1645 品目であり、一人あたりの食物品目数は 1.6 品目となった。その原因食物の内訳（複数回答）は果物が最も多く 247 例で、全体の 15.0%を占めた。以下貝類 211 例（12.8%）、甲殻類 204 例（12.4%）、魚類 157 例（9.5%）、乳・乳製品 121 例（7.4%）と続き、上記 5 品目で全体の 57.1%を占めたが、小児と比較して原因食物は多岐にわたっていた（図 1）。

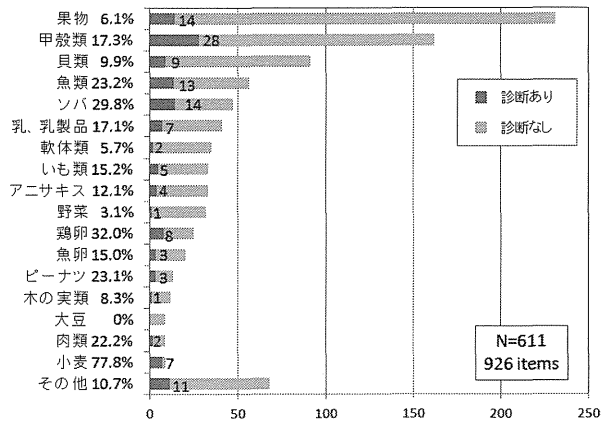
2. 現在、あなたがアレルギーのために食べないようにしている食物をすべてお選びください（医師の診断・指示の有無は問いません）。

現在、食べないようにしている食物があるとする回答は 611 名（13.1%）、男女比は 0.72、平均年齢 39.1 ±11.0 歳であった。食物品目数は 926 品目、一人あたりの品目数は 1.5 品目であった。その食物の内訳（複数回答）は、果物が 231 例（37.8%）、甲殻類 162 例（26.5%）、貝類 91 例（14.9%）、魚類 56 例（9.2%）、ソバ 47 例（7.7%）、牛乳、乳製品 41 例（6.7%）、軟体類 35 例（5.7%）、イモ類、アニサキスが各 33 例（5.4%）、野菜 32 例（5.2%）が上位 10 品目であった（図 2）。

2-1 これらの食品を食べないようにしている理由をお選びください。

“自己判断”が 726 例（78.4%）と圧倒的に多く、次いで“医師の診断・指示”が 132 例（14.3%）で、この 2 つの理由で全体の 92.7%を占めた。“医師の診断・指示”によって食べないようにしている食物があるものは 88 名（1.9%）で、アレルギーのために食べないようにしている食物がある回答者の 14.4%であった。“医師の診断・指示”によって食べないようにしている食物は、甲殻類 28 例が最も多く、次いでソバ、果物が 14 例、魚類 13 例、貝類 9 例と続いた（図 2）。除去理由のうち、“医師の診断・指示”によるものが多かった食物は小麦 77.8%（7/9）、鶏卵 32.0%（8/25）、ソバ 29.8%（14/47）であった。

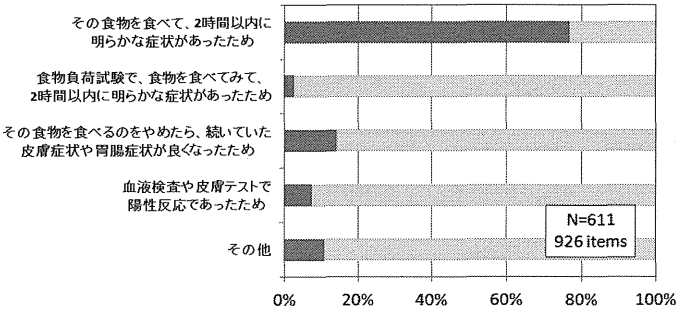
図2 現在、あなたがアレルギーのために食べないようにしている食物をすべてお選びください。（医師の診断ありの%）



2-2 これらの食物を食べないようにした方が良いと判断した理由は何ですか（複数回答）。

“即時型症状を認めた”が 712 例（76.9%）、“除去して改善した”が 131 例（14.1%）、“検査結果陽性”が 69 例（7.5%）、“負荷試験で即時症状を認めた”が 26 例（2.8%）、“その他”が 100 例（10.8%）であった（図 3）。

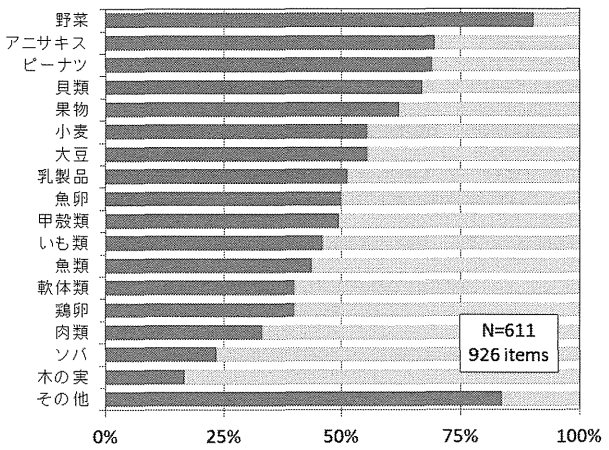
図3. 除去している食物を食べないようにした方が良いと判断した理由は何ですか。



2-3 これらの食物を食べないようにし始めた年齢をお答えください。

“10 歳未満”が 135 例（14.6%）、“10 代”が 270 例（29.2%）、“20 代”が 252 例（27.2%）、“30 代”が 165 例（17.8%）、“40 代”が 77 例（8.3%）、“50 代”は 27 例（2.9%）であった。食べないようにし始めた年齢が成人以降の割合が多かった食物は、野菜、アニサキス、ピーナツ、貝類、果物、小麦、大豆、乳製品、魚卵で、いずれも 50%以上を占めた（図 4）。

図4.食べないようにしている食物を食べないようにし始めた年齢をお答えください（20歳代以降の割合）。



3. 特定の食物を食べて 2 時間以内に症状があった回答者への追加質問

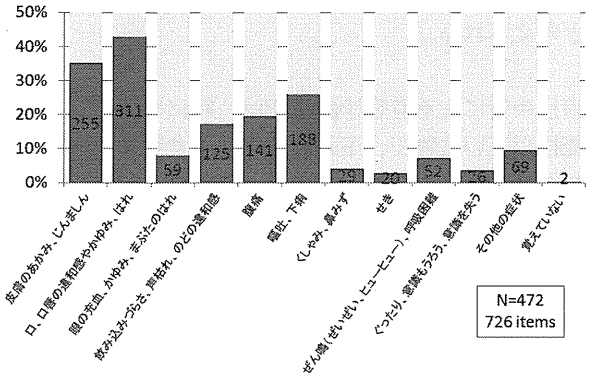
食べてから 2 時間以内に症状を認めたのは 472 名（10.1%）、726 品目で、一人あたりの品目数は 1.5 品目であった。エビ 72 例、カニ 62 例、キウイフルーツ 56 例、貝類 52 例、メロン 40 例、ソバ 34 例、魚類、ヤマイモ 28 例、モモ 25 例、牛乳・乳製品 24 例が上位 10 品目を占めた。

3-1 これらの食物を食べてから 2 時間以内に具合が悪くなったとき、どのような症状がありましたか。

食物によって誘発された症状（複数回答）は、“口、口唇の違和感やかゆみ、はれ”が最も多く 311 例

(42.8%)、次いで“皮膚のあかみ、じんましん”が255例(35.1%)、“嘔吐、下痢”が188例(25.9%)、“腹痛”141例(19.4%)、“飲み込みづらさ、声枯れ、のどの違和感”が125例(17.2%)であった。“ぐったり、意識もうろう、意識を失う”といった症状は26例(3.4%)でみられた(図5)。

図5. これらの食物を食べてから2時間以内に具合が悪くなったとき、どのような症状がありましたか。



上位10品目で食物別に臓器症状をみると、エビ、カニでは皮膚および粘膜症状、魚類、ヤマイモでは皮膚症状、キウイフルーツ、メロン、モモでは粘膜症状、ソバ、貝類、牛乳・乳製品では消化器症状の回答が多く、それぞれ回答者の50%以上を占めていた。

3-2 これらの食物を食べて、過去1年以内に明らかな症状が出たものをお答えください。

205名(4.4%)で1年以内に症状の既往を認めた。エビ32例が最も多く、続いてカニ20例、貝類19例、メロン16例、キウイフルーツ15例と続いた。また、1年以内に食物負荷試験によって症状を確認したのは10名(0.2%)17例で、ソバ3例、鶏卵・鶏卵製品、牛乳・乳製品、エビ、魚類、肉類がそれぞれ2例などであった。

4. 普段は食べても何も症状が出ない食物で、食べてからおおむね2時間くらいのうちに運動して具合が悪くなりやすかったり、強い症状がでたりする特定の食物がありますか。

“ある”と回答したのは248名(5.3%)、食物品目数は343品目であった。原因食物は、牛乳・乳製品が71例と多く、次いで果物44例、甲殻類29例、貝類23例、魚類21例であった。このうち、医師による診断があったのは26名(0.6%)50品目で、上位から牛乳・乳製品8例、小麦6例、エビ5例、カニ、鶏卵が各4例であった。しかし、回答は、前述のアレルギーのために避けている食物との重複回答も多くみられた。

4-1 これらの食物を食べてからおおむね2時間以内に運動した場合、どのような症状が出ますか。

誘発される症状は、“腹痛”が最も多く132例(38.5%)、続いて“嘔吐、下痢”が130例(37.9%)、“皮膚のあかみ、じんましん”が98例(28.6%)、“口、口唇の違和感やかゆみ、はれ”が59例(17.2%)、“飲み込みづらさ、声枯れ、のどの違和感”が41例(12.0%)であった。原因食物として最も多い牛乳・乳製品では、“腹痛”が64.8%、“嘔吐、下痢”が60.6%と、消化器症状の割合が高かった。“ぐったり、意識もうろう、意識を失う”は25例(7.3%)で、原因食物は小麦、魚類がそれぞれ4例ずつで最も多かった。

D. E. 考察、結論

インターネット調査は、調査対象者がインターネットを使うことができ、調査会社に登録しているという特殊な集団であり、何らかの強いバイアスがかかる可能性があることである。本調査においてもその可能性を否定できないが、株式会社マクロミルはインターネット調査会社の中で国内最大手であり、会員数は250万人を超している。

調査対象は、年齢・性別の割り付けを行い、成人各年齢層の食物アレルギー有症率を調査することを目的とした。地域、職種などにおいても極端に偏重のない対象集団であると考えられる。

食物による不利益な反応の既往者(食中毒を除く)は24.1%であった。これは必ずしも食物アレルギーばかりでなく不耐症など雑多なものも包含された結果である。また、過去に寛解した小児期の食物アレルギーの原因食物も含まれると考えられる。原因食物は果物が15.0%と最も多く、次いで貝類12.8%、甲殻類12.4%、魚類9.5%であった。小児期に多い牛乳・乳製品、鶏卵がこれ続き、小児と比較して上位4抗原は小児期以降で特徴的な食物であることが考えられた。

次に現病歴を推測する現在、食べないようにしている食物の回答では、13.1%(611/4678)が何らかの食物を食べないようにしていた。この原因食物も果物が最も多く、甲殻類、貝類、魚類、ソバ、牛乳・乳製品、軟体類と続いた。しかし、これら食品を現在食べないようにしている理由で最も多かったのは“自己判断”の78.4%であった。“医師の診断・指示に基づく”ものは14.3%に留まり、全体の1.9%(88/4678)であった。“自己判断”を根拠とする場合は、本来除去する必要がない食物が含まれる可能性があり、万が一、それが一過性の症状などであっても、その後除去するかどうかの判断は個人によって異なる可能性が高い。このため、13.1%を食物アレルギーの有症率とする信憑性については検討が必要と言える。

次に食べないようにしている根拠として、“食べてから2時間以内の症状(負荷試験を含む)の既往”と回答したのは、10.1%(472/4678)であった。根拠として信憑性の高いこの判断に基づく数値は、実際的な食物アレルギーの有症率に近いことが考えられる。しかし、ここでの即時型症状の既往は、医師の判断を必要としないため、症状を誤解して抽出している可能性は否定出来ない。このほか、必ずしも根拠とならない“検査陽性”が7.5%、“除去して改善した”も14.1%に及

んだ。このことは、今回の結果の中には“なるべくそのものを食べないようにしている”といったような食物が含まれている可能性があり、除去の程度についても一律でないことが推察される。

また即時型既往の時期を問わないため、必ずしも現状を反映しているとは言えない可能性がある。次に、原因食物を食べて、2時間以内に明らかな症状があった回答（食物負荷試験含む）に対して、過去1年以内のものは205名であった。これから推察される有症率は4.4%（205/4678）となる。しかし、診断後、やがて食べられるようになることが多い小児と比較し、成人では、一度除去の判断をした食物を定期的に年単位で経過をみている可能性は高くなく、過去1年以内に症状の既往があることが、必ずしも必須の条件とは言い難い。1年以内の症状誘発の原因食物としては、多いものからエビ、カニ、貝類、メロン、キウイフルーツであり、前述の“即時型症状の既往”に基づいて食べないようにしているものとも類似した結果であった。このことは、“即時型症状の既往”をもとにした有症率にもある程度の信憑性をもたらす結果と考えられる。

2時間以内に誘発された明らかな症状では、“口、口唇の違和感やかゆみ、腫れ”の粘膜症状が最も多く、次いで“皮膚のあかみ、じんましん”の皮膚症状、“嘔吐、下痢”や“腹痛”の消化器症状が続いた。“ぜん鳴、呼吸困難”や“せき”などの呼吸症状は比較的少なく、重症度の高い症状の頻度が低いことが、医療機関の受診がない原因の一つと考えられた。また、成人では小児と比較して給食などで一律に皆が同じものを食べる機会が減り、その食習慣の中で除去が比較的容易なものは特に自己判断で除去されやすい。原因食物としてもっとも多かった果物では、除去が比較的に容易であることと、口腔の粘膜症状が多く、大多数は症状が重篤化しにくい口腔アレルギー症候群（OAS）と考えられた。反対に、小麦や鶏卵、ソバなどでは、日常的に摂取する頻度が多く、軽微ではない症状が出やすいため、医療機関で診断がつけられている割合が高いと推察される。このため、比較的除去が容易で、重篤な症状を伴わない食物アレルギーをどこまで正確に抽出できるかが、有症率を導き出すための検討課題であるといえる。

普段は食べても何も症状が出ない食物で、食べてからおおむね2時間くらいのうちに運動して具合が悪くなる食物があると回答したのは、5.3%であった。医師の診断があったのは0.6%のみで、誘発される症状は、アレルギーのために食べないようにしている食物による症状とは異なり、“腹痛”、“嘔吐、下痢”が多数を占めた。特に原因食物としてもっとも多かった乳製品では、その症状の60%以上を消化器症状が占めていた。これまでに、牛乳・乳製品によるFDEIAn症例の報告は少なく、これらのことから、回答の多くは、乳糖不耐症などの症状の増悪などである可能性が考えられた。また、他の原因食物の回答の中にも、アレルギーのために食べないようにしている食物との重複回答が多くみられ、設問の意図と異なり、もともとの症状が運動によって増悪するケースが含まれている可能性があった。このため、5.3%は実際のFDEIAnの有症率としては適切とは言えず、医師の診断がある0.6%以外の有症率に関して、今回の調査で明らかにすることは難しいと考えられる。

自己申告による有症率調査では、特に不耐症などの可能性が高い食物で、不利益な症状と食物アレルギー症状の区別がつけられにくいことを考慮すべきである。今回の調査では、冒頭の設問でも食物による不利益な症状について食中毒を除くことを注釈しているが、結果では、一般的に食中毒などの原因となりやすい貝類で、不利益な症状の既往がアレルギーのために除去している食物と乖離して多くみられた。このことからも、食物による不利益な症状が、何に起因するかを、適切に判断することには困難が伴うと推察される。小児と異なり、成人の場合では、多くが自己判断で食物を避けているため、症状についての認識の違いが、有症率に大きな影響を与える可能性がある。また、重篤な症状が誘発される場合と、軽微な症状が誘発される場合でも、その認識には差が出ることが推測され、有症率を検討する上で、その症状の重篤度や臨床型も考慮する必要があることが示唆された。

今回の調査における我が国の成人の食物アレルギー有症率は、およそ1.9%（医師の診断による割合）～10.1%（即時型症状を呈する割合）であると推察された。その重篤度や臨床型は様々であると考えられるが、諸外国の調査と比較しても相応であった。

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H. 知的財産権の出願・登録状況（予定を含む）

なし

Ⅲ. 研究成果の刊行に関する一覧表

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
秀 道広	抗ヒスタミン薬・抗アレルギー薬	矢崎義男	治療薬 Up-To-Date 2013	ﾒﾃﾞｨｶﾙﾚﾋﾞｭｰ社	大阪	2013	588-592
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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
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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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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 LOWER AIRWAYS

Association between obesity and asthma in Japanese preschool children

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Abstract

Obesity may increase the risk of subsequent asthma. We have previously reported that there is a clear association between obesity and asthma in Japanese school-aged children.

To evaluate whether a similar association exists in younger children, a nationwide cross-sectional questionnaire-based survey was performed focusing on children aged 4–5 yr. A child who had experienced wheezing during the past 12 months and had ever been diagnosed with asthma by a physician was defined as having current asthma. Overweight and underweight were defined as BMI ≥90th percentile and ≤10th percentile, respectively, according to the reference values for Japanese children from 1978 to 1981.

After excluding 2547 children because of incomplete data, 34,699 children were analyzed. Current asthma was significantly more prevalent in overweight children compared with underweight and normal weight children (13.2% for overweight vs. 10.5% for underweight and 11.1% for normal weight; both $p < 0.001$). Even after adjusting for other variables, such as gender, other coexisting allergic diseases, and parental history of asthma, there was an association between overweight and current asthma (adjusted odds ratio: 1.23, 95% CI: 1.10–1.38, $p < 0.001$).

Even in preschool children, obesity is already associated with asthma, and there was no gender effect on this association. Physicians should consider the impact of obesity when managing asthma in younger children.

In the past few decades, the prevalence of both asthma and obesity has been increasing dramatically. In Japanese school-aged children, the prevalence of asthma and the prevalence of obesity have increased 2.1 times (1) and 2.5–2.6 times (2, 3), respectively, over the past 20 yr. Asthma and obesity often coexist, and obesity appears to worsen asthma control and increase asthma severity, resulting in increased numbers of prescribed medications and decreased quality of life for patients (4). Recently, many studies have shown a positive association between both disorders in school-aged children, adolescents, and adults (5–6). In contrast, there have been only a few studies performed to evaluate the association between obesity and asthma in preschool children. It has been recognized that both asthma and obesity have their beginnings in early life and that the effects of these disorders continue throughout later life (7). For instance, despite the difficulty in diagnosing asthma in young children, the available data suggest that approximately 80% of childhood asthma is diagnosed by the age of 6 yr (1). Similarly, it was reported that one-third of obese preschool children were still obese as adults (8). Therefore, it is important to examine the associations between both disorders in early life.

When evaluating younger children, there have been methodological issues that made it difficult to clarify the association between asthma and obesity. One of the issues is a lack of a standard definition of asthma in preschool children (9). A questionnaire used by the International Study of Asthma and Allergy in Childhood (ISAAC), which has been widely used as a standard questionnaire for studying the prevalence of childhood asthma, was validated for use in the school-aged

children. Another issue is that a variety of definitions of child obesity have been used (10–11). Furthermore, most of the data regarding the impact of obesity on asthma were obtained from western countries, and few data from Asian countries have been reported. It has been known that there are ethnic differences in body composition including body mass index (BMI), body fat mass, and fat distribution between Asian and Caucasian children (12, 13).

To evaluate whether there is a relationship between obesity and asthma in Japanese preschool children, we conducted a nationwide survey, in which asthma was defined as parent-reported, physician-diagnosed asthma, and overweight was defined according to the reference values of BMI for Japanese children. We also assessed the effects of potential confounders such as gender, personal history of other allergic diseases, and parental history of asthma on the association between obesity and asthma.

Methods

Study population

This study was a cross-sectional and questionnaire-based survey performed in 3- to 6-yr-old children in Japan and carried out from April through July 2008. In order to perform a nationwide survey, kindergarten classes were randomly selected from all the prefectures. The total number of children recruited was 50,959, corresponding to approximately 2% of the pediatric population, according to the data provided by the National Institute of Population and Social Security Research. This study protocol was approved by the independent review board of the National Center for Child Health and Development.

Questionnaire

The survey used a Japanese version of the ISAAC questionnaire (5, 14), which was distributed through teachers of the participating kindergartens. The questionnaires were filled by the parents. The questionnaire also included questions regarding demographics, the latest data regarding the child's height and weight, the physician's diagnosis of allergic diseases, and the parental history of asthma. Current wheeze was defined as a positive answer to the question 'Has your child had wheezing or whistling in the chest during the last 12 months?' Among the current wheezers, a child whose parent answered positively to the question 'Has your child ever been diagnosed with asthma by a physician?' was defined as having current asthma. In Japan, asthma diagnosis in preschool children is commonly based on the following criteria described in the Japanese pediatric asthma guideline (15): (i) three or more episodes of airway obstruction that was documented by wheezing, decreased air entry, and dyspnea and/or (ii) improvement of airway obstruction following bronchodilator use.

Definition of underweight and overweight

The child's weight and height were determined by the questionnaire. BMI was calculated as body weight in kilograms divided by height squared in meters (kg/m^2). The subjects were categorized into three groups based on the 10th and 90th percentiles, according to the reference values of BMI for Japanese children, which were determined during the 1978–1981 period (16). Children who were at the 10th percentile and less were defined as underweight, those at the >10th to <90th percentile were assigned to normal weight, and those with BMI $\geq$90th percentile were defined as overweight.

Statistical analyses

The chi-square test was used to evaluate the gender differences and compare the prevalence of current asthma between groups. Multivariable analysis was performed to estimate the effects of body composition and other confounding factors on current asthma. A p value <0.05 was considered to be statistically significant. All analysis was performed using the statistical package of SPSS for Windows version 17.0J (SPSS Inc, Chicago, IL, USA).

Results

Of the 50,959 children aged 3–6 yr, 47,291 replied to the questionnaire (response rate: 92.8%). Because this population was mainly composed of 4- and 5-yr-old children, 37,246 children aged 4–5 yr were selected (78.9% of the enrolled children). Finally, after omitting incomplete data, 34,699 children were analyzed (Fig. 1). The baseline characteristics of the study population are shown in Table 1. According to the reference values of BMI for Japanese children obtained in the 1978–1981 period (16), 19.5% were categorized as underweight and 10.0% were defined as overweight, showing an increasing trend in the prevalence of underweight over the past few decades. There were gender differences; both underweight and overweight were more prevalent in boys. Boys were also more likely to have ever been diagnosed with

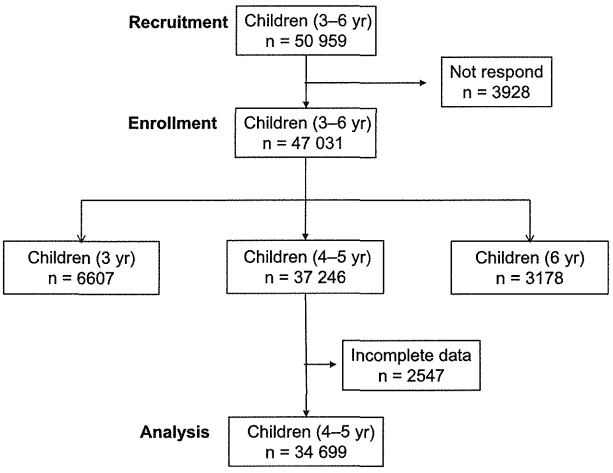

Figure 1 Participants in the cross-sectional and questionnaire-based survey.