

Factors associated with the development and remission of allergic diseases in an epidemiological survey of high school students in Japan

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ABSTRACT

Background: Allergic diseases are an important health problem for children and adults. It is important to know how allergic diseases develop and remit from infancy to adolescence. Early intervention is effective in treating allergic diseases.

Objective: We performed a large-scale questionnaire survey of high school students in Fukui Prefecture, Japan, and analyzed the factors associated with the development and remission of allergic diseases.

Methods: A total of 21,802 students participated in the epidemiologic survey, and the valid response rate was 89.3% (19,461). We applied an inverse probability weighting method with propensity scores.

Results: The present prevalence rate of allergic rhinitis (AR) was 19.2%. The remission rate of AR was 15.3%. Only children and firstborns had a significantly higher risk of developing symptoms of allergic diseases [only child: AR, 1.37; bronchial asthma (BA), 1.30; food allergy (FA), 1.33 and firstborn: AR, 1.38; BA, 1.10]. Constipation was an associated factor for development of atopic dermatitis (AD) (1.17) and AR (1.17), regular intake of lactic acid bacteria was not an associated factor for development of allergic diseases but was a factor for remission of AD (1.22). Hypohidrosis was an associated factor for development of AD (1.25). High academic performance was an associated factor for development of AR (1.20) but was a negative factor for development of BA (0.89). The values in parentheses are significant adjusted odds ratios.

Conclusion: This epidemiologic survey showed that the hygiene hypothesis and intestinal bacterial flora might influence the development of symptoms and remission of allergic diseases.

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Allergic diseases are an important global health problem for children and adults.¹ Although it is rare to die from an allergic disease, symptoms persist for a long time, and the disease has an adverse effect on work, everyday life, and quality of life.² Furthermore, allergic diseases have a significantly worse effect on labor productivity compared with hypertension or type 2 diabetes mellitus.^{3–5}

Allergic diseases have mutual relevance, so the concept of allergic march has been advocated. Allergy march is defined as the progression of allergic diseases in infancy from food allergy (FA) and atopic dermatitis (AD) to bronchial asthma (BA) and allergic rhinitis (AR). During this march, both the offending allergens and the affected organs change.⁶ It is important to know how allergic diseases develop and remit from infancy to adolescence, to elucidate their pathophysiology. In addition, early intervention and lifestyle guidance are effective in treating allergic diseases.

In 1991, the International Study of Asthma and Allergic Diseases in Childhood (ISAAC) established a standardized methodology to com-

pare the prevalence and severity of BA and atopic diseases in children.⁷ The prevalence of allergic diseases in children has been comprehensively studied worldwide due to the standardized and translated versions of ISAAC based on written and/or video questionnaires.^{8–10} The ISAAC phase-I study demonstrated major worldwide variations in the prevalence of symptoms of BA, AR (rhinoconjunctivitis), and AD in children.^{11,12} More than 700,000 children were included in the study: 257,800 from 6 to 7 years old and 463,801 from 13 to 14 years old. The ISAAC phase-III study involved repeating the phase-I survey after 5–10 years to examine trends in the prevalence of the three conditions and included new centers to expand the coverage of world prevalence maps for these conditions.^{10,13} However, although a worldwide epidemiologic survey of allergic diseases has been conducted, there has been little investigation on high school-age students. Moreover, there have been only a few epidemiologic reports that analyzed the factors associated with the development and remission of allergic diseases.

We performed a large-scale questionnaire survey of high school students and analyzed the factors associated with the development and remission of allergic diseases.

MATERIALS AND METHODS

Subjects

All students attending high school in Fukui Prefecture, Japan, were studied. Fukui Prefecture has a population of 794,043 (as of January 2014). The number of high schools in Fukui is 37. Two schools out of 37 did not participate in this study. The two schools were a part-time evening high school and a small special education high school. A total of 21,802 students participated in the survey. Because the proportion of junior high school students going on to high school in Fukui Prefecture is 98.6%,¹⁴ we could investigate approximately 90% of the persons of high school age in Fukui Prefecture. The number of valid responses was 19,461 (89.3%).

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Questionnaire

Each student completed a self-administered questionnaire between December 2012 and January 2013. The questionnaire included a computer-scored answer sheet. The questionnaire included items on the following: age, past history of allergic diseases (FA, AD, BA, and AR), present allergic diseases, remission of allergic diseases, gender, blood type, sibling status (only child or not; birth order), family history of allergic diseases, history of pet exposure, presence of abnormal bowel movement, intake of lactic acid bacteria, exposure to passive smoking, presence of dyshidrosis, and exercise habits. In regards to the presence of allergic diseases, each specialist (otorhinolaryngologist, allergist, and dermatologist) diagnosed AR, BA, FA, and AD by data of antigen specific IgE or prick test. Self-diagnosis was excepted. About intake of lactic acid bacteria, those who are taking more than one bottle of yogurt or lactic acid bacteria beverage in five days or more of a week were considered as "regular intake." In regards to the student's academic performance, it was classified according to the academic ability level of their high school. This is because the high school students are distributed strictly according to the ranking of the achievement test in Japan. The questionnaires were distributed to students via their schools. In the collection of questionnaires, assistance was received from the Prefectural Association of High School Principals.

Statistical Analysis

Responses that do not have any missing data in all items required for analysis of the questionnaire were considered as valid responses. Differences in incidence, prevalence, and remission rates between diseases were compared using χ^2 tests. We applied a weighted regression analysis using the inverse probability weighting method with propensity scores and calculated adjusted odds ratios of the factors associated with the development and remission of allergic diseases.¹⁵ The propensity score model was estimated using a logistic regression model that adjusted for the patient characteristics listed in Table 1: age, gender, blood type, residential area, sibling status (only child or not; birth order), family history of allergic diseases, history of pet exposure, presence of abnormal bowel movement, intake of lactic acid bacteria, exposure to passive smoking, presence of dyshidrosis, exercise habits, and academic performance. There were 16 possible variables, and also when dummy variables were included, there were 34 variables, which were chosen for their potential association with the outcome of interest based on clinical knowledge. We followed standard methods to estimate sample size for multiple logistic regression, with at least 10 outcomes needed for each included independent variable. For example, with an expected event rate of at least 5%, we required 6800 subjects (340 events) to appropriately perform multiple logistic regression with 34 variables. Thus, the sample size of this study was sufficient. Model discrimination was assessed with c-statistics, and model calibration was assessed with Hosmer-Lemeshow statistics.

Statistical analysis was performed using R version 2.13.1 for Mac/OSX GUI 1.40-devel Leopard build 64-bit (R-project, <http://www.r-project.org/>). $p < 0.05$ was considered statistically significant.

Ethical Issues

This study was approved by the research ethics committee of the University of Fukui. We obtained authorization from the Fukui Prefecture Education Board to conduct the study as well as the consent of the school principals.

RESULTS

Study Population and Prevalence and Remission Rates

The characteristics of participating students are shown in Table 1. The overall incidence rate of allergic disease was 37.6%, with

Table 1. Characteristics of subjects

Explanatory Variable	Number of Students (%)
Age	
15 years old	2113 (9.7%)
16 years old	7269 (33.3%)
17 years old	6914 (31.7%)
≥18 years old	5243 (24.0%)
Sex	
Male	10896 (50.0%)
Female	10464 (48.0%)
Blood type	
Type A	8213 (37.7%)
Type B	4473 (20.5%)
Type O	6071 (27.8%)
Type AB	1972 (9.0%)
Area of residence	
Northern region of Fukui	17959 (82.4%)
Southern region of Fukui	3843 (17.6%)
Sibling status	
Only child	1630 (7.5%)
Firstborn	9310 (42.7%)
Family history	
AD	2520 (11.6%)
AR	4170 (19.1%)
BA	1987 (9.1%)
Exposure to pets	
Dog	7331 (33.6%)
Cat	3646 (16.7%)
Others	7215 (33.1%)
Abnormal bowel movement	
Constipation	4773 (21.9%)
Diarrhea	792 (3.6%)
Lactic acid bacteria	
Regular intake	4590 (21.1%)
Passive smoking	
Exposure (current or past)	14385 (66.0%)
Dyshidrosis	
Hyperhidrosis	6358 (29.2%)
Hypohidrosis	1915 (8.8%)
Partial hyperhidrosis	1951 (8.9%)
Exercise habits	
Currently exercise	9581 (43.9%)
Academic performance	
High group	7991 (36.7%)
Middle group	6487 (29.8%)
Low group	7324 (33.6%)

28.5% of students having two or more diseases. The incidence rate from birth to the present was 14.3% for AD, 22.6% for AR, 8.8% for BA, and 5.7% for FA. The present prevalence rate was 7.3% for AD, 19.2% for AR, 2.8% for BA, and 2.8% for FA (Fig. 1). The incidence and prevalence rates of AR were significantly higher than those of other diseases ($p < 0.001$). In AD, AR, and FA, it was shown that the incidence and prevalence rates of female students were higher than those of male students. The remission rate from birth to the present was 49.2% for AD, 15.3% for AR, 68.1% for BA, and 50.1% for FA (Fig. 2). The remission rate of AR was significantly lower than that of other diseases ($p < 0.001$).

Factors Associated with Development

The main factors associated with the development of allergic symptoms are as follows: male (AR, 1.20; BA, 1.31; FA, 0.80), only child (AR; 1.37; BA, 1.30; FA, 1.33), firstborn (AD, 0.89; AR, 1.38;

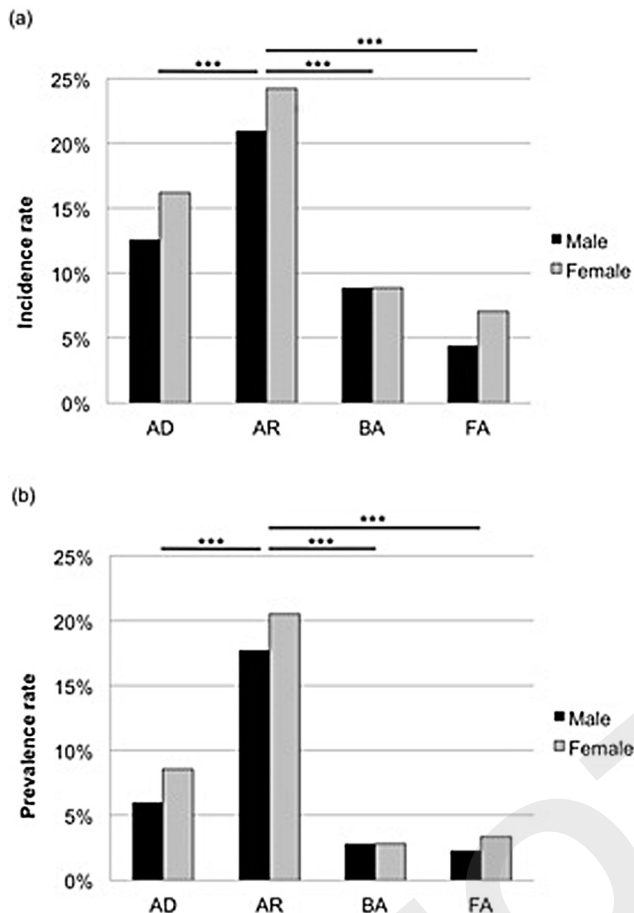


Figure 1. (A) The incidence rate of allergic diseases from birth to the present. (B) The present prevalence rate of allergic diseases. χ^2 test showed that the incidence and prevalence rates of AR were significantly higher than those of other diseases. ***, $p < 0.001$.

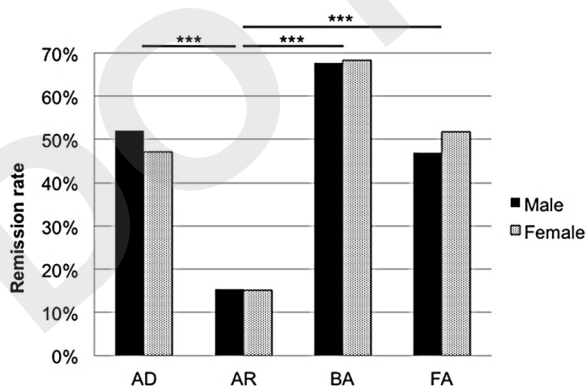


Figure 2. The remission rate of allergic diseases from birth to the present. χ^2 test showed that the remission rate of AR was significantly lower than that of other diseases. ***, $p < 0.001$.

BA, 1.10), family history of same disease (AD, 4.19; AR, 6.02; BA, 4.48), constipation (AD, 1.17; AR, 1.17), exposure to passive smoking (AD, 0.90; BA, 1.11), hyperhidrosis (AD, 0.89; AR, 1.08), hypohidrosis (AD, 1.25; FA, 1.44), and high academic performance (AR, 1.20; BA, 0.89). The values in parentheses are significant adjusted odds ratios (Table 2).

Factors Associated With Remission

The main factors associated with remission of symptoms are as follows: only child (BA, 1.96), firstborn (AD, 1.18), family history of same disease (AD, 0.49; AR, 0.50; BA, 0.48), regular intake of lactic acid bacteria (AD, 1.22), and hyperhidrosis (BA, 0.77). The values in parentheses are significant adjusted odds ratios (Table 3).

DISCUSSION

We previously conducted a survey of 1540 people aged 20–49 years in Fukui City, Japan, between 2006 and 2007 that indicated 69.7% of the adult population was positive for one of seven aeroallergen-specific IgEs (Japanese cedar pollen, two types of mites, ragweed, orchard grass, aspergillum, and candida) and found an AR prevalence of 44.2%.^{1,16} The prevalence of AR in adults has increased by 10% during the last 10 years. The Allergic Disease Surveillance Committee of the Ministry of Education, Culture, Sports, Science and Technology in Japan examined the prevalence of allergic diseases in 2004. In high school students, the prevalence rates were as follows: 4.0% for AD, 9.1% for AR, 3.6% for BA, and 1.9% for FA.¹⁷ The prevalence rates of this study were higher in every disease type, especially AR, compared with those of Ministry of Education, Culture, Sports, Science and Technology. In another investigation of changes over the years, the prevalence rates of allergic diseases also showed an increase during the past 10 years.

The reported inverse relationship between allergic disease and number of siblings, birth order, and number of older siblings has been well established.^{18,19} This association was first described by Strachan in 1989,²⁰ and he theorized that allergic diseases may be prevented by infections during childhood, passed between siblings by unhygienic contact, which he called “the hygiene hypothesis.” There is some evidence that infections are related to family size and siblings. Furthermore, there is some support for a direct protective effect of infections against allergic diseases, but this has not been consistently reported by all studies.^{21,22} In this study, only children and firstborns had a significantly higher risk of developing the symptoms of allergic diseases, and it might have been the result of the hygiene hypothesis.

Although constipation was an associated factor for the development of AD and AR, regular intake of lactic acid bacteria was not a factor for development of the diseases and was only a factor for remission of AD. There have been reports that probiotics are effective in the prevention and treatment of AD compared with other allergic diseases.²³ Compared with other allergic diseases, the development of AD symptoms is earlier, and symptoms of AD usually remit by adolescence.²⁴ Furthermore, the morbidity of AD differed with other diseases, which may be due to the relationship between indigenous bacteria of skin and intestinal bacterial flora as well as the fact that the main region of inflammation is not the respiratory mucous membrane but the skin. There was not enough evidence that probiotics play a role in the treatment of allergic airway diseases, such as AR and BA. This is consistent with recent findings that probiotic supplementation can protect infants attending childcare facilities against episodes of diarrheal illness and fever but does not protect them against respiratory illness.²⁵ The effects of probiotic supplementation are likely to be most marked in gastrointestinal disorders, or in related allergic diseases, such as AD associated with FA. Given the relative instability of the composition of infant intestinal microbiota, and the importance of FA in infants with AD, the role of probiotics in allergic disease treatment may be limited to AD and FA in young children. The heterogeneity of probiotic intake, in particular the diversity of probiotic strains, the given dosage and forms of administration, and the commencing time of ingestion make interpretation difficult. Metaanalyses and systematic reviews showed that probiotics cannot be recommended generally for primary prevention of atopic disease.²⁶ Further studies are needed to clarify the role of probiotics in AD treatment.

A factor for development of AD is hypohidrosis. Although the pathophysiology of AD is not fully known, it involves a complicated interaction of environmental and genetic factors that induce the ab-

Table 2. Analysis of the factors involved in the onset of allergic diseases

Explanatory Variable	AD		AR		BA		FA	
	Adjusted Odds Ratio	p-Value	Adjusted Odds Ratio	p-Value	Adjusted Odds Ratio	p-Value	Adjusted Odds Ratio	p-Value
Sex								
Male	0.965 (0.874–1.066)	0.484	1.198 (1.103–1.301)	<0.001***	1.306 (1.166–1.463)	<0.001***	0.797 (0.706–0.898)	<0.001***
Blood type								
AX (type A and AB)	0.974 (0.901–1.052)	0.501	1.071 (1.003–1.142)	0.039*	1.014 (0.926–1.112)	0.761	1.111 (1.008–1.225)	0.034*
BX (type B and AB)	1.110 (1.021–1.206)	0.014*	1.080 (1.007–1.159)	0.031*	0.898 (0.811–0.993)	0.037*	0.933 (0.838–1.039)	0.207
Area of residence								
Northern region of Fukui	0.928 (0.833–1.034)	0.176	0.995 (0.908–1.090)	0.913	0.827 (0.731–0.935)	0.003**	0.844 (0.740–0.962)	0.011*
Sibling status								
Only child	0.973 (0.822–1.152)	0.754	1.368 (1.200–1.560)	<0.001***	1.299 (1.090–1.547)	0.003**	1.328 (1.081–1.632)	0.007**
Firstborn	0.892 (0.821–0.965)	0.004**	1.384 (1.296–1.478)	<0.001***	1.102 (1.005–1.209)	0.040*	1.101 (0.997–1.215)	0.057
Family history								
AD	4.185 (3.751–4.670)	<0.001***	1.005 (0.891–1.135)	0.930	0.993 (0.839–1.176)	0.939	1.498 (1.272–1.763)	<0.001***
AR	1.088 (0.971–1.221)	0.147	6.017 (5.537–6.539)	<0.001***	0.984 (0.859–1.127)	0.813	1.153 (1.001–1.327)	0.048*
BA	1.063 (0.909–1.244)	0.444	1.272 (1.115–1.451)	<0.001***	4.477 (3.921–5.112)	<0.001***	1.382 (1.151–1.660)	<0.001***
Exposure to pets								
Dog	1.005 (0.924–1.092)	0.915	0.970 (0.904–1.040)	0.392	1.055 (0.957–1.164)	0.282	0.983 (0.885–1.092)	0.745
Cat	0.918 (0.822–1.026)	0.130	0.972 (0.886–1.066)	0.544	1.111 (0.981–1.259)	0.097	1.068 (0.934–1.221)	0.335
Others	0.985 (0.906–1.071)	0.727	1.105 (1.031–1.184)	0.005**	1.008 (0.913–1.112)	0.878	1.031 (0.929–1.145)	0.563
Abnormal bowel movement								
Constipation	1.165 (1.046–1.298)	0.006**	1.171 (1.069–1.284)	<0.001***	1.016 (0.889–1.160)	0.818	0.934 (0.815–1.071)	0.331
Diarrhea	0.937 (0.743–1.182)	0.584	1.093 (0.906–1.318)	0.351	1.270 (0.975–1.654)	0.076	0.970 (0.731–1.288)	0.835
Lactic acid bacteria								
Regular intake	1.084 (0.985–1.193)	0.100	1.012 (0.934–1.098)	0.763	1.096 (0.978–1.228)	0.116	0.997 (0.883–1.126)	0.963
Passive smoking								
Exposure (current or past)	0.903 (0.833–0.979)	0.013*	0.986 (0.921–1.056)	0.688	1.112 (1.008–1.227)	0.035*	0.954 (0.861–1.057)	0.369
Dyshidrosis								
Hyperhidrosis	0.889 (0.815–0.971)	0.009**	1.076 (1.002–1.155)	0.045*	1.051 (0.951–1.163)	0.331	1.036 (0.930–1.155)	0.519
Hypohidrosis	1.252 (1.097–1.429)	<0.001***	0.900 (0.798–1.016)	0.087	1.056 (0.894–1.247)	0.523	1.443 (1.232–1.690)	<0.001***
Partial hyperhidrosis	0.939 (0.817–1.081)	0.381	1.139 (1.016–1.277)	0.026*	1.109 (0.945–1.301)	0.203	1.103 (0.932–1.307)	0.255
Exercise habits								
Currently exercise	0.935 (0.854–1.024)	0.149	0.950 (0.881–1.024)	0.180	1.022 (0.918–1.137)	0.694	1.013 (0.900–1.139)	0.831
Academic performance								
High group	0.994 (0.915–1.080)	0.887	1.195 (1.117–1.280)	<0.001***	0.885 (0.802–0.978)	0.017*	0.973 (0.877–1.079)	0.601

Values in parentheses are 95% confidence intervals (propensity score analysis using inverse probability weighting method).

*, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$.

Table 3. Analysis of the factors involved in the remission of allergic diseases

Explanatory Variable	AD		AR		BA		FA	
	Adjusted Odds Ratio	p-Value	Adjusted Odds Ratio	p-Value	Adjusted Odds Ratio	p-Value	Adjusted Odds Ratio	p-Value
Sex								
Male	1.147 (0.962–1.367)	0.126	0.972 (0.792–1.193)	0.786	0.890 (0.710–1.116)	0.313	0.852 (0.672–1.078)	0.183
Blood type								
AX (type A and AB)	1.125 (0.975–1.297)	0.106	0.949 (0.813–1.108)	0.510	0.914 (0.758–1.102)	0.347	0.925 (0.767–1.115)	0.412
BX (type B and AB)	0.899 (0.771–1.048)	0.174	0.791 (0.666–0.941)	0.008**	1.024 (0.830–1.264)	0.825	0.919 (0.747–1.131)	0.427
Area of residence								
Northern region of Fukui	1.195 (0.981–1.456)	0.077	1.102 (0.882–1.376)	0.393	0.880 (0.681–1.138)	0.331	0.791 (0.609–1.028)	0.080
Sibling status								
Only child	0.761 (0.549–1.055)	0.101	1.047 (0.734–1.495)	0.799	1.964 (1.317–2.929)	<0.001***	1.253 (0.830–1.890)	0.283
Firstborn	1.183 (1.022–1.370)	0.024*	0.967 (0.827–1.130)	0.670	1.118 (0.924–1.352)	0.252	1.093 (0.902–1.324)	0.365
Family history								
AD	0.485 (0.409–0.576)	<0.001***	1.120 (0.843–1.487)	0.434	1.273 (0.917–1.768)	0.150	0.708 (0.530–0.945)	0.019*
AR	1.005 (0.820–1.232)	0.960	0.497 (0.418–0.591)	<0.001***	0.841 (0.647–1.094)	0.197	0.972 (0.752–1.255)	0.827
BA	0.991 (0.752–1.307)	0.951	1.040 (0.771–1.403)	0.797	0.478 (0.383–0.597)	<0.001***	1.151 (0.816–1.622)	0.423
Exposure to pets								
Dog	1.110 (0.952–1.294)	0.184	0.977 (0.823–1.161)	0.795	0.868 (0.709–1.063)	0.172	1.044 (0.851–1.280)	0.679
Cat	1.087 (0.883–1.340)	0.431	1.187 (0.954–1.477)	0.124	0.778 (0.602–1.007)	0.056	1.193 (0.918–1.551)	0.187
Others	1.148 (0.985–1.338)	0.078	1.042 (0.886–1.225)	0.618	1.196 (0.975–1.467)	0.086	0.961 (0.788–1.173)	0.697
Abnormal bowel movement								
Constipation	0.950 (0.787–1.148)	0.596	0.974 (0.780–1.216)	0.815	1.120 (0.861–1.457)	0.399	1.017 (0.778–1.328)	0.904
Diarrhea	1.401 (0.863–2.273)	0.173	1.276 (0.808–2.014)	0.295	1.150 (0.638–2.071)	0.642	1.321 (0.711–2.453)	0.379
Lactic acid bacteria								
Regular intake	1.216 (1.018–1.452)	0.031*	1.070 (0.883–1.295)	0.491	0.971 (0.769–1.225)	0.802	0.987 (0.775–1.257)	0.916
Passive smoking								
Exposure (current or past)	0.942 (0.811–1.094)	0.433	0.934 (0.795–1.098)	0.407	1.176 (0.957–1.445)	0.124	0.949 (0.777–1.160)	0.610
Dyshidrosis								
Hyperhidrosis	1.007 (0.854–1.186)	0.936	0.905 (0.760–1.077)	0.259	0.769 (0.624–0.947)	0.013*	1.220 (0.988–1.508)	0.065
Hypohidrosis	1.050 (0.827–1.334)	0.687	0.781 (0.560–1.089)	0.146	0.949 (0.663–1.358)	0.773	0.797 (0.586–1.084)	0.148
Partial hyperhidrosis	1.088 (0.832–1.423)	0.538	1.310 (1.021–1.680)	0.034*	1.383 (0.978–1.957)	0.067	1.116 (0.790–1.577)	0.532
Exercise habits								
Currently exercise	1.157 (0.976–1.372)	0.092	0.962 (0.802–1.155)	0.679	1.147 (0.896–1.468)	0.278	1.152 (0.911–1.456)	0.237
Academic performance								
High group	1.136 (0.972–1.329)	0.110	1.173 (0.999–1.377)	0.052	1.093 (0.887–1.346)	0.405	1.052 (0.856–1.291)	0.631

Values in parentheses are 95% confidence intervals (propensity score analysis using inverse probability weighting method).

*, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$.

normalities in the structure and function of the epidermal barrier and immune system.²⁷ The skin barrier of AD patients is known to be damaged in both eczematous lesions and also in clinically unaffected skin. Nonlesional skin of patients with AD is thus not normal healthy skin but is characterized by a subclinical eczema reaction and a disturbed barrier function not visible to the naked eye, but which can be detected instrumentally. Therefore, the use of moisturizers is considered standard therapy for the treatment of AD.²⁸ The purpose is to improve dry skin with decreased barrier functions and also to prevent recurrence of inflammation. Previous randomized controlled studies showed that moisturizer use reduced the amount of topical corticosteroid use.²⁹ It has been suggested that AD can be prevented in children who sweat less and have dry skin, when the skin is kept clean, and skin moisture is kept at a suitable level.

High academic performance was a factor for development of AR and was a negative factor for development of BA. Because the symptoms of BA are manifested earlier than those of AR and develop at a time that interferes with fundamental learning, development of BA symptoms may have caused a fall in academic performance. However, excluding the explanatory variables used for this analysis, factors such as living environment, eating habits, sleeping hours, antimicrobial drug use, income of parents, and stress may be involved with academic performance, which we should take into consideration.

In observational studies, such as this study, exposure allocation is frequently influenced by subject characteristics. Therefore, there often exist systematic differences between exposure groups in observational studies. We must use statistical methods to remove or minimize the effect of this confounding, so that valid inferences about exposure effect can be drawn from observational studies. Propensity score methods are increasingly being used to reduce or minimize the confounding that occurs frequently in observational studies of the effect of treatment or exposure on outcomes. The propensity score is the probability of exposure assignment conditional on measured baseline covariates. Conditioning on the propensity score results in unbiased estimates of linear exposure effects.³⁰

In conclusion, the results of this epidemiologic survey suggest that several factors in addition to "hygiene hypothesis" (birth order and size of sibling) and intestinal condition seem to be influential in the development of symptoms and remission of allergic diseases. By intervening at an early stage of childhood, development of symptoms of allergic diseases, from infancy to adolescence, may likely be controlled. However, because the morbidity and pathophysiology of each disease are different, further research is needed.

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