The Association of Autism Spectrum Disorders and Symptoms of Asthma, Allergic Rhinoconjunctivitis and Eczema among Japanese Children Aged 3 - 6 Years

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Abstract

There is insufficient epidemiological evidence on the relationship between autism spectrum disorder (ASD) and allergic diseases. We performed a cross-sectional survey to elucidate the associations between them using validated screening tools. The participants were children aged 3 - 6 years attending kindergarten or nursery school in Shika Town, Japan (n = 417; valid response rate = 80.4%). Autism spectrum features were scored on the Social Communication Questionnaire (SCQ). Allergic symptoms (asthma, allergic rhinoconjunctivitis, and eczema) were determined according to the criteria of the International Study of Asthma and Allergies in Childhood. A total of 15 children (4.5%) had an SCQ score of 11 points or higher. The prevalence of symptoms was 14.7% for asthma, and 5.3% for allergic rhinoconjunctivitis, and 11.4% for eczema. Logistic regression indicated that symptoms of eczema were significantly associated with SCQ scores of 11 points or higher [odds ratio (OR), 4.38; 95% confidence interval (CI), 1.41 - 13.59]. The association persisted after adjustment for age, sex, and BMI (OR, 3.84; 95% CI, 1.20 - 12.24). Moreover, asthmatic symptoms were significantly associated with male sex (OR, 2.09; 95% CI, 1.12 - 3.92) and overweight status (OR, 2.45; 95% CI, 1.03 - 5.83). This suggests that higher SCQ scores, which imply more autism spectrum features, are associated with higher prevalence of eczema symptoms. While no causal relationships can be made, ASD might be associated with

eczema.

1. Introduction

Autism spectrum disorder (ASD) is a group of developmental disorders characterized by both persistent deficits in social communication and social interaction across multiple contexts and restricted, repetitive patterns of behavior, interests, or activities [1]. The aforementioned symptoms must also be present in the early developmental period. On the other hand, allergies are hypersensitivity disorders of the immune system in which both innate and acquired immunities may contribute to the development of allergic diseases (*i.e.*, asthma, allergic rhinoconjunctivitis and eczema) [2] [3]. Although the cause of ASD remains unknown in many cases [4], recent observational studies have demonstrated that allergic diseases were more frequently seen in children with ASD compared to typically developing children, suggesting involvement of environmental factors in the development of both diseases [5]-[10]. For example, our previous study [11] found a significant association between nasal allergy and high autism score using the Autism Screening Questionnaire (ASQ) among Japanese children aged 3 - 5 years old [12]. An analysis of the National Health Insurance Database in Taiwan by Chen *et al.* revealed that atopic diathesis in early childhood elevated the future risk of developing ASD [13]. A meta-analysis by Miyazaki *et al.* reported that there was a significantly higher estimated prevalence of asthma and allergic rhinoconjunctivitis in children with ASD compared to typically developing children [14]. However, in an American study, Jyonouchi *et al.* reported that an ASD group was not associated with atopic/non-atopic asthma, allergic rhinitis, and atopic dermatitis [5]. The controversial reports in the literature and limited epidemiological evidence therefore render the association between allergic disease and ASD unclear.

Although the prevalence of ASD remains unknown in Japan due to the lack of large epidemiological studies, the prevalence of ASD is estimated to be on the increase all over the world [15]. It is estimated that the prevalence of ASD is about 1.5% of children in the U.S. [16], and 2% of children in the general population in Korea [17]. The prevalence of allergic diseases has also increased rapidly over the last few decades in developing countries, including Japan [18] [19]. Therefore, the concomitant increases of both ASD and allergic diseases represent a potentially important and unique public health burden.

Until now, prevalence and risk factors for allergic diseases have been studied extensively in school age children but there is little information about younger children. Moreover, few epidemiological studies have examined the association

between allergic diseases and ASD, especially among younger children. Another limitation of the recent epidemiological studies on allergic diseases in ASD children is that they investigated diagnosed ASD only which is not necessarily ideal in epidemiological surveys for young children. It is estimated that ASD affects approximately 2% of children in the general population and more than half of the cases are undiagnosed and untreated [17]. Moreover, in a Japanese nationwide survey of adults with high-functioning ASD, they were first diagnosed at an average age of 10 years [20]. Thus, there is a high probability of missing possible ASD cases if employing only the diagnosed cases in surveying early childhood morbidity. In addition, comprehensive diagnostic assessment is often expensive and time-consuming work completed by a multidisciplinary team of professionals [21], and this can be stressful for children being assessed as well as their parents. Screening method improvements could thusly decrease the specific problem of diagnostic bias due to gaps in socioeconomic status or access to medical services [22] [23].

In this paper, we describe the prevalence of symptoms of asthma, allergic rhinoconjunctivitis and eczema and clarify the association between allergic symptoms and autism spectrum features. Data were gathered with an epidemiological approach using validated screening tools in rural, Japanese, preschool-aged children (3 - 6 years). To assess autism spectrum features in these children, we used the Social Communication Questionnaire (SCQ) [24], formerly known as ASQ. For allergic diseases, we used a standardized questionnaire of the International Study of Asthma and Allergies in Childhood (ISAAC) [18] [19] [25] [26]. We hypothesized that the prevalence of allergic symptoms would be higher in children with autistic spectrum features than those without. We also investigated potential risk factors associated with allergic symptoms and ASD, including sex, age, and body mass index (BMI). These results could serve as guidelines for prevention and treatment of allergic diseases in children with ASD.

2. Materials and Methods

2.1. Subjects and Sampling

Our cross-sectional questionnaire-based survey was conducted in Shika Town, Ishikawa prefecture, Japan. Shika is a rural town located in the Noto peninsula with a total population of almost 22,500. The Shika study is an ongoing population-based survey which aims to investigate the lifestyle and health status of the Japanese population [27] [28]. This survey was conducted from October to November, 2013. The self-administered questionnaires and envelops were distributed for each child at all 7 preschools (1 kindergarten and 6 nursery schools) in the towns, with the parents then taking it home to be filled out. Prior to filling out the questionnaire, all participants in the study provided informed consent. The children's parents completed the questionnaire. The number of children (n = 417) accounted for 99.0% of the total population of 3- to 6-year-old children in the town (n = 421) in 2013. The questionnaire was written in Japanese

and comprised questions about sex, age, height, weight, symptoms on allergic diseases and the SCQ. After completing the form, the questionnaires were taken back to the kindergartens and nursery schools for collection and returned to our university. In the returned 406 questionnaires, there is no missing data on variables age, sex, height and weight. Regarding the SCQ, forms with more than four items missing were excluded from the statistical analysis (n = 61). Moreover, forms with missing data on allergic symptoms were excluded (n = 4), leaving a total sample of 341 and a valid response rate of 81.8%. Of the 341 children analyzed, 46.6% were male (n = 159). Their age distribution was 11.7% for 3-year-old (n = 40), 33.4% for 4-year-old (n = 114), 36.1% for 5-year-old (n = 123), and 18.8% for 6-year-old (n = 64). A median age ± SD was 4.6 ± 0.9 years old. A mean ± SD height was 106.4 ± 7.4 cm, and a mean ± SD weight was 17.7 ± 3.3 kg.

2.2. Screening Tool for ASD

The SCQ lifetime Japanese version was used [24] [29]. It is a parent-report questionnaire designed to screen children who may need a more comprehensive evaluation because of possible ASD. It is composed of 38 items that assess specific ASD-related behaviors, such as communication with other children and nonverbal contact. It is based on the Autism Diagnostic Interview—Revised (ADI-R) algorithm [30], which is accepted as a standardized interview-based diagnostic instrument. The SCQ assesses the three core areas of functioning characteristic of youth with ASD; reciprocal social interaction, language and communication, and repetitive and stereotyped patterns of behavior. The SCQ is one of the most widely used and studied screening instruments for identifying individuals at risk for ASD [31] [32] [33] [34] [35]. In the Japanese version, a question on pronoun reversal is omitted because Japanese verbal language seldom uses a pronoun (*i.e.* "you" or "s/he"). Each item was rated on a two-point scale (0 = "no" and 1 = "yes") and the range of possible scores is 0 to 38, with higher scores indicating more autistic symptomatology. Several clinical cutoff scores of the SCQ have been suggested so far (e.g. 11, 12, 15 or higher), and researchers appear to agree optimal cut-off score is dependent upon the context and nature of the study population. Among young children, a lower cut-off score is recommended [31] [32] [36]. Thus, we categorized children into 2 groups: children with SCQ scores ≥ 11 as possible ASD cases and children with SCQ scores <11 as non-ASD cases.

2.3. Measurement of Allergic Symptoms

We used the Japanese version of the ISAAC written questionnaire for 6 - 7 year olds [37]. ISAAC is an international epidemiological research program established in 1991 and formally closed in 2012. The questionnaire was originally developed to assess the worldwide prevalence of asthma, allergic rhinoconjunctivitis and eczema among children aged 6 - 7 years in the general population and to

search possible risk factors that could affect allergic diseases. However, it is now used for younger children in multiple studies [38] [39] [40] [41] [42].

Symptoms of asthma were estimated by positive answers to the following two questions: "Has your child ever had wheezing or whistling in the chest at any time in the past?" and "Has your child had wheezing or whistling in the chest in the past 12 months?" Affirmative answers to the following three questions were required to confirm the presence of symptoms of allergic rhinoconjunctivitis: "Has your child ever had a problem with sneezing, or a runny, or blocked nose when he/she did not have a cold or the flu?", "In the last 12 months, has your child had a problem with sneezing, or a runny, or blocked nose when he/she did not have a cold or the flu?" and "In the past 12 months, has this nose problem been accompanied by itchy/watery eyes?". Symptoms of eczema were defined as present in the case of positive responses to all the following three questions: "Has your child ever had an itchy rash which was coming and going for at least six months?", "Has your child had this rash at any time in the past 12 months?" and "Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes?".

2.4. Weight Abnormalities

BMI was calculated as body weight in kilograms divided by height squared in meters. International age- and sex-specific cutoff points for BMI as defined by the International Obesity Task Force (IOTF) were used to define underweight, normal weight, and overweight [43] [44] [45]. These cutoff points are linked to the widely accepted adult BMI cutoff points of 18.5 for underweight, and 25 for overweight. Obesity was not defined in this study because of the small proportion of obesity in Japanese children (*i.e.*, 2.38% of boys and 2.49% of girls in 2013) [46].

2.5. Statistical Analysis

We evaluated differences between variables of interest within each of the three allergy symptoms, using chi-square or Fisher's exact testing for categorical variables (SCQ dichotomized by cutoff score, sex and categories of BMI), t-tests for continuous variables with normal distribution (age), and Mann-Whitney U tests for continuous variables with non-normal distribution (total SCQ score). We performed univariate logistic regression analyses to calculate the unadjusted odds ratios (OR) and the 95% confidence intervals (CI) and reported the crude association of variables with likelihood of each allergic symptom (positive = 1, negative = 0). Furthermore, we performed forced entry methods of three separated multivariate logistic regression analyses. All statistical tests were two-tailed. P values less than 0.05 were regarded as indicating statistical significance. IBM SPSS for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA) was used for all statistical analyses.

2.6. Ethical Approval

We obtained informed consent for study participation from the parents. All procedures performed in studies involving human participants were in accordance with the ethical standards of both institutional and national research committees and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethical approval to conduct the present study was received from the Kanazawa University Medical Research Ethics Committee (reference number: 1464).

3. Results

Figure 1 demonstrates the range and distribution of the total SCQ scores of the 341 children. The data had a range of 0–20, with a mean (standard error: SE) of 3.66 (0.19). The distribution was not normal, and was skewed to the right (skewness = 1.67, kurtosis = 3.48). In the present sample, 15 children (4.5%) had SCQ scores ≥ 11.

Table 1 summarizes the characteristics of children, classified by each allergic symptom. A total of 50 (14.7%) children reported a symptom of asthma, 18 (5.3%) reported a symptom of allergic rhinoconjunctivitis, and 39 (11.4%) reported a symptom of eczema. Compared to girls, boys were significantly more likely to have a symptom of asthma (p = 0.018). The prevalence of a symptom of eczema was 33.3% for children with SCQ score ≥ 11% and 10.4% for children with SCQ score < 11 with this difference showing statistical significance (p = 0.019). We performed post hoc test and revealed the statistical power $(1-\beta)$ was 0.63. There were no statistically significant differences within total SCQ score age and BMI categories between two groups divided by allergic symptoms.

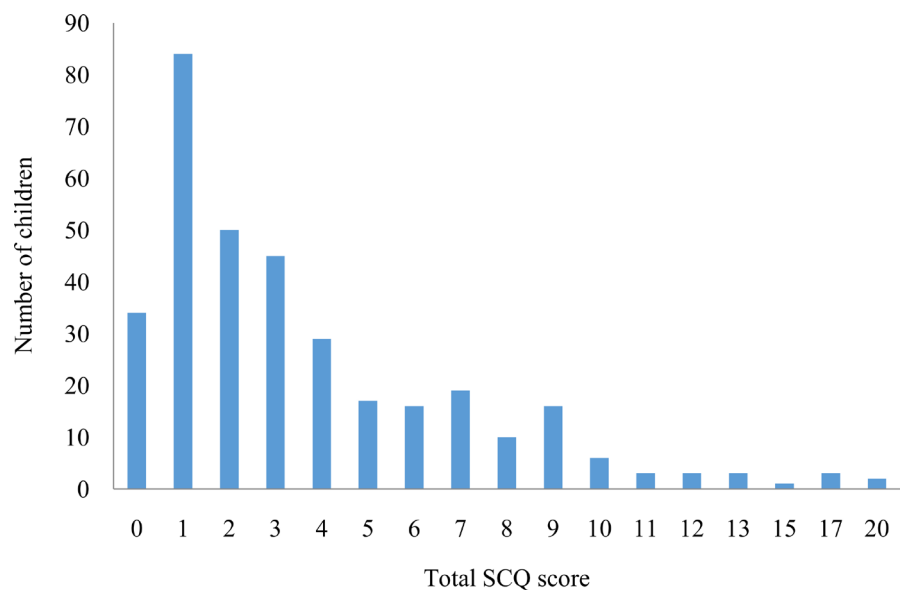ORs and 95% CIs for symptom of asthma, rhinoconjunctivitis and eczema

Figure 1. The range and distribution of total SCQ scores among children aged 3 - 6 years in Shika Town (n = 341).

Table 1. Characteristics of the children stratified by positive symptoms of asthma, rhinoconjunctivitis, and eczema (n = 341).

	Asthma symptom			Allergic rhinoconjunctivitis symptom			Eczema symptom		
	Positive	Negative	*p* value	Positive	Negative	*p* value	Positive	Negative	*p* value
	50 (14.7%)	291 (85.3%)		18 (5.3%)	323 (94.7%)		39 (11.4%)	302 (88.6%)	
SCQ score, mean (SE)									
Continuous	4.03 (0.52)	3.61 (0.21)	0.412[a]	4.89 (1.02)	3.60 (0.19)[a]	0.161[a]	4.71 (0.84)	3.54 (0.19)	0.671[a]
SCQ score, n (%)									
11 or higher	3 (20.0%)	12 (80.0%)	0.469[b]	2 (15.4%)	13 (84.6%)	0.184[b]	5 (33.3%)	10 (66.7%)	0.019[b]
Under 11	47 (14.4%)	279 (85.6%)		16 (4.9%)	310 (95.1%)		34 (10.4%)	292 (89.6%)	
Age, mean ± SD									
Continuous	4.70 ± 0.91	4.60 ± 0.92	0.500[c]	4.56 ± 0.71	4.62 ± 0.93	0.765[c]	4.41 ± 0.88	4.65 ± 0.92	0.133[c]
Gender, n (%)									
Boy	31 (19.5%)	128 (80.5%)	0.018[d]	10 (6.3%)	149 (93.7%)	0.435[d]	19 (11.9%)	140 (88.1%)	0.781[d]
Girl	19 (10.4%)	163 (89.6%)		8 (4.4%)	174 (95.6%)		20 (11.0%)	162 (89.0%)	
BMI, n (%)									
Underweight	8 (14.5%)	47 (85.5%)	0.144[d]	2 (3.6%)	53 (96.4%)	0.779[b]	9 (21.1%)	46 (15.1%)	0.448[d]
Normal weight	33 (13.1%)	218 (86.9%)		15 (6.0%)	236 (94.0%)		26 (68.4%)	225 (74.9%)	
Overweight	9 (25.7%)	26 (74.3%)		1 (2.9%)	34 (97.1%)		4 (11.4%)	31 (88.6%)	

SCQ: Social Communication Questionnaire; SE: standard error; SD: standard deviation; BMI: body mass index. a. Mann-Whitney U test; b. Fisher's exact test; c. T test; d. Chi square test.

Table 2. Results of logistic regressions on positive symptoms of asthma by SCQ score and other variables.

	Asthma symptom					
	Unadjusted			Adjusted		
	OR	95%CI	*p* value	OR	95%CI	*p* value
SCQ score (vs Under 11)						
11 or higher	1.46	(0.40 - 5.38)	0.567	1.26	(0.32 - 4.87)	0.741
Age						
Continuous	1.12	(0.81 - 1.56)	0.490	1.07	(0.76 - 1.49)	0.709
Gender (vs Girl)						
Boy	2.06	(1.11 - 3.81)	0.022	2.09	(1.12 - 3.92)	0.021
BMI (vs Normal Weight)						
Underweight	1.17	(0.51 - 2.70)	0.714	1.11	(0.48 - 2.60)	0.808
Overweight	2.37	(1.02 - 5.51)	0.046	2.45	(1.03 - 5.83)	0.043

OR: odds ratio; CI: confidence interval: SCQ: Social Communication Questionnaire; BMI: Body mass index.

corresponding to other variables are shown in Tables 2-4, respectively. In the crude model, children with an SCQ score of 11 points or higher were more likely to have eczema compared to other children (OR = 4.38; 95 % CI = 1.41 - 13.59;

Table 3. Results of logistic regressions on positive symptoms of rhinoconjunctivitis by SCQ score and other variables.

	Rhinoconjunctivitis symptom					
	Unadjusted			Adjusted		
	OR	95% CI	*p* value	OR	95% CI	*p* value
SCQ score (vs Under 11)						
11 or higher	2.94	(0.61 - 14.16)	0.178	3.32	(0.66 - 16.72)	0.146
Age						
Continuous	0.93	(0.55 - 1.55)	0.770	0.94	(0.56 - 1.58)	0.805
Gender (vs Girl)						
Boy	1.44	(0.56 - 3.76)	0.451	1.47	(0.56 - 3.85)	0.439
BMI (vs Normal Weight)						
Underweight	0.61	(0.14 - 2.77)	0.526	0.54	(0.12 - 2.49)	0.427
Overweight	0.48	(0.06 - 3.71)	0.478	0.43	(0.05 - 3.45)	0.425

OR: odds ratio; CI: confidence interval: SCQ: Social Communication Questionnaire; BMI: body mass index.

Table 4. Results of logistic regressions on positive symptoms of eczema by SCQ score and other variables.

	Eczema Symptom					
	Unadjusted			Adjusted		
	OR	95% CI	*p* value	OR	95% CI	*p* value
SCQ score (vs Under 11)						
11 or higher	4.38	(1.41 - 13.59)	0.011	3.84	(1.20 - 12.24)	0.023
Age						
Continuous	0.74	(0.51 - 1.08)	0.115	0.77	(0.53 - 1.12)	0.171
Gender (vs Girl)						
Boy	1.15	(0.59 - 2.26)	0.683	1.17	(0.59 - 2.34)	0.655
BMI (vs Normal Weight)						
Underweight	1.53	(0.65 - 3.60)	0.328	1.35	(0.56 - 3.25)	0.504
Overweight	1.15	(0.38 - 3.52)	0.808	1.06	(0.34 - 3.38)	0.916

OR: odds ratio; CI: confidence interval: SCQ: Social Communication Questionnaire; BMI: body mass index.

p = 0.011) (Table 4). When the model was adjusted for age, sex and BMI categories, the association remained statistically significant (OR = 3.84; 95% CI = 1.20 - 12.24; p = 0.023). In the adjusted model, being male (OR = 2.09; 95% CI = 1.12 - 3.92; p = 0.021) and overweight (OR = 2.45; 95% CI = 1.03 - 5.83; p = 0.043) were shown to be statistically significantly related to asthma (Table 2). Overall, allergic rhinoconjunctivitis was not associated with SCQ classification, age, sex, and weight abnormalities.

4. Discussion

In 2013, we examined the prevalence of asthma, allergic rhinoconjunctivitis and

eczema among children in kindergarten and nursery schools in Shika Town, Japan. Furthermore, we found that preschool-aged children with autism spectrum features had an increased likelihood of suffering from symptom of eczema. A statistically significant association persisted after adjusting for age, sex, and BMI categories. To our knowledge, this is the first study using validated screening measures that shows a higher prevalence of eczema symptoms in children aged 3 - 6 years with autism spectrum features compared to those without. This seminal result may be due to the effective simplicity of screening tools such as the ISAAC questionnaire and SCQ. While the cross-sectional nature of the study makes a causal conclusion impossible, the theory that autism spectrum traits would be related to eczema is supported. In contrast, we did not confirm any results from recent studies which suggest that asthma or allergic rhinoconjunctivitis are associated with ASD.

Among the participants analyzed, 4.4% (n = 15) were presumed to have ASD suggesting that some cases with SCQ scores ≥ 11 were false positives. We recognized that the SCQ could not be a replacement for a clinician-verified diagnosis and we acknowledge, as illustrated in Figure 1, that it is difficult to clearly distinguish possible ASD cases from others by screening tools. However, Sivertsen *et al.* employed the Autism Spectrum Screening Questionnaire in their study and argued that a strict categorical diagnosis would not be useful in epidemiological studies because ASD is a spectrum problem [47]. Johnson *et al.* pointed out that children with false positive screens are a high risk group for other neuro-cognitive and behavioral impairments and further assessment would be beneficial [48]. Thus, we considered that the prevalence subsumed borderline ASD cases, not implying a marked overestimate. The identification of undiagnosed and untreated ASD is important, with the potential to help parents increase knowledge of ASD and improve interaction with their children from earlier ages [49].

Epidemiological study of allergic symptoms using the ISAAC questionnaire among Japanese preschool age children is scarce in the literature. We compared the present results from Shika Town (asthma, allergic rhinoconjunctivitis, eczema; 14.7%, 5.3%, 11.4%) with those obtained using the same questionnaire in the Ogasawara Islands, and Setagaya, Japan. The prevalence of asthma symptoms found in this study was higher than the study of preschool children conducted in the Ogasawara Islands (asthma, 12.2%) [50]. The prevalence of three allergic disease symptoms found in this study was lower than in the study of 6-year-old school children conducted in Setagaya (asthma, allergic rhinoconjunctivitis, eczema; 18.2%, 19.7%, 19.6%) [51]. It is well known that asthma is more prevalent in urbanized areas as air pollution is one of the environmental factors that can exacerbate asthma. Differences in pollution levels might explain why the prevalence of current wheezing in Shika Town was higher than the Ogasawara Islands (less populated area) and lesser than Setagaya (one of the most populated area in Japan).

The prevalence of allergic rhinoconjunctivitis was only 5.3% in this study. The

prevalence of allergic rhinoconjunctivitis in general population is reported to be more than 10% in recent studies of school children in developed countries [18]. Allergic rhinoconjunctivitis generally develops with gradual aeroallergen sensitization with seasonal allergens, mainly with cedar pollen or house dust mites in Japan [52]. Its prevalence peaked at 10 years old [51]. Therefore, the low prevalence of allergic rhinoconjunctivitis in this study is plausible.

Our findings are consistent with recent studies that found eczema was significantly more prevalent in children with ASD compared to children without ASD [13] [53] [54]. We could not find significant associations of autism spectrum features with asthma or allergic rhinoconjunctivitis. At present, explanations for the mechanisms driving the high prevalence of allergic diseases in children with ASD remain speculative. One possible explanation is that eczema symptoms affected SCQ total scores because the SCQ is a scale that assesses not only social interaction and communication but also behavioral symptoms. The discomfort and pain associated with allergic diseases would aggravate behavioral symptoms in children with ASD [55]. Jyonouchi pointed out that eczema tends to be underdiagnosed in ASD children because symptoms could be masked by associated behavioral problems [5]. Due to the cross-sectional design of our study, a cause-effect relationship between allergic symptoms and high SCQ score could not be determined. A future longitudinal study is therefore required to address this issue.

It should also be noted that our results suggested a significant association between obesity and asthmatic symptoms. The result is consistent with survey in Japan [56] and a meta-analysis of prospective epidemiological studies by Beuther and Sutherland showing a higher prevalence of asthma in overweight/obese people [57]. It is also well known that asthma is more likely to occur in boys compared to girls [58]. ASD has the same tendency as asthma in regard to weight abnormalities and sex: ASD is often associated with obesity and more prevalent in boys [39] [59] [60] [61] [62]. However, there are few studies investigating ASD and BMI in Japan. By investigating the differences in BMI and sex more deeply it might elucidate the cause(s) of ASD.

This study had methodological strengths. Study subjects were homogeneous with the same residential background. We realized a high valid response rate (81.8%), surveyed 99% of the whole area population and minimized selection bias. The definitions of asthma, allergic rhinoconjunctivitis, and eczema were based on the ISAAC questionnaire which has been validated and used worldwide, however, it should be noted that wheezing in young children is not necessarily caused by allergies [63]. The definition of BMI categories were based on IOTF (now known as World Obesity) guidelines. Although a study in Belgium showed the inaccuracy of parentally reported weight and height for classifying preschool-aged children into BMI categories [64], in Japan, physical measurements are generally carried out monthly at preschools. Thus, we consider the BMI values in this study to be precise.

Limitations of the present study other than mentioned above need to be noted. First, the main limitation of our study is the sample size of 417 children, which might not be large enough to identify significant differences of allergic symptoms between children with possible ASD and those without. The relatively small number of children with SCQ score ≥ 11 suggests type II error, which restricts the power to detect relevant predictors. A careful interpretation of our findings is required in light of this. Future investigations with a larger sample could reveal significant relationships among allergic diseases and ASD. Second, we could not measure all variables that are likely to be a confounder in the association between allergic diseases and ASD (e.g. maternal status in pregnancy, or dietary habit). Third, we could not collect data from children who did not go to preschools. Children with severe behavioral problems might have been refused admission. Fourth, there is seasonal variation in reporting of allergic symptoms even though the questions asked about symptoms during the past year [65]. Finally, the extrapolation of conclusions from our study to other ethnicities/ cultures is limited by the fact that the participants were ethnically and culturally homogeneous.

5. Conclusion

Despite these limitations, this is the first study that used validated screening tools to assess the association between ASD and allergic symptoms in a general Japanese early childhood population. The study adds evidence that young children with possible ASD are more likely have eczema symptoms compared to others. These seminal results offer important clues to environmental influences on ASD and allergic diseases. Future studies using larger samples with a longitudinal design are needed to better characterize the causal association between ASD and allergic diseases.

Acknowledgements

Competing Interest

The authors declare that they have no competing interests.

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