative association between active smoking and rhinitis (3). Thus, consideration of the co-occurrence of asthma and rhinitis might have contributed to revealing the interesting negative association between rhinitis and active smoking/obesity in the current study.

A number of limitations to this study exist, as previously described (16, 17). The cross-sectional nature of the study precludes establishing temporal relationships or inferring causality. Thus, the possibility that subjects with rhinitis might be less likely to smoke or tend not to exercise resulting in obesity could be another explanation for the negative association between rhinitis and active smoking/obesity. The number of risk factors was limited, and we did not consider the possible contributions of other relevant variables, such as economic status, occupation, and passive smoking. Questions regarding the presence of nasal allergies in the ECRHS questionnaire are ambiguous, as some patients with nonallergic rhinitis might respond affirmatively, and this question cannot distinguish between seasonal and perennial rhinitis. In addition, subjects who previously had, but do not currently have, rhinitis symptoms might also have been included in the rhinitis group. Furthermore, as the reliability of the ECRHS questionnaire with subjects >45 years of age has not been widely evaluated, the associations between rhinitis and active smoking/obesity among older subjects in this study need to be cautiously interpreted. To confirm our results, further studies are needed using a prospective design with precise definitions of asthma and rhinitis, particularly for older subjects, and more confounding factors need to be considered for their possible associations with asthma and rhinitis.

We wish to emphasize that our results are not meant to change policies regarding smoking and weight management. Because of the numerous possible adverse effects, smoking and obesity should not be considered therapeutic options. Our findings could provide clues to understanding the pathogenesis of rhinitis and for therapeutic strategies for protection against rhinitis. The results of this study also encourage a more intensive investigation into the relationship between smoking and rhinitis.

In conclusion, this cross-sectional study using the ECRHS questionnaire determined the prevalence of rhinitis in Japanese population. The results of the present study suggest that smoking and obesity may have different effects on the development of rhinitis and asthma.

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Author contributions

Masami Taniguchi, Kiyoshi Takahashi, Akira Akasawa, Kazuo Akiyama, and Masaharu Nishimura involved in the design of the protocol. Satoshi Konno and Nobuyuki Hizawa involved in the analysis and writing. The other authors participated in the design of the protocol and drafting of the paper.

Conflicts of interests

The authors declare no conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Association of smoking status or BMI with the presence of rhinitis and/or asthma (20-44 years).

Table S2. Association of smoking status or BMI with the presence of rhinitis and/or asthma (45-79 years).

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ORIGINAL ARTICLE

Time Trend in the Prevalence of Adult Asthma in Japan: Findings from Population-Based Surveys in Fujieda City in 1985, 1999, and 2006

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ABSTRACT

Background: The burden of asthma is recognized as an important public health problem worldwide. In most countries, the prevalence of asthma has been reported to increase in the last few decades. However, more recent epidemiological studies have shown that the prevalence of asthma has been flat or even decreasing after the 1990s in some developed countries. The recent time trend in the prevalence of adult asthma in Japan is unknown.

Methods: Population-based surveys were conducted three times in the same region, in 1985, 1999, and 2006, at Fujieda City, Shizuoka, Japan, and the results were reported previously. We compared the results of these surveys to reveal the time trend in the prevalence of adult asthma. Although the questionnaires used in these surveys were not exactly the same, the time trend was assessed by comparing the responses to relevant questions between questionnaires.

Results: The prevalences of wheeze following a common cold and dyspneal feeling at night increased significantly from 1985 to 1999 (4.2% to 7.6%, and 3.2% to 5.3%, respectively). The prevalences of lifetime asthma and current asthma also significantly increased from 1999 to 2006 (5.1% to 6.7%, and 1.5% to 3.4%, respectively).

Conclusions: The prevalences of asthma among adults in Fujieda City consistently increased from 1985 to 2006. There was no evidence that the prevalences were in plateau or decreasing. These findings suggest that more efforts are required to stop the increase in the burden of this disease in Japan.

KEY WORDS

adult, asthma prevalence, Japan, population-based study, time trend

ABBREVIATIONS

DALYs, disability-adjusted life years; ATS-DLD, American Thoracic Society-Division of Lung Disease; ECRHS, European Community Respiratory Health Survey; ISAAC, International Study of Asthma and Allergies in Childhood.

INTRODUCTION

Asthma is one of the most common chronic respiratory diseases, affecting an estimated 300 million people worldwide, and in most countries, the prevalence of asthma has been reported to increase in the last few decades.[1,2] Because of its high prevalence, the burden of this disease is internationally recognized as

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an important public health problem. Indeed, asthma was the 25th leading cause of disability-adjusted life years (DALYs) lost worldwide in 2001.[1] However, more recently, after the 1990s, a ceiling effect or decline in the prevalence of asthma has been reported in recent studies from some developed countries.[3-5] On the other hand, reports on the time trend in asthma prevalence in Japan have been limited and the recent trend in adult asthma in Japan is unknown. Knowing the prevalence and its time trend is important for health service planning.

Population-based surveys have been conducted on the adult population three times in the same region, in 1985, 1999, and 2006, at Fujieda City, Shizuoka, Japan, and the results were reported previously.[6-8] In the 1985 survey, the prevalence of asthma (defined as meeting original criteria used for the study) among adult residents aged 15 yrs or more was reported to be 3.15%.[6] That in the 1999 survey was reported to be 4.1%, which was significantly higher than that in the 1985 survey.[7] In 2006, a postal survey was also conducted as part of a nationwide asthma prevalence survey.[8]

To reveal the time trend in adult asthma prevalence in Japan, we compared the results of these surveys. In the first and second surveys, an original questionnaire and the Japanese version of the American Thoracic Society-Division of Lung Disease (ATS-DLD) questionnaires[9] were used. However, the third survey was performed using only the Japanese version of the European Community Respiratory Health Survey (ECRHS) questionnaire.[8,10] Because we could not compare the results directly due to the difference in the questionnaires used, we compared the responses to relevant questions between questionnaires.

METHODS

DESIGN

We compared the results of population-based surveys conducted three times in the same region, in 1985, 1999, and 2006 at Fujieda City, Shizuoka, Japan. Fujieda City is located in a suburban area near Shizuoka City, which is the seat of the prefectural government of Shizuoka Prefecture. Shizuoka Prefecture is located in central Japan. Details of the three surveys are described below. This study was approved by the Ethics Committee of Sagamihara National Hospital.

1985 SURVEY

The first survey was conducted in 1985 and is described elsewhere.[6] The population of Fujieda City in 1985 was 111,985. The target subjects of this study were the entire 12,562 residents aged 15 yrs or more living in 20 selected towns, which was about 10% of the entire city population. These 20 towns are spread throughout the city and were selected after considering the location and degree of urbanization or industrialization. The survey was performed door-to-door by the staff of residents' associations. The subjects were asked to participate in the survey and complete a self-administered original screening questionnaire on asthma symptoms and diagnosis (see Appendix). Subjects suspected of having asthma on the basis of the original screening questionnaire were then asked to answer a second questionnaire.

1999 SURVEY

A second survey was conducted in 1999 and is described elsewhere.[7] The target subjects of the second survey were restricted to the entire 4187 residents aged 15 yrs or more in 4 towns, Horinouchi, Yokouchi, Kariyado, and Tanumanaka, selected from the 20 towns studied in the first survey. Horiuchi was one of the rural towns with a low asthma prevalence in the 1985 survey, and Yokouchi was one of the urban towns with a high asthma prevalence. Kariyado was selected to represent the northern part of the city with an intermediate prevalence and Tanumanaka was selected to represent the southern part of the city with an intermediate prevalence. The survey was also performed door-to-door by the staff of residents' associations. The subjects were asked to complete both the same screening questionnaire used in the 1985 survey and the Japanese version of the ATS-DLD questionnaire.[9]

2006 SURVEY

The third survey, which was a postal survey, was conducted in 2006 as part of a nationwide survey on adult asthma prevalence using the Japanese version[8,10] of the ECRHS questionnaire[11,12] and is described elsewhere.[8] The target subjects of the third survey were the entire residents aged 20-79 yrs in the 4 towns that were studied in the 1999 survey. The subjects were asked to complete only the Japanese version of the ECRHS questionnaire.

PREVALENCES OF RESPIRATORY SYMPTOMS AND ASTHMA

The questions on asthma symptoms and diagnosis in the original screening questionnaire used in the 1985 and 1999 surveys are shown in the appendix and the responses to each question were compared directly. The questionnaire used in the 2006 survey was not the same as those used in the 1985 and 1999 surveys; therefore, we compared the responses to relevant questions between the questionnaires. Lifetime asthma in the 1999 survey was considered as an affirmative response to the question "Have you ever been diagnosed with asthma?" in the Japanese version of the ATS-DLD questionnaire, and that in the 2006 survey was considered as an affirmative response to the question "Q5 Have you ever had asthma?", followed by "Was this confirmed by a doctor" in the Japanese version of the ECRHS question-

Table 1 Studied subjects, methods, and questionnaires used in the three surveys

	1985 survey[6]	1999 survey[7]	2006 survey
Subjects	Entire residents aged ≥15 yrs in 20 towns	Entire residents aged ≥15 yrs in 4 towns	Entire residents aged 20-79 yrs in 4 towns
Method of survey	Door-to-door survey by residents' associations	Door-to-door survey by residents' associations	Postal survey
Target (n)	12562	4187	3935
Responders (n)	12152	3829	2710
Response rate	96.7%	91.5%	68.9%
Questionnaire	Original screening questionnaire + Secondary questionnaire	Original screening questionnaire + ATS-DLD questionnaire[9]	Japanese version of ECRHS questionnaire[8]

ATS-DLD, American Thoracic Society - Division of Lung Disease; ECRHS, European Community Respiratory Health Survey.

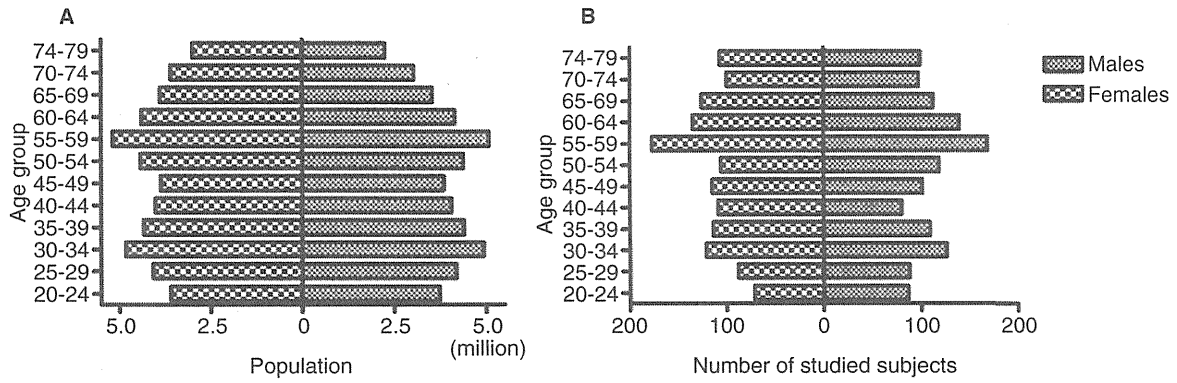

Fig. 1 Population distribution in entire of Japan (**A**) and that of subjects studied in the 2006 survey (**B**) according to age and gender.

naire.[8,10] Current asthma in the 1999 survey was defined as meeting the following two criteria: (1) an affirmative response to the question "Have you ever been diagnosed with asthma?" in the Japanese version of the ATS-DLD questionnaire and (2) affirmative responses to any of the questions about asthma symptoms in the recent 2 years. Current asthma in the 2006 survey was defined as meeting the following two criteria: (1) an affirmative response to the question "Q5 Have you ever had asthma", followed by "Was this confirmed by a doctor" in the Japanese version of the ECRHS questionnaire,[8] and (2) having at least one asthma-related symptom in the last 12 months, namely, an affirmative response to at least one of Q1-Q4 of the questionnaire. "Wheeze with breathlessness ever" in the 1999 survey was considered as an affirmative response to the question "Have you ever had an attack of wheezing that has made you feel short of breath?" in the Japanese version of the ATS-DLD questionnaire. "Wheeze with breathlessness in the last 12 months" in the 2006 survey was considered as an affirmative response to the question "Have you had wheezing or whistling in your chest at any time in the last 12 months?", followed by "Q1.1 Have you been at all breathless when the wheezing noise was present?" in the Japanese version of the ECRHS questionnaire.

ANALYSIS

Chi-square tests were carried out to assess the differences in the prevalences. The time trends of the prevalences were shown using a line chart with time in the x-axis and prevalence in the y-axis.

RESULTS

Differences in survey method, questionnaire used, and response rate are summarized in Table 1. The response rate in the 2006 postal survey was significantly lower than those in the 1985 and 1999 door-to-door surveys, because of the difference in the survey method ($p < 0.001$). Figure 1 shows the age distribution of the studied subjects in comparison with that of the entire Japanese population in 2006. Compared with the age distribution of the entire Japanese population, that of the studied subjects was slightly biased toward older individuals, reflecting that this city is located in a suburban area.

The prevalences of respiratory symptoms and asthma in the three surveys are shown in Table 2. The prevalence of patients with an affirmative response of "I have been diagnosed with asthma" in the original screening questionnaire significantly in-

Table 2 Prevalences of respiratory symptoms and asthma in each survey

	1985[6]	1999[7]	2006
Original screening questionnaire			
Wheezing following a common cold	4.2%	7.6%	ND
Dyspneal feeling at night	3.2%	5.3%	ND
Cough and wheezing during exercise	2.6%	6.8%	ND
Said to be asthmatic	3.5%	6.3%	ND
Diagnosed with asthma	2.1%	3.9%	ND
Respiratory symptoms in the Japanese version of the ATS-DLD questionnaire			
Wheeze with breathlessness ever	ND	4.4%	ND
Respiratory symptoms in the Japanese version of the ECRHS questionnaire			
Wheeze in the last 12 months	ND	ND	7.2%
Wheeze with breathlessness in the last 12 months	ND	ND	4.5%
Wheeze without a cold in the last 12 months	ND	ND	5.4%
Waking with tightness in the chest in the last 12 months	ND	ND	4.1%
Waking with an attack of shortness of breath in the last 12 months	ND	ND	2.4%
Waking with cough in the last 12 months	ND	ND	11.0%
Lifetime asthma	ND	5.1%	6.7%
Current asthma	ND	1.5% †	3.4% ‡

ATS-DLD, American Thoracic Society - Division of Lung Disease; ECRHS, European Community Respiratory Health Survey. ND, not determined.

† defined as having any asthma symptom in the last 2 years.

‡ defined as having any asthma symptom in the last 12 months.

creased from 1985 to 1999 (2.1% to 3.9%, $p < 0.001$). The prevalences of lifetime asthma and current asthma also increased significantly from 1999 to 2006 (5.1% to 6.7%, $p = 0.003$, and 1.5% to 3.4%, $p < 0.001$, respectively). The prevalences of subjects with affirmative responses to the questions on asthma symptoms in the original screening questionnaire were also increased from 1985 to 1999. The prevalence of wheeze and wheeze with breathlessness in the last 12 months in the 2006 survey was 7.2%, and 4.5%, respectively. However, they could not be compared with those in the 1999 survey because the 1999 survey did not have the same questions. The line chart of the prevalences shows a consistently increasing trend in the prevalences of asthma from 1985 to 2006 (see Fig. 2).

DISCUSSION

This study revealed an increasing trend in the prevalences of adult asthma and respiratory symptoms in Fujieda City, Shizuoka, Japan. This study is important in the sense that, although recent reports from some developed counties have shown a downward trend in asthma prevalence, our finding clearly indicates that an increasing trend still persists in this region. Even the ceiling effect was not observed. These data alert us to the possibility of further increase in the prevalence of asthma.

In terms of childhood asthma, there are controversial reports on the time trend in the prevalence in Japan. A study on elementary schoolchildren in Western Japan has shown that the prevalence of childhood asthma consistently increased from 1982 to 2002 by about two-fold.[13] However, more recently, a study in Fukuoka City has shown that the prevalence of childhood asthma did not change significantly from 1996 to 2006.[14] A population-based survey on schoolchildren in Kyoto has also shown a plateau with respect to the change in asthma prevalence from 1996 to 2006.[15] One possible reason for the discrepancy between these reports is considered to be the regional difference in the time trend. A worldwide variation in the time trend in the prevalence of childhood asthma has already been described from the comparison between phases I and III of the ISAAC (International Study of Asthma and Allergies in Childhood) study.[3] Therefore, we consider that there is a also domestic regional variation in the trend in the prevalence of childhood asthma.

In terms of adult asthma, the time trend in the prevalence is hardly reported in Japan. To the best of our knowledge, there is no other report that shows a recent time trend in the prevalence of adult asthma. Our observation was performed in one of the suburban cities in central Japan. Therefore, the time trend in the prevalence of adult asthma in other regions is unknown. However, we consider that Fujieda city is a good representative of general suburban cities in central Japan, because this city is characterized by being relatively average in terms of climate and degree of urbanization or industrialization. This city does not specialize in any specific type of industry or agriculture.

The major limitation of this study is that the survey method and questionnaire used were not exactly the same in the three surveys. In particular, in the 2006 survey, neither the original screening questionnaire nor the ATS-DLD questionnaire were used; thus, the responses to the same questions could not be directly compared. Therefore, we compared the responses to questions considered to have the same meaning in the ATS-DLD and ECRHS questionnaires. One more limitation is that age and gender standardizations could not be performed because the age distributions

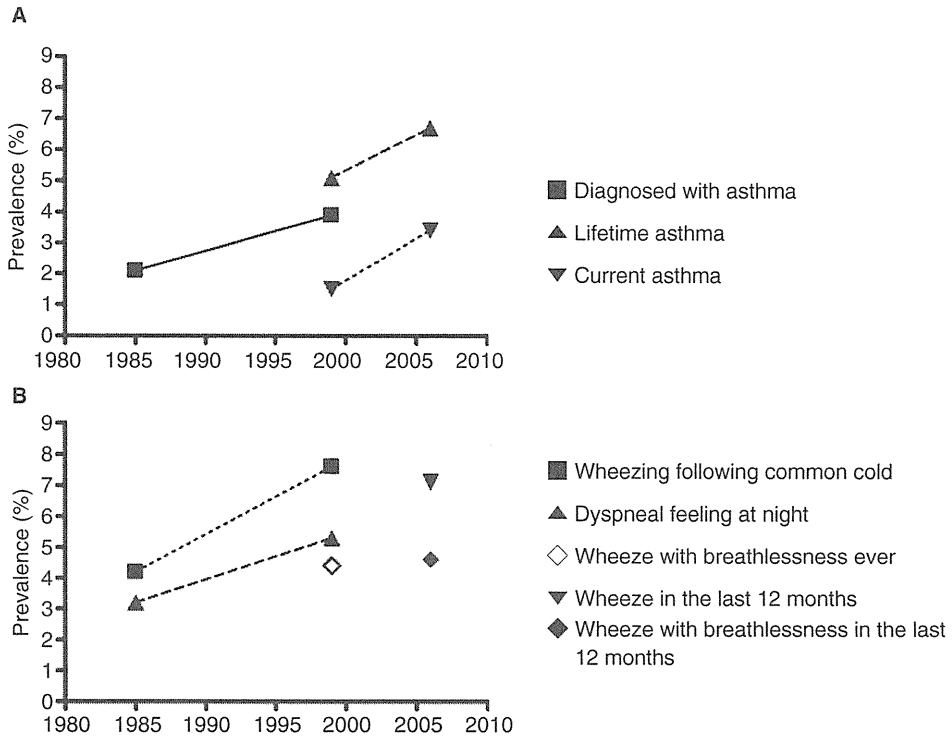

Fig. 2 Time trend in the prevalence of asthma (**A**) and respiratory symptoms (**B**) among adult residents in Fujieda City.

in the first and second surveys were obscure. However, no marked difference in asthma prevalence between age groups was observed in the 2006 survey (data not shown). We consider that the difference in the age distribution between the studies, if it exists, did not have a significant impact on the difference in the overall asthma prevalence.

In conclusion, our findings show that the prevalence of adult asthma and respiratory symptoms in Fujieda City consistently increased from 1985 to 2006. Although the time trend in the prevalence of adult asthma in other regions was not investigated, it is suspected that the prevalence of adult asthma in other regions also increased. These findings suggest that more attention should also be paid to the nationwide time trend in the prevalence of adult asthma in the next few decades. It is required to monitor the nationwide time trend in the future for better health service planning in Japan.

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CONFLICT OF INTEREST

No potential conflict of interest was disclosed.

APPENDIX

Selected items concerning asthma in the original screening questionnaire used in the 1985 and 1999 surveys.

5)-2 I suffer from wheezing following a common cold.
1. Yes 2. No

-3 I have had dyspneal feeling at night or early in the morning.
1. Yes 2. No

-4 I cough or wheeze during exercise.
1. Yes 2. No

-6 I have been said to be asthmatic.
1. Yes 2. No

-8 I have been diagnosed with asthma.
1. Yes 2. No

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ORIGINAL ARTICLE Asthma and Rhinitis

Obesity and aspirin intolerance are risk factors for difficult-to-treat asthma in Japanese non-atopic women

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Clinical & Experimental Allergy

Summary

Background Asthma is a clinical syndrome characterized by variabilities in disease expression and severity. The pathophysiological mechanism underlying anti-asthma treatment resistance is also assumed to be different between disease phenotypes.

Objective To elucidate the effect of gender and atopic phenotype on the relationship between clinical factors and the risk of treatment resistance.

Methods We compared outpatients with difficult-to-treat asthma (DTA; $n = 486$) in a tertiary hospital for allergic diseases in central Japan with those with controlled severe asthma ($n = 621$) with respect to clinical factors including body mass index (BMI) and aspirin intolerance using multivariate logistic regression analysis stratified by gender and atopic phenotype.

Results When analysis was performed on the entire study populations, obesity (BMI $\geq$ 30 kg/m^2; adjusted odds ratio (OR) 1.92; 95% confidence interval (95% CI: 1.07–3.43) and aspirin intolerance (OR: 2.56, 95% CI: 1.44–4.57) were found to be the significant risk factors for DTA. However, after the stratification by gender and atopic phenotype, the association between obesity and DTA was significant only in women (OR: 2.76, 95% CI: 1.31–5.78), but not in men (OR: 1.03, 95% CI: 0.38–2.81), and only in non-atopics (OR: 4.03, 95% CI: 1.15–14.08), but not in atopics (OR: 1.54, 95% CI: 0.79–3.02). The similar gender and phenotypic differences were also observed in the association between aspirin intolerance and DTA: namely, the association was significant only in women (OR: 3.96, 95% CI: 1.84–8.50), but not in men (OR: 1.19, 95% CI: 0.46–3.05); and only in non-atopics (OR: 5.49, 95% CI: 1.98–15.19), but not in atopics (OR: 1.39, 95% CI: 0.65–2.98).

Conclusions and Clinical Relevance Significant associations of obesity and aspirin intolerance with DTA were observed only in women and in non-atopics. These findings suggest that a phenotype-specific approach is needed to treat patients with DTA.

Keywords aspirin intolerance, asthma phenotype, difficult-to-treat asthma, gender difference, obesity

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Introduction

Although the majority of asthma patients can obtain good control of asthma, an important subgroup of patients remains symptomatic, despite high-dose treatment. This subgroup is called difficult-to-treat asthma (DTA) [1]. Although the prevalence of this subgroup is considered to be relatively low in the general asthma population, this subgroup is of high concern for healthcare providers, particularly in tertiary hospitals, because of the high risks of emergency department visit and hospital admission and high mortality. Patients with severe asthma are also known to account for a considerable portion of direct and indirect health care costs [2–4]. However, the mechanism and risk factors associated with DTA have not yet been established.

When we consider numerous epidemiological evidence of the association between an increased body mass index (BMI) and new onset of asthma [5–7], it has been hypothesized that obesity may also be associated

with severe asthma. However, studies on this association are limited, and there are conflicting reports on this association. The European Network For Understanding Mechanisms Of Severe Asthma (ENFUMOSA) has shown that BMI is associated with asthma severity in women, but not in men [8], whereas results of the Severe Asthma Research Program (SARP) study did not show a difference in BMI in relation to the degree of asthma severity [9]. Inconsistency in the association between BMI and DTA may result from the heterogeneity of the phenotypic presentation of severe asthma. Indeed, from the dataset of the SARP study, Moore et al. have reported that an unsupervised hierarchical cluster analysis identified five distinct clinical phenotypes of asthma, and the prevalence of obese patients is also different between these phenotypes [10]. Therefore, stratified analyses by asthma phenotype are required to establish the potential relationship between BMI and DTA. Furthermore, differences in the ethnic/genetic background among the studied populations may also be a cause of this inconsistency. However, studies on the association between obesity and asthma severity among Asian populations have been limited.

The aim of this study was to determine the phenotypic differences in risk factors associated with DTA in Japanese adult patients with severe persistent asthma. Atopy is a well-documented indicator of asthma phenotype. Therefore, we compared the risk factors for DTA in atopic patients with those in non-atopic patients. The gender difference in the risk factor was also examined in this study, because gender is one of the most important clinical/epidemiological parameters that determine disease expression and phenotype. A study in Japan may have the advantage of having a relatively homogenous ethnic/racial population; therefore, the association between risk factors and DTA can be determined without considering the ethnic/racial difference in the studied patients.

Methods

Subjects

We studied successive patients who visited Sagamihara National Hospital for the first time, one of the largest tertiary hospitals for allergic diseases located in central Japan, between 2000 and 2006. Their medical records were reviewed by their physician, 24 months after their first visit, and their demographical and clinical parameters, disease control and anti-asthma medication use were registered in an electronic database. Data of patients who (1) received care for asthma from the hospital for at least 24 months, (2) received asthma treatment at more than step 4 in the Global Initiative for Asthma (GINA) 2009 guideline (step 4 treatment in the GINA 2009 guideline is a medium or high dose of an inhaled glucocorticosteroid (ICS) with one or more controllers such as a long-acting beta agonist (LABA), a leukotriene receptor antagonist (LTRA) or theophylline), (3) showed good adherence to anti-asthma medication (determined from the pharmacy prescription records by their physicians), (4) did not have any comorbid cardiopulmonary disease (bronchiectasis, chronic bronchitis, old tuberculosis, interstitial pneumonitis, chronic eosinophilic pneumonia, Churg-Strauss syndrome or cardiac diseases), (5) did not have a smoking history greater than 30 pack-years and (6) were 75 years old or younger, were analysed in this study. Among the 3551 registered asthma patients, 1541 received asthma treatment at Step 4 or more. After the exclusion of 369 patients who did not meet the above criteria and 65 patients who had missing data on BMI, onset age, smoking status, atopic status or comorbidity [aspirin intolerance, allergic rhinitis (AR) and atopic dermatitis], 1107 patients were finally included in the analysis. This study was approved by the Ethics Committee of National Sagamihara Hospital, and all the patients provided written informed consent.

Definition of difficult-to-treat asthma

Patients with DTA were defined as those meeting any of the following two criteria: (1) having 'uncontrolled' asthma symptoms in the recent 4 weeks and (2) having one or more unscheduled visits/hospitalizations or rescue steroid bursts in the recent 12 months. Patients with 'uncontrolled' asthma symptoms were defined as those meeting any of the following: having daytime symptoms more than twice/week, having any limitation of activity, having any nocturnal symptoms/awaking or having used a reliever more than twice/week. Patients who did not meet any of these criteria were considered as having controlled asthma.

Potential risk factors and atopic phenotype

Body mass index, duration of asthma, smoking status, atopic phenotype, aspirin intolerance and comorbidity of AR, atopic dermatitis and sinusitis were considered as potential risk factors for DTA. Weight and height were measured by a medical technologist, and BMI was calculated. BMIs were categorized according to the World Health Organization classification [11]: underweight, <18.5 kg/m^2; normal range, 18.5–24.9 kg/m^2; overweight, 25.0–29.9 kg/m^2; obese, ≥ 30.0 kg/m^2. Aspirin intolerance was defined as being 'present' if a patient shows positive results in a provocation test or has an apparent history of severe exacerbation induced by the ingestion of non-steroidal anti-inflammatory drugs. The aspirin provocation test was performed as

previously reported [12]. In brief, doubling doses (25, 50, 100 and 200 mg equivalent to aspirin) of lysine aspirin were intravenously administered to patients in a stable condition. Provocation was stopped at appearance of a positive reaction. A positive reaction in the airways was defined as when the forced expiratory volume in 1 s fell 20% or more from the baseline. Considering the frequent overdiagnosis and underdiagnosis of aspirin intolerance, all the patients suspected of having aspirin-intolerant asthma in our hospital are advised to undergo the aspirin provocation test. Consequently, 32 of 61 patients with aspirin-intolerant asthma in this study were diagnosed on the basis of positive results of the provocation test. Patients with a suspicious history of aspirin intolerance, but not confirmed by the provocation test were classified as 'suspicious'. Patients who showed one or more positive results in a skin test or serum-specific IgE test for eight screened allergens, namely, mite, Japanese cedar pollen, grass pollen, ragweed pollen, cat dander, dog dander, alternaria and aspergillus, were considered as atopic. Others were considered as non-atopic.

Statistical analysis

Descriptive statistics were generated by comparing DTA and controlled asthma patients. Significance testing was performed using Chi-squared analysis for categorical variables and Student t-test or ANOVA for continuous variables. Descriptive statistics comparing BMI categories were also generated for each gender. Adjusted odds ratio (OR) with 95% confidence interval (95% CI) was estimated using multivariate logistic regression analysis with adjustment where necessary for potential confounding variables. The effects of gender and atopic phenotype on the relationship between risk factors and DTA were assessed using repeating multivariate logistic regression analysis after stratifying patients by gender and atopic phenotype. The statistical interactions of gender and atopic phenotype in the relationship between risk factors and DTA were analysed by including interaction terms in logistic regression analysis.

Results

Among 1107 patients studied, 486 were considered as having DTA, and 621 were considered as having controlled severe asthma. The characteristics of the patients are shown in Table 1. DTA patients were more likely than controlled severe asthma patients to be older, have aspirin intolerance and a longer duration of asthma, and be non-atopic. They were similar with respect to other demographical and clinical factors.

Multivariate logistic regression analysis was performed to identify risk factors associated with DTA.

Table 1. Characteristics of study patients

	Difficult-to-treat asthma (N = 486)	Controlled severe asthma (N = 621)	P-value
Age, mean ± SD (years)	52.6 ± 14.7	47.9 ± 15.0	<0.001
Gender, no. (%)			n.s.
Men	194 (40)	224 (36)	
Women	292 (60)	397 (64)	
Duration of asthma, mean ± SD, years	24.7 ± 15.5	19.6 ± 13.6	<0.001
Early-onset asthma (≤12 years), no. (%)	136 (28)	183 (30)	n.s.
Smoking status, no. (%)			
Non-smoker	264 (54)	354 (57)	n.s.
Past smoker	136 (28)	145 (23)	
Current smoker	86 (18)	122 (20)	
Smoking history (pack-years), no. (%)*			n.s.
0	264 (55)	354 (57)	
>0–<10	114 (24)	132 (21)	
≥10	103 (21)	132 (21)	
Body mass index (kgm^2), no. (%)			n.s.
<18.5	41 (8)	44 (7)	
18.5–24.9	324 (67)	429 (69)	
25.0–29.9	90 (19)	125 (20)	
≥30.0	31 (6)	23 (4)	
Atopic phenotype, no. (%)			0.014
Atopy	349 (72)	486 (78)	
Non-atopy	137 (28)	135 (22)	
Aspirin intolerance			<0.001
Absent	431 (89)	588 (95)	
Suspicious	14 (3)	14 (2)	
Present	41 (8)	19 (3)	
Comorbidity, no. (%)			
Allergic rhinitis	271 (56)	402 (65)	0.003
Atopic dermatitis	45 (9)	81 (13)	n.s.
Sinusitis	87 (18)	108 (17)	n.s.
Medication use			
Dose of ICSs, mean±SD, μg/day†	1377 ± 643	1197 ± 485	<0.001
LABA, no. (%)	329 (68)	419 (68)	n.s.
LTRA, no. (%)	170 (35)	199 (32)	n.s.
Theophylline, no. (%)	328 (68)	363 (59)	0.002
Maintenance OCS use (mg), no. (%)‡			
0	398 (82)	587 (95)	<0.001
1–5	63 (13)	27 (4)	
6–10	22 (5)	6 (1)	
≥11	3 (1)	1 (0)	
Uncontrolled asthma symptoms, no. (%)	305 (63)	0 (0)	<0.001
Frequency of unscheduled visits or hospitalization per year, no.			<0.001

(continued)

