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Original Article

# Obesity, but not metabolic syndrome, as a risk factor for late-onset asthma in Japanese women

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ALT, alanine transaminase; AST, aspartate aminotransferase; ERC, reserve expiratory volume; FRC, functional residual volume; HbA1c, hemoglobin A1c; HDL, high density lipoprotein; ICD-10, International Classification of Diseases, 10th Revision; LDL, low density lipoprotein; LTRA, leukotriene receptor antagonist; NGSP, National Glycohemoglobin Standardization Program; SCG, sodium cromoglycate; TG, triglyceride; WHO, World Health Organization

ABSTRACT

*Background:* Several cross-sectional studies have suggested an association between obesity and asthma. However, few studies have investigated this relationship longitudinally, especially in middle-aged subjects. Although metabolic syndrome is a well-known risk factor for many non-communicable diseases, its contribution to asthma remains controversial.

*Methods:* From 2008, specific health checkups for metabolic syndrome have been conducted throughout Japan. To seek relationships of obesity and metabolic syndrome with late-onset asthma in Japan, we analyzed data collected from health insurance claims and specific health checkups for metabolic syndrome at three large health insurance societies. Among subjects aged 40–64 years (n = 9888), multivariate logistic regression analyses were performed to investigate the relationships of obesity and metabolic syndrome in fiscal year 2012 (from April 2012 to March 2013) with the incidence of late-onset asthma in the following two years (from April 2013 to March 2015).

*Results:* In women, BMI 25–29.9 kg/m$^2$ or ≥30 kg/m$^2$, waist circumference ≥90 cm, and waist-to-height ratio ≥0.5 were shown to be significant risk factors for asthma, with adjusted odds ratios (95% CI) of 1.92 (1.35–2.75), 2.24 (1.23–4.09), 1.89 (1.30–2.75), and 1.53 (1.15–2.03), respectively. Significance was retained even after adjustment for metabolic syndrome, and there were no significant relationships between metabolic syndrome itself and the incidence of asthma in men or women.

*Conclusions:* Only the obesity measures, not metabolic syndrome, were shown to be significant risk factors for the incidence of late-onset asthma but only in middle-aged Japanese women, and not in men.


## Introduction

Asthma is a common disorder worldwide, and can develop in middle-aged or older adults, as well as in children and young adults. Unlike asthma at younger age, the risk factors for late-onset asthma are still unclear. In particular, there have been few reports of longitudinal investigations of risk factors thus far. However, some longitudinal studies conducted mainly in Western countries

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have shown a positive relationship between obesity and the incidence of asthma,[1,2] but most of these were in the young population. Very few have confirmed a causal relationship in middle-aged populations. Moreover, such data from Asian populations are essentially lacking.

Interest in metabolic syndrome as an important risk factor for cardiovascular disease and other non-communicable diseases is increasing worldwide.[3,4] In Japan, there is a universal health insurance system for almost all citizens, and from 2008 the government (Ministry of Health, Labor and Welfare) has obliged all health insurance societies throughout Japan to conduct “specific health checkups”. These checkups specifically identify metabolic syndrome among all residents aged 40–74 years with public health insurance coverage, commonly known as "*Metabo Kenshin*".

More recent studies have focused on the possibility that the relationship between obesity and asthma is mediated by metabolic syndrome because abdominal obesity is one of the components of the latter.[5,6] However, even in Western countries, studies investigating this relationship have been limited and the results are conflicting.[5,6] In particular, there have been no longitudinal studies focused on the relationship between metabolic syndrome and the incidence of late-onset asthma.

The present study aimed to investigate relationships between obesity, metabolic syndrome and the incidence of late-onset asthma in Japan using longitudinal data from health insurance claims and the results of specific health checkups.

## Methods

### *Study design*

A retrospective cohort design was used for this study. Databases of health insurance claims and the results of specific health checkups were collected from three health insurance societies which have enrolled a total of approximately 100,000 subjects. These three cover the medical expenses of all salaried employees of the large companies participating in such schemes, along with all their dependent family members. The database of health insurance claims contains information on diagnoses, prescriptions, any outpatient treatments, hospitalizations etc. In the present study, asthma was defined using these data (see below). The details of specific health checkups are described later. After excluding subjects with any asthma diagnosis or medication in fiscal years 2011 and 2012 (from April 2011 to March 2013, designated the screening period), we investigated the relationships of metabolic syndrome and obesity in fiscal year 2012 with the incidence of asthma in fiscal years 2013 and 2014 (the observation period). The Ethics Committee of Sagamihara National Hospital approved the study protocol (No. 2016-20).

### *Data collection*

Data were extracted from databases of health insurance claims and the results of specific health checkups from April 2011 to March 2015 by MHI Co., Ltd. which is a company engaged in the inspection of health insurance claims, medical cost analyses and disease analyses in response to requests from health insurers. The two databases were then linked and converted into anonymous data by the company. Thereafter, the database was provided to researchers with the agreement of the health insurance societies.

Data on health insurance claims for each subject were organized as annual data by summing up all the information from April of the year to March of the following year. Total annual prescription days for oral medicines, total annual number of prescriptions for units for inhalation, and total annual number of prescriptions for patches were calculated. Total annual numbers of infusions of anti-asthma agents or uses of nebulizers in medical institutions, and hospitalizations related to acute asthma exacerbation, were also calculated.

### *Definition of asthma*

Table 1 shows the definitions of asthma used in this study. If the subject satisfied both condition I and II in the same fiscal year, a positive asthma diagnosis during the corresponding fiscal year was made. For sensitivity analyses, stricter criteria for asthma definition were used, i.e., satisfying both condition I and II′ in the same fiscal year.

### *Specific health checkups*

According to Japanese law, insurers are obliged to conduct specific health checkups once per year on subscribers aged 40–74 years. The Ministry of Health, Labor and Welfare has set the target for specific health checkup implementation rates by all insurers at 70%, and if the rate is significantly lower, a financial penalty can be levied on the health insurance organization. In the present study, the checkup rate in fiscal year 2012 was 74.0% and 48.0% in eligible-aged men and women, respectively. The rate in women was relatively low, presumably because women were more likely to be employees' dependents.

The following are the specific core items covered by the routine health checkups: interview (lifestyle habits, behavioral habits), physical examination, body measurements (height, weight, waist circumference), blood pressure, blood examinations (TG, HDL/LDL cholesterol, AST, ALT, γ-GTP, blood glucose, HbA1c [NGSP]), urinal sugar, and urinal protein. Body measurements were mainly carried out by medical staff.

### *Study population*

The primary dataset consisted of 145,249 subjects with at least one data point in 4 fiscal years. From these, we narrowed down the study population according to the following scheme. In order to exclude possible new entrants to and resignees from the health insurance societies, we omitted 94,879 subjects without data for any one of the 4 consecutive fiscal years. Next, we excluded 29,519 subjects under the age of 40 or over 65 years at the end of fiscal year 2012. We excluded those under the age of 40 because specific

**Table 1**
Definitions of asthma.

| |
|---|
| **Definition of asthma used in the main analyses:** |
| Satisfying both conditions I and II in the same fiscal year. |
| **Stricter definition of asthma for sensitivity analyses:** |
| Satisfying both conditions I and II′ in the same fiscal year. |
| **Condition I** |
| • Labeled as asthma according to ICD-10: J45 and J46, or presence of “*Zensoku* [asthma in text data written in Japanese but not directly coded (coded as 0000999). |
| **Condition II** |
| • Satisfying one of the following: |
| 1. Outpatient treatment for acute asthma exacerbation (drip or nebulizer) ≥once per year. |
| 2. Hospitalization related to asthma ≥ once per year. |
| 3. Total annual prescriptions: ICS ≥1 canister, LTRA ≥150 days, LABA ≥30 days, SABA ≥1 canister, xanthine formulation ≥30 days, or inhaled SCG ≥30 days. |
| **Condition II′** |
| • Satisfying one of the following: |
| 1. Outpatient treatment for acute asthma exacerbation (drip or nebulizer) ≥twice per year. |
| 2. Hospitalization related to asthma ≥ once per year. |
| 3. Prescription of ICS ≥2 canisters per year. |

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health checkups begin at that age and we wanted to focus on risk factors for the incidence of late-onset asthma. Those over 65 were excluded because of the increasing possibility of misclassifying asthma as chronic obstructive pulmonary disease (COPD) in older people.[2] Then, 5299 subjects without data from specific health checkups in fiscal year 2012 were excluded. After that, to investigate the incidence of asthma, we excluded 4982 subjects who met condition I or II of the definition of asthma (suggesting the possibility of having asthma) in the screening period (2011–2012 fiscal years), and then also excluded 682 subjects missing some data necessary for the analyses. Finally, a total of 9888 subjects, 5915 men and 3973 women, was analyzed (Fig. 1). Age distribution of this population is shown in Figure 2.

*Metabolic syndrome and its components*

Because this research mainly focused on the Japanese population, the diagnosis of metabolic syndrome was made on the basis of the 2005 recommendations of the Japanese Society of Internal Medicine[7] and a statement of the Ministry of Health, Labor and Welfare. Japanese criteria for metabolic syndrome consist of 4 components, i.e., abdominal obesity, hyperglycemia, dyslipidemia and hypertension. Abdominal obesity is defined by an increase of waist circumference and is an indispensable component of the Japanese criteria. The cutoff levels are 85 cm for men and 90 cm for women. Hyperglycemia is defined by having elevated fasting blood glucose (≥110 mg/dL) or being under medical treatment for diabetes, i.e., prescription of insulin or oral anti-diabetic agents. If data on fasting blood glucose are not available, HbA1c (NGSP) ≥6.0% may be used instead. Dyslipidemia is defined as elevated blood TG (≥150 mg/dL), diminished blood HDL (<40 mg/dL) or being under medical treatment for dyslipidemia, i.e., prescription of clofibrate or statins. Hypertension is defined as elevated systolic blood pressure (≥130 mmHg), elevated diastolic blood pressure (≥85 mmHg) or being under medical treatment for hypertension. If a subject satisfies the abdominal obesity criterion and two or three of the hyperglycemia, dyslipidemia, and hypertension criteria, he/she is diagnosed as having metabolic syndrome. If a subject satisfies the abdominal obesity criterion but only one of the other three criteria, he/she is diagnosed as having signs of incipient metabolic syndrome. In the present study, subjects were categorized into three groups for analysis, i.e., as having metabolic syndrome, incipient metabolic syndrome or no metabolic syndrome. To be under

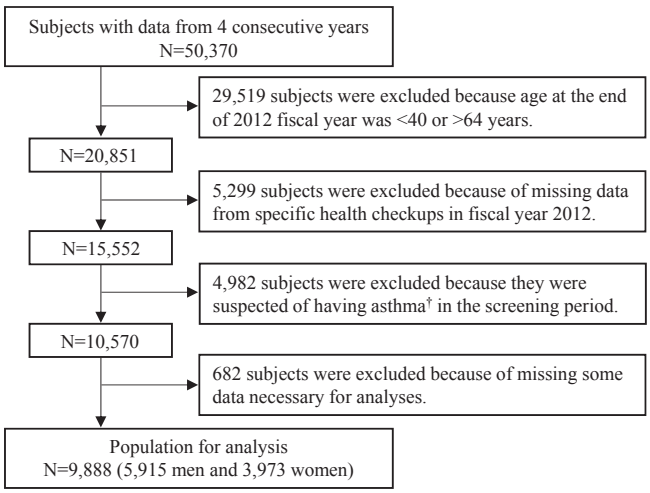


**Fig. 1.** Flow chart showing the study population. † Matching condition I or II for asthma definition.

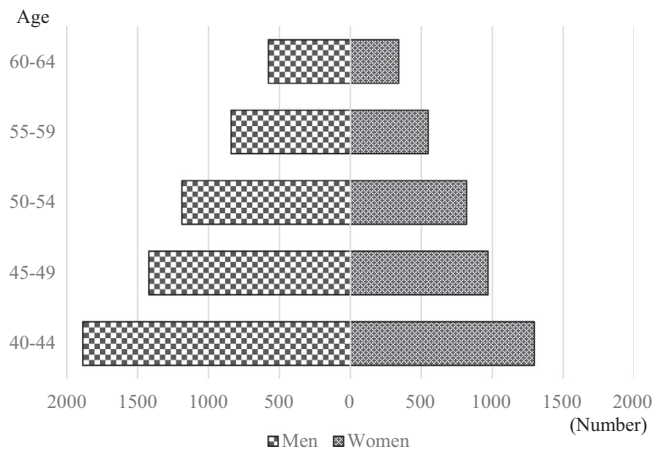


**Fig. 2.** Age distribution of the analyzed population at the end of fiscal year 2012.

medical treatment was defined as receiving any prescription for those corresponding agents in health insurance claims during fiscal year 2012.

*Obesity measures*

BMI was stratified into 4 groups, i.e., <18.5 kg/m$^2$, 18.5–24.9 kg/m$^2$, 25–29.9 kg/m$^2$ and ≥30 kg/m$^2$. Waist circumference was divided into 3 groups, i.e., ≤84 cm, 85–89 cm and ≥90 cm. Finally, waist-to-height ratio was assessed as <0.50 or ≥0.50.[8,9]

*Statistical analyses*

The outcome values for this study were incidence of asthma during the observation period (fiscal years 2013–2014). First, characteristics of the study populations divided by sex and incidence of asthma were examined using the Mann–Whitney U test for continuous variables and the $\chi$-square test for binary variables. Second, the relationships of metabolic syndrome, its components, BMI, and waist-to-height ratio in fiscal year 2012 with incidence of asthma during the observation period were examined using multivariate logistic regression analyses. Risks were expressed as adjusted odds ratios (aORs) and their 95% confidence intervals (95% CI) after adjustment for age, smoking status, and allergic rhinitis (model 1). In model 2, both obesity measures and metabolic syndrome were simultaneously entered into the statistical models as independent variables in order to compare the impact of those factors on the outcome. Furthermore, in sensitivity analyses, multivariate logistic regression analyses of the same models were repeated using the stricter asthma definition as the outcome variable. All the analyses were separately performed in men and women considering possible sex differences in the relationships between obesity and risk of asthma. Possible interactions between sex and each variable were assessed by including interaction terms of sex × each variable into the logistic regression models. A p value of <0.05 was considered statistically significant. Analyses were performed using IBM SPSS Statistics 24.

## Results

During the observation period, 213 (3.6%) men and 211 (5.3%) women developed asthma. Table 2 shows the subjects' characteristics stratified by sex and incidence of asthma. In men, asthma developed at a lower frequency in current smokers and those with lower systolic blood pressure, $\gamma$-GTP, and BS; obesity measures

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**Table 2**
Characteristics of the subjects by incidence of asthma.

| | Men | | | Women | | |
|---|---|---|---|---|---|---|
| | Asthma incidence | | *P* value | Asthma incidence | | *P* value |
| | + | − | | + | − | |
| Subjects | 213 | 5702 | | 211 | 3762 | |
| Age (y.o.) | 47 (11) | 48 (11) | 0.29 | 47 (9) | 48 (11) | 0.04 |
| Current smoker, No. (%) | 64 (30.0) | 2216 (38.9) | 0.01 | 29 (13.7) | 574 (15.3) | 0.62 |
| BMI (kg/m$^2$) | 23.6 (4.0) | 23.5 (4.1) | 0.60 | 21.6 (5.5) | 21.1 (4.2) | 0.01 |
| Waist circumference (cm) | 84 (10) | 84 (11) | 0.96 | 79 (15) | 77 (12) | 0.01 |
| Waist-to-height ratio | 0.49 (0.06) | 0.49 (0.07) | 0.77 | 0.50 (0.10) | 0.49 (0.08) | 0.01 |
| Systolic blood pressure (mmHg) | 120 (19) | 121 (20) | 0.02 | 110 (22) | 112 (22) | 0.08 |
| Diastolic blood pressure (mmHg) | 75 (13) | 77 (14) | 0.11 | 70 (16) | 70 (16) | 0.30 |
| TG (mg/dL) | 111 (98) | 111 (91) | 0.86 | 77 (46) | 70 (45) | 0.01 |
| HDL (mg/dL) | 53 (18) | 54 (19) | 0.45 | 67 (21) | 70 (22) | 0.03 |
| LDL (mg/dL) | 121 (37) | 122 (41) | 0.55 | 116 (43) | 117 (41) | 0.74 |
| AST (U/L) | 22 (8) | 21 (8) | 0.78 | 19 (6) | 19 (6) | 0.81 |
| ALT (U/L) | 22 (17) | 23 (16) | 0.93 | 15 (9) | 15 (7) | 0.32 |
| γ-GTP (U/L) | 34 (29) | 35 (38) | 0.44 | 17 (13) | 17 (13) | 0.50 |
| BS (mg/dL) | 97 (15) | 97 (15) | 0.57 | 90 (11) | 90 (11) | 0.87 |
| HbA1c NGSP (%) | 5.5 (0.5) | 5.5 (0.6) | 0.53 | 5.4 (0.5) | 5.5 (0.5) | 0.47 |

Mann–Whitney *U* test for continuous variables and χ-square test for binary variables.
Data are expressed as median (IQR) or No. (%).

were not different in subjects who did or did not develop asthma. However, unlike in men, in women, all the obesity measures, i.e. BMI, waist circumference and waist-to-height ratio, were significantly greater in subjects who developed asthma.

Table 3 shows the relationships between metabolic syndrome and its components, i.e. waist circumference, hyperglycemia, dyslipidemia and hypertension, and the incidence of asthma. In men, no clear relationships were detectable. However, univariate analyses and model 1 indicated that ORs for asthma development were 1.24–1.63 in women with incipient or overt metabolic syndrome relative to those without, but these differences failed to achieve statistical significance.

Regarding other components of metabolic syndrome, male subjects with hypertension were unexpectedly less likely to develop asthma, whereas in women, with the exception of waist circumference, there were no significant relationships between other components of metabolic syndrome and the incidence of asthma.

Table 4 shows the relationships between obesity measures and the incidence of asthma. There were no significant relationships between obesity measures and incidence of asthma in men at all, whereas, again, in women, BMI ≥25 kg/m$^2$, waist circumference ≥90 cm and waist-to-height ratio ≥0.5 were all significant risk factors. Additionally, statistically significant interactions were

**Table 3**
Relationships of incipient and overt metabolic syndrome with incidence of asthma.

| Sex | | Asthma incidence | | Crude OR | Model 1 Adjusted OR[†] | Model 2 Adjusted OR[‡] |
|---|---|---|---|---|---|---|
| | | + | − | | | |
| Men | Metabolic syndrome | | | | | |
| | Not meeting criteria | 136 | 3571 | 1 | 1 | 1 |
| | Incipient group | 41 | 977 | 1.10 (0.77–1.57) | 1.12 (0.78–1.59) | 1.10 (0.73–1.64) |
| | Meeting criteria | 36 | 1154 | 0.82 (0.56–1.19) | 0.84 (0.57–1.22) | 0.82 (0.52–1.29) |
| | Components of metabolic syndrome | | | | | |
| | Waist circumference ≥85 cm | 98 | 2691 | 0.95 (0.72–1.25) | 0.95 (0.72–1.26) | NA |
| | Elevated blood pressure[§] or use of antihypertensive agents | 71 | 2386 | 0.69 (0.52–0.93)* | 0.69 (0.51–0.93)* | NA |
| | TG ≥ 150 mg/dL or HDL <40 mg/dL or use of antidyslipidemic agents | 90 | 2299 | 1.08 (0.82–1.43) | 1.14 (0.86–1.50) | NA |
| | Elevated fasting blood glucose[¶] or use of antidiabetic drugs | 34 | 1032 | 0.86 (0.59–1.25) | 0.90 (0.62–1.32) | NA |
| Women | Metabolic syndrome | | | | | |
| | Not meeting criteria | 190 | 3488 | 1 | 1 | 1 |
| | Incipient group | 12 | 141 | 1.56 (0.85–2.87) | 1.63 (0.89–3.00) | 0.95 (0.47–1.89) |
| | Meeting criteria | 9 | 133 | 1.24 (0.62–2.48) | 1.36 (0.68–2.73) | 0.76 (0.35–1.65) |
| | Components of metabolic syndrome | | | | | |
| | Waist circumference ≥90 cm | 38 | 419 | 1.75 (1.22–2.53)**, ‖ | 1.82 (1.26–2.63)**, ‖ | NA |
| | Elevated blood pressure[§] or use of antihypertensive agents | 52 | 916 | 1.02 (0.74–1.40) | 1.12 (0.80–1.57) | NA |
| | TG ≥ 150 mg/dL or HDL <40 mg/dL or use of antidyslipidemic agents | 33 | 566 | 1.05 (0.71–1.53) | 1.15 (0.78–1.70) | NA |
| | Elevated fasting blood glucose[¶] or use of antidiabetic drugs | 10 | 226 | 0.78 (0.41–1.49) | 0.85 (0.44–1.65) | NA |

Total n = 5915 men and 3973 women. Total asthma subjects = 213 men and 211 women.
Each variable was not mutually adjusted.
**P* value < 0.05. ***P* value < 0.01.
NA, Not Accessed.
[†] Adjusted for age, smoking status, and allergic rhinitis.
[‡] Adjusted for age, smoking status, allergic rhinitis, and BMI.
[§] Systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg.
[¶] Fasting blood glucose ≥110 mg/dL or if there were no data for fasting blood glucose, HbA1c ≥ 6.0%.
‖ *P*-interaction between men and women <0.01.

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**Table 4**
Relationships of obesity measures and incidence of asthma.

| Sex | | | Asthma incidence | | Crude OR | Model 1 Adjusted OR† | Model 2 Adjusted OR‡ |
|---|---|---|---|---|---|---|---|
| | | | + | − | | | |
| Men | BMI (kg/m$^2$) | −18.4 | 3 | 130 | 0.62 (0.19–1.96) | 0.65 (0.20–2.06) | 0.64 (0.20–2.04) |
| | | 18.5–24.9 | 141 | 3760 | 1 | 1 | 1 |
| | | 25.0–29.9 | 60 | 1528 | 1.05 (0.77–1.42) | 1.04 (0.77–1.42) | 1.10 (0.76–1.59) |
| | | 30.0– | 9 | 284 | 0.85 (0.43–1.68) | 0.83 (0.42–1.65) | 0.94 (0.44–1.98) |
| | Waist circumference (cm) | −84.9 | 115 | 3011 | 1 | 1 | 1 |
| | | 85–89.9 | 46 | 1187 | 1.01 (0.72–1.44) | 1.01 (0.71–1.43) | 0.97 (0.59–1.60) |
| | | 90– | 52 | 1504 | 0.91 (0.65–1.26) | 0.91 (0.65–1.27) | 0.89 (0.52–1.53) |
| | Waist-to-height ratio | <0.5 | 122 | 3121 | 1 | 1 | 1 |
| | | ≥0.5 | 91 | 2581 | 0.90 (0.68–1.19) | 0.91 (0.69–1.21) | 0.90 (0.62–1.30) |
| Women | BMI (kg/m$^2$) | −18.4 | 25 | 504 | 1.02 (0.66–1.59) | 1.03 (0.66–1.60) | 1.03 (0.66–1.59) |
| | | 18.5–24.9 | 129 | 2661 | 1 | 1 | 1 |
| | | 25.0–29.9 | 44 | 481 | 1.89 (1.32–2.69)**,§ | 1.92 (1.35–2.75)**,§ | 2.02 (1.38–2.96)**,§ |
| | | 30.0– | 13 | 116 | 2.31 (1.27–4.21)**,§ | 2.24 (1.23–4.09)**,§ | 2.65 (1.26–5.54)**,§ |
| | Waist circumference (cm) | −84.9 | 147 | 2947 | 1 | 1 | 1 |
| | | 85–89.9 | 26 | 396 | 1.32 (0.86–2.02) | 1.35 (0.87–2.07) | 1.34 (0.87–2.07) |
| | | 90– | 38 | 419 | 1.82 (1.25–2.64)**,¶ | 1.89 (1.30–2.75)**,¶ | 2.33 (1.37–3.96)**,¶ |
| | Waist-to-height ratio | <0.5 | 103 | 2182 | 1 | 1 | 1 |
| | | ≥0.5 | 108 | 1580 | 1.45 (1.10–1.91)**,§ | 1.53 (1.15–2.03)**,§ | 1.48 (1.10–1.99)**,§ |

Total n = 5915 men and 3973 women. Total asthma subjects = 213 men and 211 women.
Each variable was not mutually adjusted.
**$P$ value < 0.01.
† Adjusted for age, smoking status, and allergic rhinitis.
‡ Adjusted for age, smoking status, allergic rhinitis, and metabolic syndrome.
§ $P$-interaction between men and women <0.05.
¶ $P$-interaction between men and women <0.01.

observed between sex and these obesity measures, suggesting that women are more likely to be affected by obesity as a risk factor for late-onset asthma. Furthermore, these relationships remained significant even after adjustment for metabolic syndrome (model 2).

Table 5 shows relationships of metabolic syndrome and its components with the incidence of asthma using the stricter definition of the latter. However, the only factor reaching significance was once more waist circumference in women. Data in Table 6 also consider obesity measures and the incidence of asthma using the stricter definition. This analysis revealed that BMI 25–29.9 kg/m$^2$, BMI ≥30 kg/m$^2$, or waist circumference ≥90 cm remained related to asthma occurrence in women even after adjustment for metabolic syndrome (model 2). Statistical significance for the interaction terms sex × BMI 25–29.9 kg/m$^2$, BMI ≥30 kg/m$^2$, and sex × waist

**Table 5**
Relationships of incipient and overt metabolic syndrome with the incidence of asthma according to the stricter definition.

| Sex | | Asthma incidence | | Crude OR | Model 1 Adjusted OR† | Model 2 Adjusted OR‡ |
|---|---|---|---|---|---|---|
| | | + | − | | | |
| Men | Metabolic syndrome | | | | | |
| | Not meeting criteria | 55 | 3652 | 1 | 1 | 1 |
| | Incipient group | 17 | 1001 | 1.13 (0.65–1.95) | 1.14 (0.66–1.97) | 1.22 (0.65–2.28) |
| | Meeting criteria | 15 | 1175 | 0.85 (0.48–1.51) | 0.86 (0.48–1.53) | 0.94 (0.46–1.91) |
| | Components of metabolic syndrome | | | | | |
| | Waist circumference ≥85 cm | 41 | 2748 | 1.00 (0.65–1.53) | 1.00 (0.65–1.52) | NA |
| | Elevated blood pressure§ or use of antihypertensive agents | 31 | 2426 | 0.78 (0.50–1.21) | 0.76 (0.48–1.21) | NA |
| | TG ≥ 150 mg/dL or HDL <40 mg/dL or use of antidyslipidemic agents | 38 | 2351 | 1.15 (0.75–1.76) | 1.20 (0.78–1.85) | NA |
| | Elevated fasting blood glucose¶ or use of antidiabetic drugs | 14 | 1052 | 0.87 (0.49–1.55) | 0.89 (0.50–1.61) | NA |
| Women | Metabolic syndrome | | | | | |
| | Not meeting criteria | 81 | 3597 | 1 | 1 | 1 |
| | Incipient group | 5 | 148 | 1.50 (0.60–3.76) | 1.60 (0.64–4.02) | 0.79 (0.28–2.27) |
| | Meeting criteria | 2 | 140 | 0.63 (0.15–2.61) | 0.72 (0.18–2.99) | 0.34 (0.07–1.55) |
| | Components of metabolic syndrome | | | | | |
| | Waist circumference ≥90 cm | 16 | 441 | 1.74 (1.00–3.01)* | 1.83 (1.05–3.18)* | NA |
| | Elevated blood pressure§ or use of antihypertensive agents | 21 | 947 | 0.97 (0.59–1.60) | 1.14 (0.68–1.91) | NA |
| | TG ≥ 150 mg/dL or HDL <40 mg/dL or use of antidyslipidemic agents | 15 | 584 | 1.16 (0.66–2.04) | 1.36 (0.76–2.43) | NA |
| | Elevated fasting blood glucose¶ or use of antidiabetic drugs | 3 | 233 | 0.55 (0.17–1.76) | 0.64 (0.20–2.07) | NA |

Total n = 5915 men and 3973 women. Total asthma subjects = 87 men and 88 women.
Each variable was not mutually adjusted.
*$P$ value < 0.05.
NA, Not Accessed.
† Adjusted for age, smoking status, and allergic rhinitis.
‡ Adjusted for age, smoking status, allergic rhinitis, and BMI.
§ Systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg.
¶ Fasting blood glucose ≥110 mg/dL or if there were no data of fasting blood glucose, HbA1c ≥ 6.0%.

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**Table 6**
Relationships of obesity measures and incidence of asthma according to the stricter definition.

| Sex | | | Asthma incidence | | Crude OR | Model 1 Adjusted OR[†] | Model 2 Adjusted OR[‡] |
|---|---|---|---|---|---|---|---|
| | | | + | − | | | |
| Men | BMI (kg/m$^2$) | −18.4 | 2 | 131 | 0.96 (0.23–3.97) | 1.00 (0.24–4.16) | 1.04 (0.25–4.33) |
| | | 18.5–24.9 | 61 | 3840 | 1 | 1 | 1 |
| | | 25.0–29.9 | 21 | 1567 | 0.84 (0.51–1.39) | 0.84 (0.51–1.38) | 0.77 (0.43–1.39) |
| | | 30.0– | 3 | 290 | 0.65 (0.20–2.09) | 0.64 (0.20–2.06) | 0.59 (0.17–2.07) |
| | Waist circumference (cm) | −84.9 | 46 | 3080 | 1 | 1 | 1 |
| | | 85–89.9 | 20 | 1213 | 1.10 (0.65–1.87) | 1.10 (0.65–1.87) | 1.08 (0.51–2.30) |
| | | 90– | 21 | 1535 | 0.92 (0.54–1.54) | 0.91 (0.54–1.54) | 0.92 (0.40–2.10) |
| | Waist-to-height ratio | <0.5 | 51 | 3192 | 1 | 1 | 1 |
| | | ≥0.5 | 36 | 2636 | 0.85 (0.56–1.31) | 0.86 (0.55–1.32) | 0.78 (0.44–1.40) |
| Women | BMI (kg/m$^2$) | −18.4 | 12 | 517 | 1.18 (0.62–2.21) | 1.18 (0.63–2.23) | 1.18 (0.62–2.22) |
| | | 18.5–24.9 | 54 | 2736 | 1 | 1 | 1 |
| | | 25.0–29.9 | 16 | 509 | 1.59 (0.90–2.80) | 1.64 (0.93–2.89) | 1.83 (1.01–3.30)* |
| | | 30.0– | 6 | 123 | 2.47 (1.04–5.86)* | 2.34 (0.98–5.57) | 3.51 (1.19–10.30)* |
| | Waist circumference (cm) | −84.9 | 60 | 3034 | 1 | 1 | 1 |
| | | 85–89.9 | 12 | 410 | 1.48 (0.79–2.77) | 1.54 (0.82–2.91) | 1.54 (0.82–2.89) |
| | | 90– | 16 | 441 | 1.83 (1.05–3.21)* | 1.95 (1.11–3.42)* | 2.92 (1.42–6.01)** |
| | Waist-to-height ratio | <0.5 | 44 | 2241 | 1 | 1 | 1 |
| | | ≥0.5 | 44 | 1644 | 1.36 (0.89–2.08) | 1.48 (0.97–2.28) | 1.49 (0.95–2.34) |

Total n = 5915 men and 3973 women. Total asthma subjects = 87 men and 88 women.
Each variable was not mutually adjusted.
*$P$ value < 0.05. **$P$ value < 0.01.
[†] Adjusted for age, smoking status, and allergic rhinitis.
[‡] Adjusted for age, smoking status, allergic rhinitis, and metabolic syndrome.

circumference ≥90 cm in this model was marginal (p-interaction, 0.11, and 0.08, and 0.11 respectively).

Additionally, we examined relationships between the use of antihypertensive agents, statins, clofibrate, insulin or oral antihyperglycemic agents and the incidence of asthma, but no significant relationships were found (data not shown). Neither did these variables affect the relationships of metabolic syndrome or obesity measures and the incidence of asthma (data not shown).

## Discussion

This retrospective cohort study performed in Japan using databases of health insurance claims and the results of specific health checkups documented obesity as a risk factor for the incidence of late-onset asthma in women (but not in men). However, metabolic syndrome was not significantly associated with the incidence of late-onset asthma either in men or women. These findings confirm the importance of obesity as a risk factor for the incidence of asthma in middle-aged women based on longitudinal analysis of a relatively large dataset of the general adult population.

Although earlier studies seeking associations between metabolic syndrome and asthma have been limited, several are available from Western countries. For example, in a large cross-sectional study in France, metabolic syndrome and its components were reported to be associated with a decline in pulmonary function, abdominal obesity being the most important factor.[10] A large-scale retrospective cohort study from Norway also found that metabolic syndrome, waist circumference and hyperglycemia were significantly related to the incidence of asthma.[6] On the other hand, a population-based longitudinal study among young adults in the USA reported that the relationship between metabolic syndrome and asthma incidence was significant only before adjustment for BMI.[5] In the present study, we found that metabolic syndrome or its components (except for waist circumference in women) were not significantly related to the incidence of asthma.

Cutoff values for waist circumference in the diagnostic criteria of metabolic syndrome vary from country to country. In Japan, it is 85 cm for men and 90 cm for women. From the view point of the risk for asthma incidence, 90 cm for Japanese women seems to be appropriate because waist circumference ≥90 cm proved to be a significant risk factor for the incidence of asthma in women. On the other hand, no significant relationship was detected between waist circumference and incidence of asthma in men. The World Health Organization (WHO) classifies a BMI ≥25 kg/m$^2$ as overweight and ≥30 kg/m$^2$ as obese, but this is based on relationships between BMI and mortality seen mainly in Western countries.[11–13] However, because average physique is clearly different in Asians and Westerners, it is essential to consider racial differences when discussing obesity.[14,15] In the present study, we found that BMI ≥25 kg/m$^2$ and waist circumference ≥90 cm were significant risk factors, with cutoff points that are lower than in Western countries. The results of this study can therefore be applied to daily clinical practice in Japan.

Because obesity, hypertension, dyslipidemia, and diabetes mutually influence one another, it may be difficult to determine which factor truly affects the incidence of asthma. In the present study, hypertension, dyslipidemia, and diabetes were found not to be associated with the incidence of asthma, suggesting that hypertension and lipid or sugar metabolism do not have significant effects on the physiological mechanisms causing obesity-related asthma. On the other hand, a significant relationship between obesity and asthma may be explained by the role of adipokines. For a long time, adipose tissue had been thought to be merely a way of storing excess energy, but recently several studies have shown that adipose tissue itself has a physiological role by secreting physiologically active substances called adipokines, including leptin and adiponectin.[16,17] These adipokines regulate inflammation and thereby, along with the mechanical effects of abdominal obesity on airways, may contribute to the development of asthma.

Here, we focused on relationships between obesity and late-onset asthma, and showed that these are stronger in women than men. Several studies using cluster analysis have repeatedly indicated that there is a group of patients with asthma characterized by female sex, late-onset, and obesity.[18,19] The results of our study are compatible with these earlier investigations. Although it is still unclear why the association between obesity and asthma is stronger in women than men, several studies have implicated

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estrogen.[20,21] Also, differences in ectopic fat distribution and the resulting differences in leptin/adiponectin profiles between men and women may affect the obesity-asthma relationship.[22]

There is a universal health insurance system in Japan and almost all citizens are covered. This system is managed by multiple insurers of different types such as municipalities, the Japanese Health Insurance Association, health insurance societies, mutual aid associations, etc. Of these, there are about 1400 health insurance societies and they cover medical expenses of all salaried employees belonging to mainly large private companies, and also cover employees' dependents. Three health insurance societies which were chosen for extraction of the subjects' data for our study covered quite heterogeneous populations including different professions and encompassing blue-to white-collar workers. In this way, the population reflects more the general health insurance landscape as a whole.

There are some limitations to this study. The first is the possibility of misclassification errors, because the diagnosis of asthma was based on information from the health insurance claims database, and the definition of asthma used in this study had not been officially validated. Several studies had tried to identify asthma cases by reviewing medical records, but because there are no established diagnosis criteria for asthma itself, case identification is usually based on the registered diagnostic code combined with a record of specific treatment for asthma.[23] In the present study, we had carefully crafted a definition in order to identify cases with asthma. Furthermore, because the results of sensitivity analyses using stricter asthma definition criteria were almost the same as those of the main analyses, the definition of asthma was considered appropriate. The second limitation of the present study is that because obesity indicators used here consisted only of the size and weight of the body, high values might not reflect obesity or adiposity especially in men with greater muscle mass than women. Another limitation of this study was the short duration of the observation period, which at 2 years was shorter than previous studies.[5,6] One of the reasons for this was that specific health checkups started only fairly recently in Japan. Further investigations with longer observation periods are needed in future.

In conclusion, this study confirmed the significance of abdominal obesity as a risk factor for the incidence of late-onset asthma in women. Metabolic syndrome and its components, except for waist circumference, were not significantly related to the incidence of asthma. These findings from the present study unequivocally document the significance of obesity as a risk factor for the development of asthma in women, but not men, later in life.

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*Conflict of interest*

MI is an employee of Nihon Medical Insurance Institute Ltd. and was formerly an employee of MHI Co., Ltd. KA is an employee of MHI Co., Ltd. The rest of the authors have no conflict of interest.

*Authors' contributions*

All authors contributed to this report. YF and MT developed the concept; MI and KA were responsible for collecting and cleaning the data; YT, HH, YK, KS, YF, YN, CO, TS were responsible for analyses and interpretation of results; YT wrote the manuscript; and, YH, YF and MT contributed to the critical revision of the manuscript.

## References

1. Beuther DA, Sutherland ER. Overweight, obesity, and incident asthma: a meta-analysis of prospective epidemiologic studies. *Am J Respir Crit Care Med* 2007;**175**:661–6.
2. Brumpton B, Langhammer A, Romundstad P, Chen Y, Mai XM. General and abdominal obesity and incident asthma in adults: the HUNT study. *Eur Respir J* 2013;**41**:323–9.
3. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *JAMA* 2002;**287**:356–9.
4. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American heart association/national heart, lung, and blood Institute scientific statement. *Circulation* 2005;**112**:2735–52.
5. Assad N, Qualls C, Smith LJ, Arynchyn A, Thyagarajan B, Schuyler M, et al. Body mass index is a stronger predictor than the metabolic syndrome for future asthma in women. The longitudinal CARDIA study. *Am J Respir Crit Care Med* 2013;**188**:319–26.
6. Brumpton BM, Camargo Jr CA, Romundstad PR, Langhammer A, Chen Y, Mai XM. Metabolic syndrome and incidence of asthma in adults: the HUNT study. *Eur Respir J* 2013;**42**:1495–502.
7. Matsuzawa Y. [Metabolic syndrome-definition and diagnostic criteria in Japan]. *Nihon Naika Gakkai Zasshi [J Jpn Soc Int Med]* 2005;**94**:188–203 (in Japanese).
8. Ashwell M, Hsieh SD. Six reasons why the waist-to-height ratio is a rapid and effective global indicator for health risks of obesity and how its use could simplify the international public health message on obesity. *Int J Food Sci Nutr* 2005;**56**:303–7.
9. Ma J, Xiao L. Association of general and central obesity and atopic and non-atopic asthma in US adults. *J Asthma* 2013;**50**:395–402.
10. Leone N, Courbon D, Thomas F, Bean K, Jego B, Leynaert B, et al. Lung function impairment and metabolic syndrome: the critical role of abdominal obesity. *Am J Respir Crit Care Med* 2009;**179**:509–16.
11. Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. *Diabetes Care* 1994;**17**:961–9.
12. Manson JE, Willett WC, Stampfer MJ, Colditz GA, Hunter DJ, Hankinson SE, et al. Body weight and mortality among women. *N Engl J Med* 1995;**333**:677–85.
13. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser* 2000;**894**:i–xii, 1-253.
14. Tan CE, Ma S, Wai D, Chew SK, Tai ES. Can we apply the national cholesterol education program adult treatment panel definition of the metabolic syndrome to Asians? *Diabetes Care* 2004;**27**:1182–6.
15. Grundy SM, Brewer Jr HB, Cleeman JI, Smith Jr SC, Lenfant C, American Heart Association, et al. Definition of metabolic syndrome: report of the national heart, lung, and blood institute/American heart association conference on scientific issues related to definition. *Circulation* 2004;**109**:433–8.
16. Sood A. Obesity, adipokines, and lung disease. *J Appl Physiol (1985)* 2010;**108**:744–53.
17. Sood A, Qualls C, Schuyler M, Thyagarajan B, Steffes MW, Smith LJ, et al. Low serum adiponectin predicts future risk for asthma in women. *Am J Respir Crit Care Med* 2012;**186**:41–7.
18. Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, et al. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008;**178**:218–24.
19. Moore WC, Meyers DA, Wenzel SE, Teague WG, Li H, Li X, et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med* 2010;**181**:315–23.
20. Varraso R, Siroux V, Maccario J, Pin I, Kauffmann F; Epidemiological Study on the Genetics and Environment of Asthma. Asthma severity is associated with body mass index and early menarche in women. *Am J Respir Crit Care Med* 2005;**171**:334–9.
21. Romieu I, Fabre A, Fournier A, Kauffmann F, Varraso R, Mesrine S, et al. Post-menopausal hormone therapy and asthma onset in the E3N cohort. *Thorax* 2010;**65**:292–7.
22. Sood A. Sex differences: implications for the obesity-asthma association. *Exerc Sport Sci Rev* 2011;**39**:48–56.
23. Desai JR, Wu P, Nichols GA, Lieu TA, O'Connor PJ. Diabetes and asthma case identification, validation, and representativeness when using electronic health data to construct registries for comparative effectiveness and epidemiologic research. *Med Care* 2012;**50**(Suppl):S30–5.

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