



Epidemiological study on the involvements of environmental factors and allergy in child mental health using the Autism Screening Questionnaire[☆]

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ABSTRACT

Although autism is now recognized as being very common (Buie et al., 2010) and as developing due to not only genetic but also environmental factors, there is insufficient epidemiological evidence on the relationship between autism and allergy. In this study, therefore, we attempted to clarify the association of environmental factors with autism and allergy using a population-based epidemiological study and to propose a newly developed screening method with improved validity by determining the relationship between ASD (autism spectrum disorders) subscales. We examined the association among autistic score from the Autism Screening Questionnaire (ASQ Japanese version), living environment factors, and allergic disease in 1407 children aged 3–5 years old. We recognized that children with higher ASD score have significantly higher prevalence of nasal allergy and associated with significantly factors of boy and first in terms of birth order and maternal smoking. In addition, nasal allergy were observed to be associated with “reciprocal social interaction”, “language and communication”, and “repetitive and stereotyped patterns of behaviors” as subscales of ASD. These results suggest that autism in children were closely related to allergy and environmental factors. Investigation of allergy symptoms in addition to subscale of ASD seem to enable more efficient screening of autism tendency at an earlier stage.

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Autism spectrum disorders (ASD) (Noterdaeme & Hutzelmeyer-Nickels, 2010) are pervasive developmental disorders (PDD) (Palmen & van Engeland, 2004) with neurological origins (Akshoomoff, Pierce, & Courchesne, 2002; Bailey et al., 1995; Brambilla et al., 2003; Courchesne, Redcay, & Kennedy, 2004; Palmen & van Engeland, 2004). Autism is not a disease but a syndrome with multiple non-genetic and genetic causes (Muhle, Trentacoste, & Rapin, 2004). The symptoms of autism vary substantially and those affected range from individuals with severe disorders to those without mental disabilities. Although it is considered to have previously been rare, autism is now recognized as a common condition (Movsas & Paneth, 2012; Schieve et al., 2012). The increase in ASD prevalence in recent years is partly due to changing diagnostic criteria, which has resulted in an increase in children with possible autism or borderline autism (Charman et al., 2009). Furthermore,

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accumulated evidence has demonstrated that not only genetic but also environmental factors are involved in the development of ASD (Hussain, Woolf, Sandel, and Shannon, 2007). Indirect evidence for an environmental contribution to autism comes from studies demonstrating the sensitivity of the developing brain to external exposures such as to lead, ethyl alcohol, and methyl mercury (Landrigan, 2010). Epigenetic research has also identified maternal factors as potential causes of autism (Muhle et al., 2004) and that the expression of the autism gene(s) may be influenced by environmental factors (Johnson, Myers, & American Academy of Pediatrics; Council on Children with Disabilities, 2007). Although many studies have examined the relationship between environmental factors and acquired factors such as maternal smoking and sleep duration and autism, the precise involvements of environmental factors in autism remain to be elucidated. In addition, some study reported that allergy is frequently encountered in children with autism (Mir, Panjabi, & Shah, 2012). Magalhães et al. (2009) reported that the frequency of atopic dermatitis, asthma and predominantly rhinitis were increased in Asperger patients compared to healthy controls. Jyonouchi et al. (2011) suggested that the discomfort and pain associated with allergic diseases could aggravate behavioral symptoms in ASD children. Feitosa et al. (2011) observed an association between behavioral problems and pediatric asthma, suggesting the need to include mental health care in the provision of services for asthma morbidity. Thus, autism and allergy can coexist as health problems in childhood, which can aggravate their individual impacts. Another explanation for allergy as a comorbidity of autism is that environmental factors are common risk factors for both autism and allergy. Furthermore, it has proposed that allergy itself is a risk factor for autism, and vice versa (Jyonouchi et al., 2011). Not only physical constitution and genetic predisposition, but also eating habits, nutrition (Pallapies, 2006; Staple & Teach, 2011), and lifestyle factors (Feitosa et al., 2011), which are related to autism, are thought also to be associated with the development of allergic diseases such as atopic dermatitis. Although environmental risk factors may contribute to the development of both autism and allergy, there is insufficient epidemiologic evidence for this relationship. In this study, therefore, we attempted to clarify the association of environmental factors and acquired factors such as maternal smoking, sleep duration and birth order with autism and allergy using a population-based epidemiological approach. With this goal, we examined the association among autistic score from the Autism Screening Questionnaire (ASQ Japanese version), living environment factors, and allergic disease in children aged 3–5 years old. The association between ASD subscales, environmental factors, and allergy has not been investigated to date. Therefore, the second aim of this study is to examine the relationship between ASD subscale and related factors including allergy.

1. Method

1.1. Participants

We asked the caregivers of 2357 children aged 3–5 years, who went to 18 kindergartens and 11 nursery schools selected out of 38 kindergartens and 112 nursery schools in Kanazawa city, to complete self-administered questionnaires. A total of 1409 children (kindergarten $n = 1073$, nursery school $n = 333$, response rate 59.7%) whose caregivers gave their informed consent participated in this study. The subjects were 8.7% of the population of 16,238 3- to 5-year-old infants in Kanazawa city. Ethical approval to conduct the present study was received from the Kanazawa University Medical Research Ethics Committee. This investigation was performed from September to November, 2009.

1.2. Investigation items

The self-rating questionnaire was used to investigate characteristics about the child (age, gender, height, weight, number of siblings, birth order, sleep duration, diet habit, diet preference, educational institution), family environment (family size, maternal smoking, mother with job), living environment (age of house, traffic volume, heating appliance, have a pet), lifestyle, and allergic symptoms.

1.3. Questionnaire

Questionnaires regarding allergic disease (asthma, nasal allergy, Japanese cedar pollinosis, eczema) were completed according to the diagnosis of a medical doctor. Japanese version of the Autism Screening Questionnaire (ASQ Japanese version: Dairoku et al.) was used: this is the Japanese version of the ASQ, which was first developed by Berument, Rutter, Lord, Pickles, and Bailey (1999), with 39 questions, covering social skills, communication, attention to detail, and imagination as subcategories. The validity and reliability of the ASQ Japanese version were recognized to be high enough to screen autism when the cutoff point is set a high score of 13 points (Dairoku et al.). The responses to each item in the subcategories is scored using 0 or 1 according to the answer “yes” or “no” (Berument et al., 1999). Higher scores indicate higher ‘autistic’ traits.

1.4. Statistical analysis

In analyzing environmental factors, such as characteristics of the child, family and living environment, lifestyle, and allergic symptoms, we dichotomized results, dividing each factor into two categories (yes or no; more or less; higher or lower). We showed the age-specific ASD score of the participant in Table 1. After classifying ASD score into two categories

Table 1

The number of children by ASD score and age.

ASD score	Age (years)							
	3 (N = 485)		4 (N = 480)		5 (N = 444)		Total (N = 1409)	
	N	%	N	%	N	%	N	%
0–1	123	(25.4%)	147	(30.7%)	133	(29.9%)	403	(28.6%)
2–3	114	(23.5%)	122	(25.4%)	117	(26.3%)	353	(25.0%)
4–5	105	(21.6%)	87	(18.1%)	90	(20.3%)	282	(20.1%)
6–7	74	(15.3%)	60	(12.6%)	50	(11.3%)	184	(13.1%)
8–12	62	(12.8%)	48	(10.0%)	43	(9.7%)	153	(10.8%)
13–33	7	(1.4%)	16	(3.2%)	11	(2.5%)	34	(2.4%)

(higher value ≥ 8.0 and lower value < 8 points), we examined the relationship between the factors and ASD statistically using Chi-square test. Furthermore, we used the forced entry method of multiple logistic regression analysis to examine the contribution of each factor to ASD classification. In multiple logistic analysis, we used dichotomy as independent variables where dichotomy in variables such as maternal age (34 years old) and sleep duration (10 h) were set average scores. Statistical analysis was performed using SPSS (IBM SPSS Statistics) version 19.0 for Windows. All statistical tests were two-tailed. *p* values less than 0.05 were regarded as indicating statistical significance.

2. Results

2.1. Age-specific ASD score and proportion of prevalence of allergy

Table 2 shows the characteristics of the study participants. ASD scores in those aged 3, 4 and 5 years old were 4.11 ± 3.47 (mean $\pm$ SD), 3.83 ± 3.69 , and 3.67 ± 3.62 , respectively, with no statistically significant difference. Asthma was seen in 53 (11.0%), 54 (11.3%) and 58 (13.4%) children among those aged 3, 4 and 5 years old, respectively; there was no significant difference among the age groups. Nasal allergy was seen significantly less frequently in 48 (9.9%) 3-year-old children than in 82 (17.2%) 4-year-old and 76 (17.4%) 5-year-old children ($p < 0.01$). Conversely, 47 (10.8%) 5-year-old children showed Japanese cedar pollinosis, which was more frequent than in the other groups ($p < 0.01$).

2.2. Association between ASD and other factors

Chi-square test showed significant relationships between ASD classification (8 points or more vs less than 8 points) and environmental factors of children and allergic disease (asthma, nasal allergy, Japanese cedar pollinosis, eczema) (Table 3). Regarding 3-year-old children, we recognized significant relationships between ASD score and first in terms of birth order ($p < 0.01$), family size ($p < 0.05$) and nasal allergy ($p < 0.001$). The proportion of children that were nasal allergy with an ASD score of 8 points or more (23.2%) was significantly greater than that for those with a score of less than 8 points (7.7%). Similarly, the proportions of children with small family size and nasal allergy showing an ASD score of 8 points or more were significantly greater than those with a score less than 8 points.

Regarding 4-year-old children, the proportions of boys ($p < 0.01$), and short sleep duration ($p < 0.05$), first in terms of birth order ($p < 0.05$), children with maternal smoking ($p < 0.001$), and Japanese cedar pollinosis ($p < 0.05$) showing an ASD score of 8 points or more were significantly greater than those with a score less than 8 points. Regarding 5-year-old children, the proportions of boys ($p < 0.05$), and no sibling ($p < 0.05$) were significantly greater than those with a score less than 8 points.

In total children, we recognized a significantly higher proportion of children with an ASD score of 8 points or more than those with a score of less than 8 points.

Table 2

ASD scores and numbers of children with allergic symptoms by age.

Age	ASD score		Allergy											
	N	Mean $\pm$ SD	Asthma				Nasal allergy [*]				Japanese cedar pollinosis [*]			
			(+)		(-)		(+)		(-)		(+)		(-)	
			N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
3	485	4.11 ± 3.47	53	(11.0)	429	(89.0)	48	(9.9)	435	(90.1)	9	(1.9)	469	(98.1)
4	480	3.83 ± 3.69	54	(11.3)	423	(88.7)	82	(17.2)	396	(82.8)	26	(5.5)	450	(94.5)
5	444	3.67 ± 3.62	58	(13.4)	374	(86.6)	76	(17.4)	360	(82.6)	47	(10.8)	390	(89.2)
Total	1409	3.87 ± 3.60	156	(11.9)	1226	(88.1)	206	(14.7)	1191	(85.3)	82	(5.9)	1309	(94.1)

χ^2 test demonstrated significant differences in the allergy prevalences among ages.

^{*} $p < 0.01$.

Table 3

Association between environmental factor including allergy symptoms and ASD score in the children.

	Age (years)	3		4		5		Total		<i>p</i>
	ASD score	<8	8≤	<8	8≤	<8	8≤	<8	8≤	
	<i>N</i>	415	69	416	64	389	54	1220	187	
Gender (boy)	<i>N</i>	201	41	198	45**	208	37*	608	123	0.000
	(%)	(48.4)	(59.4)	(47.6)	(70.3)	(53.1)	(68.5)	(49.7)	(65.8)	
Educational institution (nursery school)	<i>N</i>	94	20	84	18	100	17	278	55	0.046
	(%)	(22.6)	(29.0)	(20.2)	(28.1)	(25.6)	(31.5)	(22.7)	(29.4)	
Sleep duration (≤10 h)	<i>N</i>	316	45	313	57*	326	46	963	148	0.856
	(%)	(76.0)	(65.2)	(75.2)	(89.1)	(84.7)	(85.2)	(78.6)	(79.1)	
Birth order (first)	<i>N</i>	212	50**	206	42*	193	27	612	119	0.001
	(%)	(51.0)	(72.5)	(50.0)	(65.6)	(50.4)	(50.0)	(50.2)	(63.6)	
Sibling (no sibling)	<i>N</i>	62	13	63	12	39	11†	165	36	0.028
	(%)	(15.9)	(20.3)	(15.9)	(20.7)	(10.7)	(21.2)	(14.2)	(20.7)	
Mother with job (+)	<i>N</i>	162	21	166	28	162	29	498	78	0.824
	(%)	(41.0)	(31.8)	(40.8)	(44.4)	(43.5)	(54.7)	(42.1)	(42.9)	
Maternal smoking (current smoker)	<i>N</i>	36	6	39	18***	39	5	115	29	0.011
	(%)	(9.4)	(9.1)	(9.6)	(28.6)	(10.4)	(9.4)	(9.8)	(15.9)	
Age of house (≤4 years)	<i>N</i>	112	23	144	24	109	11	366	58	0.840
	(%)	(29.1)	(34.8)	(35.2)	(38.7)	(28.9)	(20.4)	(31.0)	(31.9)	
Family size (≤4 parson)	<i>N</i>	289	56*	287	51	239	33	816	140	0.026
	(%)	(69.5)	(81.2)	(69.0)	(79.7)	(61.3)	(61.1)	(66.6)	(74.9)	
Allergy										
Asthma (+)	<i>N</i>	46	7	44	10	46	9	140	26	0.337
	(%)	(11.1)	(10.1)	(10.7)	(15.6)	(12.3)	(17.0)	(11.6)	(14.0)	
Nasal allergy (+)	<i>N</i>	32	16***	68	14	68	8	168	38	0.019
	(%)	(7.7)	(23.2)	(16.4)	(21.9)	(17.9)	(15.1)	(13.8)	(20.4)	
Japanese cedar pollinosis (+)	<i>N</i>	6	3	19	7*	43	3	69	13	0.469
	(%)	(1.5)	(4.5)	(4.6)	(11.1)	(11.4)	(5.6)	(5.7)	(7.1)	
Eczema (+)	<i>N</i>	266	48	277	43	277	29	776	120	0.995
	(%)	(64.4)	(69.6)	(67.4)	(67.2)	(60.4)	(53.7)	(64.2)	(64.2)	

χ^2 test demonstrated significant differences in the frequencies of the environmental factors including allergy between children with ASD score more and less than 8 points.

* $p < 0.05$.

** $p < 0.01$.

*** $p < 0.001$.

2.3. Association between ASD subscale item and allergic symptoms

Table 4 shows the relationship between allergy and ASD item. Chi-square test showed significant relationships between ASD subscale and allergy as follows. Regarding in total children, we observed significant relationships between asthma and “10. Inappropriate facial expression” ($p < 0.05$), “14. Circumscribed interests” ($p < 0.05$), “4. Stereotyped utterances” ($p < 0.05$), and significant relationships between nasal allergy and “10. Inappropriate facial expression” ($p < 0.01$), “11. Use of other's body to communicate” ($p < 0.05$), “26. Eye gaze” ($p < 0.05$), “36. Interest in children” ($p < 0.05$), “8. Verbal rituals” ($p < 0.05$), “9. Compulsion's and rituals” ($p < 0.001$), “12. Unusual preoccupations” ($p < 0.05$), “15. Unusual sensory interests” ($p < 0.001$), “16. Hand and finger mannerisms” ($p < 0.01$), “17. Complex body mannerisms” ($p < 0.01$), “5. Inappropriate questions” ($p < 0.05$), and “35. Imitative play” ($p < 0.05$). We recognized significant relationships between Japanese cedar pollinosis and “9. Compulsion s and rituals” ($p < 0.05$), “4. Stereotyped utterances” ($p < 0.05$), and “5. Inappropriate questions” ($p < 0.01$), and significant relationships between eczema and “28. Showing and directing attention” ($p < 0.05$), “29. Offering to share” ($p < 0.05$), “30. Seeking to share enjoyment” ($p < 0.05$), “31. Offering comfort” ($p < 0.05$), “8. Verbal rituals” ($p < 0.01$), “13. Repetitive use of objects” ($p < 0.05$), “4. Stereotyped utterances” ($p < 0.05$), “7. Neologisms” ($p < 0.05$), “21. Imitation” ($p < 0.05$), “22. Pointing to express interest” ($p < 0.01$), and “24. Nodding to mean “yes”” ($p < 0.01$).

2.4. Multiple logistic-regression analysis about environmental factors and allergy for ASD score

Multiple logistic analysis demonstrated gender (odds ratio, 1.94: 95% CI 1.38–2.72), birth order (odds ratio, 1.56: 95% CI 1.09–2.25), mother smoking (odds ratio, 1.86: 95% CI 1.16–2.98), and nasal allergy (odds ratio, 1.61: 95% CI 1.01–2.56) were shown to be significantly positively related to higher ASD score (Table 5).

3. Discussion

Previously, autism spectrum disorders (ASD) were considered to be emotional disturbances related to character development and childcare provided by parents. Recently, they have been defined as pervasive developmental disorders

Table 4

Association between ASD item and allergy symptoms in children.

ASD item		Number upper column and proportion of ASD item corresponding to lower column							
		Asthma		Nasal allergy		Japanese cedar pollinosis		Eczema	
		(+) N = 166	(−) N = 1156	(+) N = 206	(−) N = 1194	(+) N = 82	(−) N = 1312	(+) N = 896	(−) N = 499
<i>Social reciprocal interaction</i>									
10	Inappropriate facial expression	22 (13.3%)	94 ⁺ (7.7%)	28 (13.7%)	88 ^{**} (7.4%)	7 (8.6%)	110 (8.4%)	80 (8.9%)	37 (7.4%)
11	Use of other's body to communicate	10 (6.1%)	57 (4.7%)	16 (7.8%)	51 ⁺ (4.3%)	5 (6.2%)	63 (4.8%)	45 (5.0%)	21 (4.2%)
20	Friends	7 (4.2%)	46 (3.8%)	7 (3.4%)	46 (3.9%)	3 (3.7%)	50 (3.8%)	31 (3.5%)	22 (4.4%)
26	Eye gaze	21 (12.7%)	143 (11.7%)	33 (16.2%)	133 ⁺ (11.2%)	8 (9.8%)	157 (12.1%)	108 (12.1%)	60 (12.1%)
27	Social smiling	10 (6.1%)	46 (3.8%)	13 (6.4%)	43 (3.6%)	5 (6.2%)	52 (4.0%)	39 (4.4%)	18 (3.6%)
28	Showing and directing attention	9 (5.5%)	87 (7.2%)	14 (6.9%)	81 (6.9%)	4 (4.9%)	92 (7.1%)	49 (5.5%)	47 ⁺ (9.5%)
29	Offering to share	7 (4.2%)	43 (3.5%)	7 (3.4%)	43 (3.6%)	3 (3.7%)	48 (3.7%)	24 (2.7%)	27 ⁺ (5.4%)
30	Seeking to share enjoyment	2 (1.2%)	18 (1.5%)	6 (2.9%)	15 (1.3%)	0 (0.0%)	22 (1.7%)	9 (1.0%)	13 ⁺ (2.6%)
31	Offering comfort	5 (3.0%)	22 (1.8%)	4 (2.0%)	23 (1.9%)	1 (1.2%)	27 (2.1%)	12 (1.3%)	16 ⁺ (3.2%)
32	Quality of social overtures	8 (4.9%)	70 (5.7%)	13 (6.4%)	66 (5.5%)	5 (6.2%)	75 (5.7%)	52 (5.8%)	28 (5.6%)
33	Range of facial expression	2 (1.2%)	17 (1.4%)	4 (2.0%)	15 (1.3%)	1 (1.2%)	20 (1.5%)	12 (1.3%)	9 (1.8%)
36	Interest in children	7 (4.2%)	73 (6.0%)	19 (9.3%)	62 ⁺ (5.2%)	8 (9.9%)	74 (5.7%)	56 (6.3%)	27 (5.4%)
37	Response to other children's approaches	32 (19.8%)	187 (15.4%)	39 (19.2%)	181 (15.3%)	10 (12.5%)	210 (16.2%)	154 (17.5%)	67 (13.5%)
39	Imaginative play with peers	7 (4.4%)	71 (5.9%)	16 (8.0%)	62 (5.3%)	4 (4.9%)	75 (5.8%)	45 (5.1%)	35 (7.2%)
40	Group play	9 (5.5%)	86 (7.1%)	17 (8.4%)	79 (6.7%)	5 (6.2%)	88 (6.8%)	58 (6.5%)	39 (7.9%)
<i>Repetitive behavior and stereotyped patterns</i>									
8	Verbal rituals	55 (33.5%)	340 (27.9%)	75 (36.9%)	318 ⁺ (26.9%)	29 (35.8%)	363 (27.9%)	284 (31.9%)	109 ^{**} (22.0%)
9	Compulsions and rituals	34 (20.7%)	269 (21.9%)	68 (33.2%)	238 ^{***} (20.0%)	27 (32.9%)	279 ⁺ (21.3%)	209 (23.4%)	96 (19.3%)
12	Unusual preoccupations	17 (10.4%)	89 (7.3%)	23 (11.3%)	83 ⁺ (7.0%)	10 (12.2%)	99 (7.6%)	72 (8.1%)	34 (6.9%)
13	Repetitive use of objects	55 (33.5%)	432 (35.6%)	69 (33.8%)	419 (35.5%)	27 (33.3%)	461 (35.5%)	331 (37.2%)	154 ⁺ (31.4%)
14	Circumscribed interests	28 (17.2%)	130 ⁺ (10.6%)	31 (15.3%)	128 (10.8%)	11 (13.6%)	147 (11.3%)	103 (11.5%)	55 (11.1%)
15	Unusual sensory interests	25 (15.2%)	146 (11.9%)	44 (21.5%)	126 ^{**} (10.6%)	14 (17.1%)	157 (12.0%)	117 (13.1%)	52 (10.5%)
16	Hand and finger mannerisms	6 (3.7%)	26 (2.1%)	10 (4.9%)	22 ^{**} (1.8%)	4 (4.9%)	28 (2.1%)	22 (2.5%)	9 (1.8%)
17	Complex body mannerisms	17 (10.4%)	119 (9.7%)	31 (15.1%)	105 ^{**} (8.8%)	12 (14.6%)	124 (9.5%)	92 (10.3%)	42 (8.5%)
19	Unusual attachment to objects	8 (4.9%)	37 (3.0%)	6 (2.9%)	40 (3.4%)	2 (2.4%)	42 (3.2%)	30 (3.4%)	16 (3.2%)
<i>Communication</i>									
2	Social chat	2 (1.2%)	27 (2.2%)	7 (3.4%)	22 (1.9%)	2 (2.4%)	28 (2.1%)	14 (1.6%)	15 (3.0%)
3	Conversation	5 (3.0%)	34 (2.8%)	6 (2.9%)	33 (2.8%)	2 (2.5%)	38 (2.9%)	21 (2.4%)	19 (3.8%)
4	Stereotyped utterances	70 (42.7%)	475 ⁺ (39.2%)	89 (43.6%)	457 (38.8%)	41 (50.6%)	506 ⁺ (39.1%)	379 (42.6%)	167 ⁺ (34.1%)
5	Inappropriate question	30 (18.3%)	155 (12.7%)	37 (18.0%)	149 ⁺ (12.5%)	19 (23.2%)	167 ^{**} (12.8%)	124 (13.9%)	63 (12.7%)
6	Pronoun reversal	51 (31.3%)	355 (29.1%)	65 (31.7%)	343 (28.9%)	22 (26.8%)	382 (29.3%)	262 (29.3%)	142 (28.8%)
7	Neologisms	58 (35.8%)	402 (32.9%)	68 (33.3%)	392 (33.0%)	28 (34.1%)	433 (33.2%)	316 (35.4%)	142 ⁺ (28.7%)

Table 4 (Continued)

ASD item		Number upper column and proportion of ASD item corresponding to lower column							
		Asthma		Nasal allergy		Japanese cedar pollinosis		Eczema	
		(+)	(–)	(+)	(–)	(+)	(–)	(+)	(–)
		N = 166	N = 1156	N = 206	N = 1194	N = 82	N = 1312	N = 896	N = 499
21	Imitation	42 (25.8%)	305 (24.9%)	57 (27.9%)	293 (24.6%)	16 (19.8%)	334 (25.6%)	212 (23.8%)	139 [*] (27.9%)
22	Pointing to express interest	16 (9.8%)	88 (7.2%)	19 (9.3%)	87 (7.3%)	5 (6.1%)	103 (7.9%)	58 (6.5%)	50 ^{**} (10.1%)
23	Gesture	56 (35.0%)	440 (36.5%)	76 (37.6%)	425 (36.2%)	34 (42.0%)	468 (36.3%)	309 (35.2%)	193 (39.1%)
24	Nodding to mean “yes”	4 (2.4%)	40 (3.3%)	10 (4.9%)	35 (2.9%)	5 (6.1%)	40 (3.1%)	21 (2.4%)	24 ^{**} (4.8%)
25	Head-shaking to head “no”	26 (15.9%)	154 (12.6%)	28 (13.7%)	153 (12.9%)	10 (12.3%)	169 (12.9%)	114 (12.8%)	65 (13.1%)
34	Imitative social play	7 (4.3%)	103 (8.5%)	16 (7.8%)	95 (8.0%)	5 (6.1%)	106 (8.2%)	70 (7.9%)	41 (8.2%)
35	Imitative play	2 (1.2%)	25 (2.0%)	8 (3.9%)	19 [*] (1.6%)	3 (3.7%)	26 (2.0%)	14 (1.6%)	15 (3.0%)
Not in algorithm									
	Self-injury	2 (1.2%)	23 (1.9%)	4 (2.0%)	21 (1.8%)	1 (1.2%)	24 (1.8%)	16 (1.8%)	9 (1.8%)
	Attention to voice	8 (4.9%)	70 (5.7%)	12 (6.0%)	66 (5.6%)	4 (5.0%)	73 (5.6%)	48 (5.4%)	31 (6.3%)

χ^2 test demonstrated significant differences in the frequencies children corresponding to the ASD item with and without the allergy symptom.

* $p < 0.05$.

** $p < 0.01$.

*** $p < 0.001$.

showing social deficits, communication difficulties, stereotyped or repetitive behaviors and interests, and/or cognitive delays due to functional brain disorder. Many studies have shown that genetics, prenatal and perinatal factors including neuroanatomical abnormalities, and environmental factors are responsible for the onset of symptoms.

The autism spectrum disorders show a wide spectrum of developmental disorders characterized by impairments in the following 3 behavioral domains: (1) reciprocal social interaction, (2) language and communication, and (3) repetitive and stereotyped patterns of behaviors. According to this characteristic of ASD, autism screening questionnaire (ASQ) has been developed to screen ASD in an early stage. The 39 question items are based on ADI-R (Autism Diagnostic Interview Revised), which includes an interview standard of autism for DSM-IV (Sell, Giarelli, Blum, Hanlon, & Levy, 2012) and ICD-10 (Winneke, 2011). Berument et al. (1999), who performed a discriminant study on PDD, demonstrated that the ASQ has good validity with respect to the separation of PDD from non-PDD diagnoses with a cut-off of 8 points.

Using ASQ, we found associations between autism and other symptoms and environmental factors. Some studies have suggested an association between autism and sleep disorder (Couturier et al., 2005; Goldman, Richdale, Clemons, & Malow, 2011; Krakowiak, Goodlin-Jones, Hertz-Picciotto, Croen, & Hansen, 2008; Souders et al., 2009). Malow et al. (2006) reported that sleep difficulties, particularly insomnia, occur in 50–80% of children with autism spectrum disorders. Sleep disorder may exacerbate core and related symptoms of autism including social interactions, repetitive behaviors, affective problems, and

Table 5

Multiple logistic-regression analysis about ASD score for environmental factor and allergy symptom in total subjects.

Variable	Regression coefficient	SE	p-Value	Odds ratio	95% confidence interval
Age (3–5 years)	0.105	(0.107)	0.325	0.11	(0.90–1.37)
Gender (boy vs girl)	0.660	(0.173)	0.000	1.94	(1.38–2.72)
Birth order (first vs not first)	0.447	(0.185)	0.016	1.56	(1.09–2.25)
Sleep duration (≥ 10 vs < 10)	0.037	(0.206)	0.857	1.04	(0.69–1.56)
Family size (≥ 4 vs < 4)	0.161	(0.202)	0.425	1.18	(0.79–1.75)
Mother age (≥ 34 vs < 34)	0.158	(0.171)	0.355	1.17	(0.84–1.64)
Mother with job (– vs +)	0.003	(0.172)	0.386	1.00	(0.72–1.41)
Maternal smoking (current smoker vs non smoker)	0.622	(0.240)	0.009	1.86	(1.16–2.98)
Asthma (– vs +)	0.086	(0.245)	0.727	1.09	(0.67–1.76)
Nasal allergy (– vs +)	0.473	(0.238)	0.047	1.61	(1.01–2.56)
Japanese cedar pollinosis (– vs +)	–0.030	(0.376)	0.936	0.97	(0.47–1.99)
Eczema (– vs +)	–0.030	(0.177)	0.986	1.00	(0.71–1.41)

inattention/hyperactivity (Gabriels, Cuccaro, Hill, Ivers, & Goldson, 2005; Goldman et al., 2009, 2011; Malow et al., 2006; Schreck, Mulick, & Smith, 2004). In this study, children sleeping less than 10 h per day tended to show a greater ASD score than those with more than 10 h, a trend which was statistically significant in 4-year-old children. Our results support previous data showing an association between little sleep and autism (Sivertsen, Posserud, Gillberg, Lundervold, & Hysing, 2011).

Furthermore, our study showed a significantly higher proportion of subjects with a high score of ASD in boys than in girls. Ozonoff et al. (2011) reported that autism is more frequently seen in boys, specifically, approximately 80% of cases. Their report (Ozonoff et al., 2011) and observation by Hattier, Matson, Tureck, and Horovitz (2011) seem to agree well with our result suggesting a higher prevalence of autism in boys.

Our study demonstrated that higher score of ASD was more frequently seen in children born first, in terms of birth order and those having no siblings. A significant association between the birth order, boy, and ASD score was seen in total children even after adjusting for environmental factors by logistic regression analysis. Becker (2007) suggested that factors related to autism include allergic diseases and birth order, which is also related to allergic diseases (Bernsen, de Jongste, & van der Wouden, 2003). In cases of both autism and allergic diseases, being the firstborn may carry a greater risk for disease than being born later. Zwaigenbaum et al. (2005) performed a longitudinal study of high-risk infants, showing that all firstborn children with high risk were diagnosed as having an autistic spectrum disorder (Gardener, Spiegelman, & Buka, 2009; Spiker et al., 1994). There is accumulating evidence for the involvement of allergy in autism. Kinra et al. (2006) found that the odds ratio for having at least one allergic disease decreased with increasing number of siblings, with individuals who had three or more siblings having a 30% lower risk of being affected than those without siblings (Karmaus & Botezan, 2002; Mazefsky, Goin-Kochel, Riley, Maes, & Consortium, 2008). Strachan, Taylor, and Carpenter (1996) showed that the prevalence of hay fever was reduced among children of younger mothers and those from larger families. Similarly, Matricardi et al. (1998) observed an association between atopy and the number of older siblings (Jarvis, Chinn, Luczynska, & Burney, 1997).

Some reports have showed that asthma and allergic diseases were more frequently seen in children with autism, demonstrating that asthma and allergic rhinitis remained significantly associated with autism after adjustment for maternal factors (Croen, Grether, Yoshida, Odouli, & Van de Water, 2005; Money, Bobrow, & Clarke, 1971; Trottier, Srivastava, & Walker, 1999). Thus, the combination of allergic diseases and autism seems likely to be common in children. This study also showed that children with an ASD score of 8 points or more had a higher prevalence of allergic disease. In particular, we found that the ASD subscale was associated with nasal allergy. Jyonouchi et al. (2011) pointed out that allergic diseases can cause neuropsychiatric symptoms, such as irritability and hyperactivity, which are also likely to occur in children with ASD (Kushak, Lauwers, Winter, & Buie, 2011). Moreover, the discomfort and pain associated with allergic diseases could aggravate behavioral symptoms in children with ASD.

Taken together with our results showing significant co-existence of ASD and allergy, we can speculate that the central nervous system (CNS) is involved in allergy as well as autism via similar pathologic mechanisms. Regarding the involvement of CNS in allergy, Hussain et al. (2007) reviewed that some environmental chemicals are harmful to the brain, subsequently leading to the development of autism and allergy, but that it is uncertain how these chemicals play roles in specific disabilities such as attention deficit hyperactivity disorder and autism, as well as allergy.

More importantly, our findings shows that children with higher ASD score were more frequency in children with mother smoking suggested association maternal smoking in pregnancy and child mental health than paternal smoking, as Larsson, Weiss, Janson, Sundell, and Bornehag (2009) have reported. To clarify a causal relationship between allergy and autism, it is necessary to perform a longitudinal study in children without ASD or allergy, which may determine causal relationship as well as common environmental risks factors between allergy and autism, i.e., allergy causes ASD; ASD causes allergy; allergy and ASD share the same causative agents.

Next, we analyzed the association between ASD subscale and allergy in detail, and observed that “range of interests and activities” as one of the characteristics of ASD was closely associated with nasal allergy. These results suggest that a special behavioral pattern regarding “repetitive and stereotyped patterns of behaviors” may be observed in children with an autistic tendency developing nasal allergy. The problem of “repetitive actions” seen in autism can disturb not only personal relationships, but also feeding behavior, selective ability for food, development of taste sense, and malnutrition in rapidly growing children. Although it is difficult to determine whether allergy itself aggravates autism, or unpleasant symptoms associated with allergy lead to autism development including behavioral problems related to emotion, or vice versa, our observation using ASD subscales seems to provide new evidence for a close relationship between allergy and autism. That is, the allergic diseases were recognized to be associated with “social interaction”, “language, communication, and imaginative play”, and “behavioral domains” as subscales of ASD. The relationship between allergy and autism is particularly noteworthy because the 3 characteristics of the subscales are assumed to be most fundamental components seen in autism. Because of this close relationship, investigations of allergy symptoms in addition to subscale of ASD can screen for autism tendency more efficiently at an early stage. The methods for screening for autism tendency, which would help parents and care staff monitor the mental states of children, should be incorporated into systems for sharing information between medical, educational, and caring institutions. In future studies, the validity and reliability of screening methods must be confirmed by follow-up study using more objective diagnosis for allergy, including food allergy. We recognized lack of consistency of statistical association between ASD and maternal smoking and nasal allergy in 3–5 ages of children. Furthermore, we observed the involvement of nasal allergy, but not asthma in ASD score. Lack of significant relationship between ASD score and asthma in our study are considered to be due to not large sample size. Therefore, it is necessary to conduct epidemiology

on mental health in child much larger sample. When we analyze the relationship between ASD including subscale of ASD and related factors including allergy using much larger population in future study, we could solve the problems in interpretation of the results following multiple testing where we must correct p value according to the number of the statistical test.

In conclusion, we recognized that children with higher ASD score have higher prevalence of allergic diseases, and identified the predictive factors of boy first in terms of birth order and no siblings (not have any brothers or sisters). In addition, allergic diseases were observed to be associated with “reciprocal social interaction”, “language and communication”, “repetitive and stereotyped patterns of behaviors” as subscales of ASD. The results seem to demonstrate a closer relationship between autism and allergy than previously reported. Investigations of allergy symptoms in addition to subscale of ASD may enable more efficient screening for autism tendency at an early stage.

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