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Manami Kimura, MD[1], Ai Ikeda, PhD[1], Yohei Suzuki, MD[1], Koutatsu Maruyama, PhD[2], Hiroo Wada, MD[1], Takeshi Tanigawa, MD[1]*

[1] Department of Public Health, Graduate School of Medicine, Juntendo University, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan.

[2] Department of Bioscience, Graduate School of Agriculture, Ehime University, 3-5-7 Tarumi, Matsuyama, Ehime 790-8566, Japan.

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* Correspondence:

Prof. Takeshi Tanigawa, MD, PhD

Department of Public Health, Graduate School of Medicine, Juntendo University, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan.

Phone: +81 (3) 5802-1049 Fax: +81 (3) 3814-0305

Email address: tataniga@juntendo.ac.jp

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Abstract

Background. Studies on the association between asthma and anxiety in Asian children are limited. Therefore, we aimed to evaluate the association between asthma and anxiety among Japanese elementary school students.

Methods. A cross-sectional study of the association between asthma and anxiety in primary school children in Matsuyama City was conducted in 2014. The questionnaires included inquiries on asthma, anxiety, and other demographic variables. After excluding missing values, 17,752(51.5% male) children were included in the analysis. The presence of asthma(yes/no) was answered by guardians. A score of four or more on the emotional symptom subscale of the Strengths and Difficulties Questionnaire was considered as having anxiety. A Rohrer Index score of 145 or more was considered as overweight. We estimated the prevalence ratio(PR) of having anxiety in relation to the presence of asthma based on the Poisson regression model.

Results. The multivariate PR(95% Confidence Interval) of having anxiety in asthmatic boys compared to non-asthmatic boys was 1.56(1.21-1.99). The association was more evident in older than younger boys, where PR=1.32(0.93-1.88) for younger vs. 1.87(1.32-2.64) for older boys(p for interaction=0.08); and in non-overweight boys than overweight, where PR = 1.64 (1.27-2.13) and 0.94(0.41-2.19)(p for interaction=0.22),

respectively. Similar associations were not found for girls.

Conclusion. Asthma was significantly associated with anxiety in boys, particularly in older boys.

Introduction

Asthma is the most common global chronic disease in children, and its prevalence has increased since the 1980s [1]. Although it seems to have plateaued in recent years, the current prevalence for asthma in children younger than 18 years in the United States is estimated to be as high as 8.4%, according to data from 2017 [1, 2]. In Japan, a nationwide survey in 2015 reported that 8.2%–10.2% of children aged 6 to 15 years had asthma [3]. It is important to appropriately manage asthma symptoms to ensure they are controlled, as severe asthma attacks can be fatal [4]. Chronic asthma symptoms can also have an adverse effect on a child's daily activities and school attendance [4].

In addition to these physical symptoms, the association between asthma and psychological symptoms or socio-behavioral characteristics have also been previously reported. Several studies have identified characteristics such as immaturity of personality [5], lower social adaptability [6], as well as higher levels of distress [7], anxiety, and depression [8] among children with asthma. A previous study conducted on asthmatic children reported that comorbid mental illness may be associated with more severe asthma symptoms [9].

In children, the associations between being overweight, and exhibiting symptoms of asthma and mental illness have been previously reported. Overweight

asthmatic children have been reported to experience more severe asthma symptoms [10] or a decreased response to therapies [11]. On the other hand, a number of studies have reported that being overweight may be associated with a higher risk of having anxiety, depressive symptoms [12], or exhibiting poorer emotional functioning [13] in children. Although severe asthma symptoms and mental health problems are both clearly associated with being overweight, the intermediate effect of being overweight on the association between asthma and anxiety remains unclear.

Moreover, age differences were found in the prevalence of both asthma and mental illness [4, 14]. Therefore, the association between asthma and mental illness in children is expected to differ between age groups. However, to date, no studies have examined the effect of age on the association between asthma and mental illness.

Although a previous study conducted in the United Arab Emirates has reported the association between asthma and psychiatric morbidity in a community sample of children [15], the study population (n = 911 children) was relatively small. To our knowledge, no similar studies have been conducted in a large sample of community-dwelling children in Japan, where the prevalence of child overweight or obesity is relatively low. Therefore, we aimed to evaluate the association between asthma and anxiety and the effect of age on this association in a large community sample of

elementary school students in Japan. Since previous studies have suggested that the prevalence of anxiety differs by sex [16, 17], we hypothesized that the association between anxiety and asthma may differ according to sex, and we stratified all analyses by sex.

Methods

1. Subjects

A cross-sectional study was conducted in 2014 on all 46 elementary schools in Matsuyama City, a regional city in Japan with an approximate population of 500,000. Schools delivered self-administered questionnaires to the parents or guardians of the students. Parents or guardians of the students signed an informed consent form prior to participating in the survey. The response rate was 90.1%. Of the 24,296 students, students whose gender were not able to be determined were excluded; thus, 22,035 students remained. Moreover 6,544 of the responses obtained were excluded due to insufficient data on height, weight, and other items; therefore, total of 17,752 (51.5% male) students were included in the analysis. The study protocol was approved by the Juntendo Human Research Ethics Committee (#2014085).

2. Questionnaires

The self-administered questionnaire included questions regarding the student's asthma and anxiety, as well as biological variables such as age, height, and weight. The answers 'no' and 'yes' to the question 'Is your child diagnosed with asthma?' were defined as 'no asthma' and as 'having asthma', respectively. Anxiety

was evaluated using the emotional symptoms subscale of the Strength and Difficulties Questionnaire (SDQ). We also compared “younger” and “older” children based on school grade in order to examine the effect modification of age. Japanese elementary school consists of first to sixth grades as follows: first grade (6−7 years old), second grade (7−8 years old), third grade (8−9 years old), fourth grade (9−10 years old), fifth grade (10−11 years old), and sixth grade (11−12 years old). We defined children in the first to third grades as “younger” children and those in the fourth to sixth grades as “older” children. We estimated the genders of the students from their given names, and the students whose gender could not be determined were excluded from the analysis. Although estimating children’s gender from their given names might have led to misclassification, it is culturally easy in Japan to distinguish gender based on given names [18]. Therefore, we believe that we were able to appropriately identify gender with high accuracy. The Rohrer Index, which is a widely-used anthropometric statistic, was used to measure levels of obesity in children.

Assessment of Anxiety

The original SDQ was developed by Goodman as a brief behavioral screening tool for children, and is now available in various languages [16]. The SDQ can be answered by

parents, teachers, or children themselves [16]. In the present study, parents were asked to complete the questionnaire. The SDQ comprises 25 question items divided over five subscales: emotional symptoms (5 items), hyperactivity symptoms (5 items), conduct problems (5 items), peer relationship problems (5 items), and prosocial behavior problems (5 items) [19]. The Emotional Symptoms Scale is shown in Appendix 1. Possible responses to each item include “not true”, “somewhat true” or “certainly true”. Each item is scored 0 for “not true”, 1 for “somewhat true”, and 2 for “certainly true”. The total emotional symptoms score reflects the sum of the five items and ranges from 0 to 10 [19]. Matsuishi et al. previously validated the Japanese version of the SDQ and defined “normal”, “borderline”, and “clinical” (or “abnormal”) ranges for each subscale within the Japanese community-based normative sample to allow for accurate comparison across countries. In the Emotional Symptoms Scale, “normal” is defined as a score of 0 to 3, “borderline” as a score of 4, and “clinical” (or “abnormal”) as a score of 5 to 10 [16]. Since the cut-off point of 4 demonstrated 100% sensitivity for detecting generalized anxiety disorder in a study conducted on children in a Brazilian community [20], our study regarded an Emotional Symptoms Subscale score of ≥ 4 as an indication of anxiety symptoms.

Assessment of Overweight

The Rohrer Index (calculated as weight [kg]/height [cm]^3 $\times 10^7$) [21] was used to assess child obesity in the present study. This index is often used in school-based screening in Japan [22]. Since the Rohrer Index is calculated using only the factors of weight and height, it changes with age, and may underestimate obesity in school-aged children [22]. Although gender, age, and height-specific assessment (percent ideal body weight method) have more commonly been used to evaluate obesity in recent pediatric settings [22], we used the simpler Rohrer Index to assess child obesity in the present study. In general, children who have a Rohrer Index of 145 and over are considered to be overweight in Japan. Therefore, we defined children as overweight if they had a Rohrer Index ≥ 145 and non-overweight if they had a Rohrer Index <145.

3. Statistical methods

The prevalence ratio (PR) was estimated using the Poisson regression model for all subjects and for each gender in order to examine the association between asthma and anxiety. The “no asthma” group was used as a reference. Age, gender and Rohrer Index score were included in the multivariate analysis. We also conducted stratified analyses to examine the effect modification of gender and overweight status (Rohrer

Index<145 vs. ≥145) and age group (first to third grades vs. fourth to sixth grades) on the association between asthma and anxiety. All statistical analyses were performed using SAS version 9.4 software (SAS Institute Inc., Cary, NC, USA).

Results

Table 1 shows characteristics of all the subjects in this study. In all subjects, the mean age was 9.5 (SD±1.7) years old, the percentage of younger children was 48.9%, the mean score of the Rohrer Index was 124.1 (SD±15.2), and the prevalence of being overweight, having asthma, or having anxiety were, 9.3%, 6.0% and 7.8%, respectively. The prevalence of being overweight and having asthma was higher in boys than in girls (9.9%, in boys vs. 8.8% in girls for being overweight (P=0.01); 6.9% in boys vs. 5.0% in girls for having asthma (P<0.01)). The prevalence of anxiety was higher in girls than in boys (7.4% in boys vs. 8.3% in girls (P=0.03)).

Table 2 shows characteristics of subjects according to gender and the presence of asthma. The prevalence of anxiety in boys with “no asthma” and in boys “having asthma” was 7.1% (n=607) and 11.2% (n=71), respectively. Meanwhile, anxiety was present in 8.2% (n=671) of girls with “no asthma” and 9.8% (n=42) who had asthma.

Table 3 shows the PRs (95% Confidence Interval [CI]) for anxiety according to the presence of asthma. The multivariate PR (95% CI) of having anxiety in asthmatic compared to non-asthmatic children was 1.39 (1.15-1.68).

The multivariate PR (95% CI) was greater in boys, at 1.56 (1.21-1.99), compared with 1.19 (0.87-1.62) for girls, although the interaction was not significant (p for

interaction=0.17).

Table 4 shows that the association in boys was more evident in older than younger boys, where PR = 1.32 (0.93-1.88) for younger vs. 1.87 (1.32-2.64) for older boys (p for interaction=0.08); and in non-overweight boys than overweight, where PR = 1.64 (1.27-2.13) and 0.94 (0.41-2.19), respectively (p for interaction=0.22). In girls, no significant association was found in either younger or older girls, where PR = 1.07 (0.67-1.69) for younger vs. 1.30 (0.85-1.99) for older girls. In addition, no significant association was found in either non-overweight or overweight girls, where PR = 1.27 (0.92-1.76) and 0.66 (0.21-2.09), respectively (Appendix 2).

Discussion

In our study, asthma was significantly associated with anxiety among boys but not among girls. In the stratified analysis, asthma was significantly associated with anxiety only among non-overweight boys, but not among overweight boys, or either category of girls (overweight and non-overweight).

Asthma was associated with anxiety among children in the present study, which is consistent with previous findings [8]. Although the potential mechanisms underlying the association between asthma and anxiety remain unclear, some biological mechanisms have been considered. These include the activation of fear-based neural networks [23] or an activation of the suffocation alarm system [24] due to repeated attacks of breathlessness. Among asthmatic children, the occurrence of an asthma attack was associated with anxiety [25]. Thus, repeated breathlessness due to asthma attacks may cause abnormalities in the fear-based neural network or poor regulation of the suffocation alarm system in the central nervous system, which may then cause children to have an excessive fear of asthma symptoms. The excessive fear of an asthma attack may lead to anxiety.

On the other hand, there is some evidence that mental illness can contribute to the subsequent course of asthma [9]. One of the explanations for this association is the

dysregulation of the neurobiological stress response system. Children with mental illness show high autonomic nervous system reactivity, principally in the parasympathetic branch [26], which can cause a contraction of bronchial airways and lead to asthma. Psychological stress also causes the release of stress hormones [27], increase immune responses arising from helper T2 (Th2) cells [27], and induce IgE production and mast cell degranulation, which exacerbates allergic inflammation in asthma [27]. Given these mechanisms, it is conceivable that asthma and anxiety may have a bidirectional association.

Asthmatic children experience many difficulties on a daily basis, due to disease symptoms or treatment requirements. Children with asthma more often have an activity limitation due to their condition [4], causing them to miss more school days than children without asthma [4, 28]. In school, asthmatic children may have less friends to play with [29], may be more often confronted with "rejection by peers" [28] and more frequently experience bullying [29]. Physical activity provides an opportunity for social interaction, improvement in physical self-perceptions, and independence; all of which promote positive mental health [30]. Asthmatic children may lack equal opportunities to fully participate in those activities.

In the present study, the PRs (95% CI) of having anxiety in children with

asthma compared to those without tended to be higher in older boys. In a longitudinal study on adults, patients with longer elapsed time since their initial asthma diagnosis had a higher incidence of anxiety [31]. It can be expected that older asthmatic boys may have been diagnosed as asthmatic at a younger age. Older asthmatic boys may have experienced activity limitations for a longer time than younger asthmatic boys, which means the former may have felt stressed for a longer period. This may explain the higher prevalence of anxiety in this category. Therefore, our results suggest the importance of appropriate mental health assessment in older children with asthma and of the adequate management of asthma symptoms in younger asthmatic children to prevent future mental illness.

Boys and girls may perceive and respond to stress differently. Lahaye et al. suggested that boys with asthma are particularly vulnerable to difficulties in their psychological and social functioning [32]. In a prospective cohort study, Milam et al. also reported a strong dose-response relationship between parental stress at baseline, and child wheezing at the 1-year follow-up in boys, but not in girls [33]. Moreover, as stated above, asthmatic children are generally less active [4]. In children, the level of physical activity is inversely related to emotional functioning [13]. Although light physical activity has been shown to decrease peer problems in both boys and girls, more intense physical

activity may achieve this only in boys [34]. In contrast to boys, sedentary leisure-time activity (e.g. art activities) is also associated with fewer mental problems in girls [35]. Therefore, the limitation of physical activity may affect the child's stress, and the effect may be stronger in boys than in girls.

Although there were no significant interactions between asthma, anxiety and being overweight, the association between asthma and anxiety tended to be more evident among non-overweight students. Being overweight may thus have a potential effect on the association between asthma and anxiety.

The strengths of our study are the large sample size (as a result of recruiting all elementary school students in Matsuyama City) and the very high response rate (90%). We may therefore be able to generalize our findings to an Asian population.

There are some limitations in this study. First, we did not use the Diagnostics and Statistical Manual of Mental Disorder- 5 (DSM-5) [36] for the diagnosis of anxiety. Nonetheless, the SDQ has been diagnostically validated for parents identifying anxiety symptoms, as mentioned by Silva et al [20]. In our study, the prevalence of anxiety was 7.8%. This prevalence was similar to previous studies (i.e., 7.1% for the U.S. population [14], 6.0% to 6.2% for the Brazilian population [37]). Therefore, it may be appropriate to generalize our results to other populations. Second, there may have been a potential

misclassification of the diagnosis of asthma due to the dichotomous (yes/no) responses to the questionnaire. However, the prevalence of asthma in the present study was similar to that found in a general survey that used a similar asthma assessment [38]. Third, although a previous study showed that the occurrence of an asthma attack was associated with anxiety [25], we did not obtain information about the frequency of asthma attacks. Therefore, we were not able to examine the effect of asthma attack frequency on anxiety in the present study. Fourth, we were not able to consider the effects of other unknown factors (i.e., history of atopy, cigarette smoke exposure, preterm birth, rescue medication use) due to the lack of data. Fifth, as a cross-sectional study, any causal relations could not be shown. Hence, the associations between asthma, anxiety, and obesity need to be further confirmed in a longitudinal study.

Conclusion

This study demonstrated an association between asthma and anxiety among community-dwelling children in Japan. Comorbid mental illness in asthmatic children is associated with increased health care utilization and significantly higher health care costs compared to asthmatic children without comorbid mental illness [39]. Therefore, it is important to assess not only asthma symptoms but also mental status, particularly in older elementary school children.

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Conflicts of interest

The authors stated no conflict of interest regarding this manuscript.

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Table 1: Characteristics of the study subjects

	All	Boys	Girls	P value
N	17,752	9,138	8,614	
Age mean (SD)	9.5 (1.7)	9.5 (1.7)	9.5 (1.7)	0.55
Younger (grade=1 to 3) n(%)	8673 (48.9)	4499 (51.9)	4174 (48.1)	0.30
Rohrer Index mean (SD)	124.1 (15.2)	124.8 (15.3)	123.4 (15)	<0.01
Overweight*[a] n (%)	1,658 (9.3)	903 (9.9)	755 (8.8)	0.01
Asthma n (%)	1,062 (6.0)	632 (6.9)	430 (5.0)	<0.01
Anxiety*[b] n (%)	1,391 (7.8)	678 (7.4)	713 (8.3)	0.03

*[a] Rohrer Index ≥ 145, *[b] Emotional symptoms score ≥ 4

Table 2: Characteristics of the study subjects according to the presence of asthma

	All	Asthma (-)	Asthma (+)	P value
Boys				
N	9,138	8,506 (93.1)	632 (6.9)	
Age mean (SD)	9.5 (1.7)	9.5 (1.7)	9.4 (1.7)	0.03
Rohrer Index mean (SD)	124.8 (15.3)	124.7 (15.3)	126.1 (15.6)	0.03
Overweight*[a] n (%)	903 (9.9)	824 (9.7)	79 (12.5)	0.02
Anxiety*[b] n (%)	678 (7.4)	607 (7.1)	71 (11.2)	<0.01
Girls				
N	8,614	8,184 (95.0)	430 (5.0)	
Age mean (SD)	9.5 (1.7)	9.5 (1.7)	9.3 (1.7)	<0.01
Rohrer Index mean (SD)	123.4 (15)	123.3 (15)	125.3 (15.4)	<0.01
Overweight*[a] n (%)	755 (8.8)	711 (8.7)	44 (10.2)	0.27
Anxiety*[b] n (%)	713 (8.3)	671 (8.2)	42 (9.8)	0.25

*[a] Rohrer Index ≥ 145, *[b] Emotional symptoms score ≥ 4

Table 3: Prevalence Ratios (95% CI) for anxiety according to the presence of asthma

	Asthma (-)		Asthma (+)	
All				
Anxiety*[a] n (%)	1,278	(7.2)	113	(10.6)
Univariate model	1		1.39	(1.15-1.68)
Multivariate model1*[b]	1		1.39	(1.15-1.68)
Boys				
Anxiety*[a] n (%)	607	(7.1)	71	(11.2)
Univariate model	1		1.57	(1.23-2.01)
Multivariate model2*[c]	1		1.56	(1.21-1.99)
Girls				
Anxiety*[a] n (%)	671	(8.2)	42	(9.8)
Univariate model	1		1.19	(0.87-1.62)
Multivariate model2*[c]	1		1.19	(0.87-1.62)

*[a] Emotional symptoms score ≥ 4, *[b] Adjusted for age, sex, Rohrer Index, *[c] Adjusted for age, Rohrer Index

Table 4: Prevalence Ratios (95% CI) for anxiety according to the presence of asthma after stratification by age and overweight status among boys

	Asthma (-)		Asthma (+)	
Younger (grade=1 to 3)				
Anxiety*[a] n (%)	324	(7.8)	35	(10.3)
Multivariate model*[b]	1		1.32	(0.93-1.88)
Older (grade=4 to 6)				
Anxiety*[a] n (%)	283	(6.5)	36	(12.3)
Multivariate model*[b]	1		1.87	(1.32-2.64)
Overweight*[c] (-)				
Anxiety*[a] n (%)	541	(7.0)	65	(11.8)
Multivariate model*[b]	1		1.64	(1.27-2.13)
Overweight*[c] (+)				
Anxiety*[a] n (%)	66	(8.0)	6	(7.6)
Multivariate model*[b]	1		0.94	(0.41-2.19)

*[a] Emotional symptoms score ≥ 4, *[b] Adjusted for age, Rohrer Index, *[c] Rohrer Index ≥ 145

Appendix 1: The emotional symptom subscale of the Strengths and Difficulties Questionnaire

1. Often complains of headaches, stomach-aches or sickness
2. Many worries or often seems worried
3. Often unhappy, depressed or tearful
4. Nervous or clingy in new situations, easily loses confidence
5. Many fears, easily scared

Goodman R. The Strengths and Difficulties Questionnaire: a research note. J Child Psychol Psychiatry 1997; 38: 581-6.

Appendix 2: Prevalence Ratios (95% CI) for anxiety according to the presence of asthma after stratification by age and overweight status among girls

	Asthma (-)		Asthma (+)	
Younger (grade=1 to 3)				
Anxiety*[a] n (%)	319	(8.1)	19	(8.6)
Multivariate model*[b]	1		1.07	(0.67-1.69)
Older (grade=4 to 6)				
Anxiety*[a] n (%)	352	(8.3)	23	(11)
Multivariate model*[b]	1		1.30	(0.85-1.99)
Overweight*[c] (-)				
Anxiety*[a] n (%)	594	(8.0)	39	(10.1)
Multivariate model*[b]	1		1.27	(0.92-1.76)
Overweight*[c] (+)				
Anxiety*[a] n (%)	77	(10.8)	3	(6.8)
Multivariate model*[b]	1		0.66	(0.21-2.09)

*[a] Emotional symptoms score ≥ 4, *[b] Adjusted for age, Rohrer Index, *[c] Rohrer Index ≥ 145