

DR CHIKAE YAMAGUCHI (Orcid ID : 0000-0002-4776-2438)

DR MASAKI FUTAMURA (Orcid ID : 0000-0002-7442-9649)

DR YUKIHIRO OHYA (Orcid ID : 0000-0002-1560-3942)

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Title: Do allergic clinical manifestations increase the risk of behavioral problems in children? A cross-sectional study

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Chikae Yamaguchi¹, Takeshi Ebara², Masaki Futamura³, Yukihiro Ohya⁴, Midori Asano⁵

1. Department of Community Health Nursing, Nagoya City University Graduate School of Nursing, Nagoya, Japan

2. Department of Occupational and Environmental Health, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

3. Division of Pediatrics, National Hospital Organization Nagoya Medical Center

4. Allergy Center, National Center for Child Health and Development, Tokyo, Japan

5. Department of Integrated Health Sciences, Nursing Sciences, Nagoya University Graduate School of Medicine, Nagoya, Japan

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Running title: Allergies and behavioral characteristics

Corresponding author:

Chikae Yamaguchi,

Department of Community Health Nursing,

Nagoya City University Graduate School of Nursing,

1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya, Aichi 467-8601, Japan.

Email: cyamagu@med.nagoya-cu.ac.jp

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ABSTRACT

Background: Children with allergic clinical manifestations tend to have behavioral or emotional problems such as hyperactivity or worse mental health. However, previous studies on this association did not adequately adjust for confounders like parenting stress, demographic characteristics, or allergy presentation. This study aimed to investigate the relationship between childhood allergic clinical manifestations and behavioral problems, adjusting for confounders like demographic characteristics, parenting stress, and allergy-related variables.

Methods: We conducted an online cross-sectional survey among caregivers of children aged 2–6 years (n=633). The Strengths and Difficulties Questionnaire (SDQ) was used to determine children's behavioral characteristics as the primary outcome. Allergic clinical manifestations, wheeze, rash, and nose symptoms were the exposure variables. Associations were estimated using logistic regression analyses with propensity scores to adjust for confounders.

Results: We analyzed 633 caregivers of children aged 2–6 years (valid rate, 61.5%). Univariate analyses showed that wheezing was associated with conduct problems (odds ratio [OR]=1.48, 95% confidence interval [CI]:1.01–2.16), a behavioral component of the SDQ. Rash was also associated with hyperactivity (OR=1.62, 95% CI: 1.02–2.57). Furthermore, nose symptoms were associated with conduct problems (OR=1.65, 95% CI:1.16–2.33) and emotional symptoms (OR=1.62, 95% CI:1.06–2.45). After adjusting for potential confounders, wheezing (adjusted OR=1.69, 95% CI:1.04–2.75) and nose symptoms (adjusted OR=1.56, 95% CI: 1.05–2.34) remained associated with conduct problems.

Conclusions: This study revealed that a history of wheezing and nose symptoms in children is associated with an increased risk of behavioral problems, in particular, conduct problems.

Keywords: International Study of Asthma and Allergies in Childhood, Strengths and Difficulties Questionnaire, wheeze, rhinitis, eczema, propensity score, behavioral problems, pediatrics

Key message: This study revealed an association between allergic clinical manifestations and behavioral problems in children. The history of wheezing and nose symptoms may increase the risk of conduct problems. The strength of this study is that it was adjusted for confounding factors using propensity scores to increase the reliability and validity of the findings.

INTRODUCTION

Allergy is a hypersensitivity reaction initiated by immunologic mechanisms.¹ The prevalence of allergic diseases is increasing worldwide, including in Japan. The 1999 International Study of Asthma and Allergies in Childhood (ISAAC) reported that the prevalence of atopic dermatitis ranged from <2% in Iran to >16% in Japan and Sweden among children aged 6–7 years.² Phase III of the same study completed 7 years later reported an increase in the prevalence of asthma, rhinoconjunctivitis, and eczema in many countries except for asthma among adolescents aged 13–14 years.³

Previous studies have shown that children with eczema or atopic dermatitis achieved higher scores on the Strengths and Difficulties Questionnaire (SDQ), indicating that the presence of eczema may be associated with worse mental health.⁴⁻⁷ Similar findings have been reported for conditions such as attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders (ASD) among children with eczema. Children with atopic dermatitis have been shown to be at an increased risk of ADHD or ASD.⁸⁻¹³

Similar associations have been reported for asthma and rhinitis⁵. A systematic review found that children with ADHD had a higher rate of asthma than those without ADHD.¹⁴ A separate meta-analysis suggested that patients with asthma, particularly those with severe symptoms, should be considered at higher risk of behavioral difficulties that may necessitate psychosocial interventions.¹⁵ In a nationwide population-based prospective study, Chen suggested that asthma was a risk factor for further development of ADHD. In addition, asthma in very early life has been shown to increase the risk of developing ADHD during school years.¹⁶ Suwan reported increased rates of allergic sensitization in ADHD cases.¹⁷ The prevalence of allergic rhinitis among children with ADHD has also been reported as higher than that among children without ADHD.¹⁷ A study based on the Taiwan National Health Insurance Research Database reported that allergic disorders, in particular, bronchial asthma and allergic rhinitis, but not atopic dermatitis, were risk factors for ADHD.¹⁸

This evidence notwithstanding, previous studies on the relationship between allergic clinical manifestations and childhood behavioral problems often failed to consider the impact of parental factors associated with children's psychosocial development. A study by Tokunaga et al. examined the impact of parenting stress in this context and found that paternal stress was significantly associated with the risk of child hyperactivity/inattention, while maternal stress was significantly associated with difficulties in peer relationships and emotional symptoms.¹⁹ However, parenting stress may be the effect, not the cause, of childhood behavioral problems. Parenting stress may increase because of a child's behavioral problems. This relationship can also be bi-directional.

This study aimed to investigate the relationship between allergic clinical manifestations and children's behavioral problems, adjusting for potential confounding factors such as demographic characteristics, parenting stress, and allergy-related variables. In this study, behavioral problems of children refer to their strengths and difficulties in terms of four aspects: conduct problems, hyperactivity, emotional symptoms, and peer problems.

METHODS

Study design and setting

This cross-sectional study was conducted in June 2019 as an online survey of 2,215 candidates registered at a private online research firm, Macromill, Inc, Japan, that raised preschool children; among them, 1,030 completed the questionnaire (response rate, 46.5%). Details are shown in Figure 1. Participants were primary caregivers of children aged 2–6 years. We thought it would be difficult to judge problematic behaviors in children younger than 2 years old because they are not yet mature enough to understand language and social skills and are not at age covered by the SDQ, a scale that measures behavioral problems; we limited our study to 6-year-olds (preschool children) because their development tasks of preschool children are different from those of school-age children who are expected to be industrious in their school work.

Before answering the questionnaire, the website administrator provided consent forms to respondents and

informed them that completing the questionnaire was equivalent to their agreement to study participation. This study adhered to the Declaration of Helsinki and was approved by the ethics committee of Nagoya City University Graduate School of Nursing (Approval No. 19014-2).

Outcomes, exposures, and covariates

The questionnaire collected data on SDQ domains used as a measure of children's behavioral problems, demographic characteristics of children and their caregivers, Parenting Stress Index short form (PSI-SF), and ISAAC²⁰ scores. SDQ is an instrument used to evaluate both positive and negative infant, child, and adolescent behavior²¹. It includes 25 items scored on a 3-point Likert-type scale across 5 domains; conduct problems, hyperactivity, emotional symptoms, peer problems and prosocial behavior. The total difficulties score assessed in this study consisted of the 4 domains excluding prosocial score, as that domain alone had a positive value²¹. The prosocial score is one of the subdomains that assesses the positive aspects of SDQ; however, it was not included in the total score because it is heterogeneous from the other subscales. Hence, we thought it was appropriate to exclude it in this study. The total difficulties score was used as an outcome in this study. The Japanese SDQ, translated from the original version developed in the United Kingdom, has been validated and is considered applicable to children in Japan.²²

The PSI is a self-reported measure of stress associated with childcare.²³ The PSI-SF, an abridged version of PSI, consists of 19 items scored on a 5-point Likert-type scale. The Japanese PSI-SF has been validated and applied in this study.²⁴ Parenting stress was categorized into parent- and child-associated domains and assessed comprehensively based on the total score. Higher scores indicated higher stress levels.

Statistical Analysis

The primary outcome was the total difficulties score for SDQ in each domain: conduct problems, hyperactivity, emotional symptoms, and peer problems. Each score can be interpreted as “normal,” “borderline,” and “clinical” on a scale from the lowest to highest score. Matsuishi proposed the total difficulties score classification as

“normal,” “borderline,” and “clinical,” corresponding to 0–12, 13–15, and 16–40 points, respectively. Matsuishi set the ranges for the domains of emotional symptoms, conduct problems, and peer problems as 0–3 for “normal,” 4 for “borderline,” and 5–10 for “clinical.” The ranges for the hyperactivity domain were defined as 0–5 for “normal,” 6 for “borderline,” and 7–10 for “clinical.”²² Goodman, the SDQ author, suggested that the “borderline” cutoffs (normal vs. borderline and clinical) can be used for studies of high-risk samples where false positives are not a major concern, and the “abnormal” cutoffs (normal and borderline vs. clinical) can be used for studies of low-risk samples where it is more important to reduce the rate of false positives²¹. We used the recommended borderline cutoff scores as criteria for dichotomizing primary outcome variables because we needed to extract behavioral problems with high sensitivity from the population at risk of allergies.

Exposure variables used in this study were history of allergic clinical manifestations such as wheezing, rash, and nose symptoms since birth. The potential confounding variables were age and sex (demographic characteristics), PSI-SF scores (parents’ psychological aspect), diagnosis of allergic disease by physician (subjective responses obtained from caregivers), and family history of allergic diseases such as atopic dermatitis, food allergy, asthma, rhinoconjunctivitis, and hay fever, as well as other items of the ISAAC.

We performed logistic regression analyses to estimate crude and adjusted odds ratios (OR), accounting for propensity scores yielded by all confounding variables. The items used to determine propensity scores are shown in Supplementary Table 1. To control for the impact of collinearity, which was likely between variables that represent similar concepts, we performed adjustments using propensity scores. When integrating all confounders into one variable as a propensity score and determining the propensity score variables for each exposure, variables relevant to simultaneous factors inducing collinearity, such as a history of diseases or prevalence period, were excluded. The analyses applied a complete case analysis. As the online survey prevented responders from submitting their forms with missing values, the dataset involved no missing values. All statistical analyses were performed using the International Business Machines Corporation Statistical Package for Social Sciences (SPSS) version 22.0 (SPSS Inc,

Chicago, Ill).

RESULTS

Data from a total of 633 surveys were included in the analysis (valid rate, 61.5%) (Figure 1). Participants were 633 primary caregivers. Of these, 52.4% were boys, and 35.2% had children with diagnosed atopic dermatitis (11.7%), food allergy (9.6%), asthma (10.7%), rhinoconjunctivitis (12.8%), and hay fever (8.7%). A total of 221 children had general behavioral problems as measured by the total difficulties score; 187(29.5%) had conduct problems, 148 (23.4%) had hyperactivity, 113 (17.9%) had emotional symptoms, and 171 (27.0%) had peer problems. Participant characteristics and their SDQ scores are presented in Table 1 and Supplementary Table 2.

In crude logistic regression models, a higher risk of conduct problems was observed among children with a wheezing history than among those without it (OR= 1.48, 95% confidence interval [CI]: 1.01-2.16). A similar association was observed between nose symptoms and conduct problems, indicating a higher risk of conduct problems among children with nose symptoms than those without it (OR=1.65, 95% CI: 1.16-2.33). Additional associations were observed between rash and hyperactivity (OR=1.62, 95% CI: 1.02-2.57) and nose symptoms and emotional symptoms (OR=1.62, 95% CI: 1.06-2.45) (Table 2).

Adjusted ORs indicated that only history of wheezing (adjusted OR=1.69, 95% CI: 1.04-2.75) and nose symptoms (adjusted OR=1.56, 95% CI: 1.05-2.34) affected the risk of conduct problems. No other associations between childhood allergic clinical manifestations and behavioral problems were detected after adjusting for propensity scores.

DISCUSSION

This study found that a history of wheezing and nose symptoms in children was associated with an increased risk of developmental problems, in particular, conduct problems. Previous studies have investigated the relationship

between the presence of allergies and behavioral characteristics of children. However, unlike previous studies, the present study analyses included adjustments for possible confounding factors such as demographic characteristics, parenting stress, and allergy-related variables. Allergy-related variables included ISAAC items, clinician's diagnosis of allergies, and family history of allergies. To control for the impact of collinearity, which was likely between the variables that represent similar concepts, we performed adjustments using propensity scores. Adjusted estimates indicated an association between a history of wheezing and that of nose symptoms and childhood conduct problems.

A previous study reported that rhinitis and asthma, but not eczema, were associated with an increased risk of ADHD.¹⁸ Although it is not equivalent to ADHD, which has clear diagnostic criteria, it is considered that some children with conduct problems may also have ADHD. A separate cross-sectional study using SDQ as an outcome measure and logistic regression analyses adjusted for gender, age, and primary caregiver's educational level has shown that children with current asthma symptoms were more likely to present with conduct problems than those without symptoms.⁵ This study differed from ours in that no significant association between conduct problems and "known asthma ever" or "known hay fever ever" was observed. Known asthma ever was synonymous with the wheeze ever used in our study. In addition, known hay fever ever is thought to be similar in meaning to the nose symptoms ever used in our study. This discrepancy might be due to between-study differences in the definition of outcomes and associated cutoff scores. For example, Hammer-Helmich et al. adopted the "clinical" value as a cutoff score, whereas we adopted the "borderline" value. Goodman suggested that the "borderline" cutoff score can be used in studies of high-risk samples where false positives are not a major concern²¹; however, we believe that using a highly sensitive threshold is appropriate to reduce the danger of overlooking an association. Another possible reason for between-study differences in findings is the use of different confounders for adjustment during analysis. The present study adjusted for different types of confounders, using the propensity score technique. Following these adjustments, our results indicate an association between history of wheezing and/or nose symptoms in children and conduct problems; this finding may inform selection of confounders and support new perspectives in future studies.

Biologically, allergy-sensitized children appear to have elevated levels of inflammatory cytokines. It is the Th2 lineage cells that promote the allergic response, which is known to be associated with cytokines such as IL-4, IL-6, and IL-10.²⁵ Although their experiments were conducted in mice, Wei et al. suggest that mice with elevated IL-6 in the brain display many autistic features, including impaired cognitive abilities, deficits in learning, abnormal anxiety traits and habituations, as well as decreased social interactions.²⁶ Another study proposed that the release of inflammatory cytokines caused by allergic inflammation and/or elevated levels of psychological stress as a result of the chronic disease interfere with the maturation of prefrontal cortex regions and neurotransmitter systems involved in ADHD pathology.²⁷ These mechanisms shown in previous studies may help to explain the association between the presence of allergies and behavioral problems in children, as shown in the present study.

In the present study, the history of wheezing and nose symptoms affected the risk of conduct problems in children after adjustment for potential confounders. Both wheezing and nose symptoms cause respiratory symptoms, which may lead to sleep disorders. Poor sleep quality can adversely affect the behavior of children.²⁸ In addition, a previous systematic review revealed the presence of sleep disorders in children with ADHD²⁹; a separate review reported that associations between sleep and psychopathology are complex and likely bidirectional.³⁰ Therefore, additional studies are needed to elucidate the association between ADHD-like behavioral characteristics and sleep.

Given these findings, we believe that high impulsiveness can be attributed, in part, to the psychological effect of elevated levels of inflammatory cytokines triggered by allergic sensitization; in addition, low quality of sleep is likely to play a role in the tendency toward behavioral irritation. However, further studies are needed to confirm these associations.

This study has several strengths and limitations. This study is the first to adjust for confounding factors, including participant demographic characteristics, parenting stress, and allergy-related variables. Although this study is a cross-sectional study and therefore causality cannot be determined, our findings suggest that in clinical settings, allergies especially wheezing and nose symptoms, may be associated with behavioral problems in children. Moreover,

such an association could contribute to paying attention to the developmental status of children with allergic clinical manifestations early in their lives. The study limitations are as follows. First, while we adjusted for multifaceted confounders, we did not adjust for unmeasured or residual confounding factors such as sleep and psychopathological characteristics. Second, as this was a cross-sectional study, the presented findings preclude meaningful discussions of causality. Further studies are warranted to confirm our findings; such studies should involve a longitudinal design and a representative sample. Third, we did not adjust for the impact of medications that could affect sleep or mental health, such as antihistamines. Finally, caregivers may have reported increased parenting stress due to duties associated with the care of children with allergies; however, we could not account for this factor in this study.

In conclusion, this study revealed that a history of wheezing and nose symptoms in children is associated with an increased risk of behavioral problems, in particular, conduct problems.

Author contributions:

Chikae Yamaguchi: Conceptualization (lead); Data curation (lead); Formal analysis(lead); Funding acquisition (lead); Methodology (equal); Writing-Original Draft (lead); Writing-review and editing (lead). **Takeshi Ebara:** Data curation (equal); Formal analysis (equal); Methodology (lead); Writing-review and editing (equal). **Masaki Futamura:** Conceptualization (equal); Writing-review and editing (equal). **Yukihiro Ohya:** Writing-review and editing (equal). **Midori Asano:** Conceptualization (supporting); Writing-review and editing (equal).

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Table 1. Demographic characteristics of participating children and their caregivers (n=633)

Table 2. Logistic regression of associations between children's characteristics (Strengths and Difficulties Questionnaire) and history of allergic clinical manifestations

Figure legends: Figure 1. Flow diagram of study data selection

Appendix: Supplementary Table 1. Demographic stratified by allergic clinical manifestation (n=633)

Supplementary Table 2. Items used to estimate propensity scores

Table 1. Demographic characteristics of participating children and their caregivers (n=633)

Children		n	%
Diagnosis of allergic disease by physician*	Atopic dermatitis	74	11.7
	Food allergy	61	9.6
	Asthma	68	10.7
	Rhinoconjunctivitis	81	12.8
	Hay fever	55	8.7
History of allergic clinical manifestations	wheeze ever	162	25.6
	rash ever	106	16.7
	nose symptoms ever	331	52.3
Age(y)	2	153	24.2
	3	145	22.9
	4	148	23.4
	5	143	22.6
	6	44	7.0
Sex	Boy	332	52.4
	Girl	301	47.6
Primary daytime caregiver	kindergarten	237	37.4
	nursery school	176	27.8
	authorized child institution	76	12.0
	none	144	22.7
Caregivers		n	%
Age of father		35.8	6.3
Father's employment status	full-time employment	560	88.5
	part-time employment	2	0.3
	self-employed	37	5.8
	unemployed	2	0.3
	other	3	0.5
	absence of father	29	4.6
Father's academic background	junior high school	42	6.6
	high school	174	27.5
	junior college /vocational school	110	17.4
	university or above	278	43.9
Age of mother		33.4	6.1
Mother's employment status	full-time employment	85	13.4
	part-time employment	152	24.0
	self-employed	8	1.3
	side job at home	19	3.0
	unemployed	315	49.8
	absence from work	32	5.1
	other	20	3.2
	absence of mother	2	0.3
Mother's academic background	junior high school	22	3.5
	high school	181	28.6
	junior college /vocational school	213	33.6
	university or above	212	33.5
	other	3	0.5
Parental marital status	married/common-law marriage	595	94.0
	divorced/separated	31	4.9
	unmarried /single	7	1.1
Family income	<2 million yen	18	2.8
	2 to less than 4 million yen	125	19.7
	4 to less than 6 million yen	178	28.1
	6 to less than 8 million yen	82	13.0
	8 to less than 10 million yen	32	5.1
	10 to less than 12 million yen	10	1.6
	12 to less than 15 million yen	4	0.6
	15 to less than 20 million yen	3	0.5
	>20 million yen	2	0.3
	other	52	8.2
Strengths and difficulties questionnaire score		n	%
Total difficulties score	range (0-30), mean 11.0(±5.3)		
	Normal	412	65.1
Conduct problems	Borderline, Clinical	221	34.9
	range (0-10), mean 2.7(±1.7)		
Hyperactivity	Normal	446	70.5
	Borderline, Clinical	187	29.5
Emotional symptoms	range (0-10), mean 3.9(±2.2)		
	Normal	485	76.6
Peer problems	Borderline, Clinical	148	23.4
	range (0-10), mean 1.9(±1.9)		
Peer problems	Normal	520	82.1
	Borderline, Clinical	113	17.9
Peer problems	range (0-9), mean 2.5(±1.8)		
	Normal	462	73.0
	Borderline, Clinical	171	27.0

*Subjective responses obtained from caregivers

Table 2. Logistic regression of associations between children's characteristics(Strengths and Difficulties Questionnaire) and history of allergic clinical manifestations

	Strengths and difficulties questionnaire components									
	total difficulty score		conduct problems		hyperactivity		emotional symptoms		peer problems	
	crude model	adjusted model	crude model	adjusted model	crude model	adjusted model	crude model	adjusted model	crude model	adjusted model
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
wheeze ever	1.26 (0.87-1.82)	1.48 (0.93-2.37)	1.48 (1.01-2.16)	1.69 (1.04-2.75)	1.32 (0.87-1.98)	1.24 (0.73-2.10)	1.54 (0.99-2.39)	1.50 (0.85-2.63)	0.59 (0.38-0.91)	0.69 (0.40-1.18)
rash ever	1.34 (0.87-2.05)	1.06 (0.63-1.77)	1.15 (0.74-1.81)	0.87 (0.50-1.50)	1.62 (1.02-2.57)	1.21 (0.69-2.13)	1.01 (0.58-1.73)	0.87 (0.45-1.67)	1.08 (0.68-1.72)	1.11 (0.63-1.93)
nose symptoms ever	1.27 (0.91-1.76)	1.40 (0.96-2.05)	1.65 (1.16-2.33)	1.56 (1.05-2.34)	1.22 (0.84-1.77)	1.23 (0.80-1.89)	1.62 (1.06-2.45)	1.45 (0.89-2.35)	0.84 (0.59-1.19)	1.09 (0.73-1.63)

Dependent variable: Strength and Difficulties Questionnaire (Conduct problems, Hyperactivity, Emotional symptoms, Peer problems, and Total difficulty score)

Independent variable: History of allergic clinical manifestations (Wheeze ever, Rash ever, and Nose symptoms ever)

Propensity score: Age, Sex, Parenting Stress, International Study of Asthma and Allergies in Childhood (ISAAC), Diagnosis of allergic disease by physician, and Family history

SDQ, strengths and difficulties questionnaire; OR, odds ratio; 95% CI, 95% confidence interval

Figure 1. Flow diagram of study data selection