
Breastfeeding and prevalence of allergic diseases in Japanese university students

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Background: Although historical support exists for the concept that breastfeeding might be protective against allergic diseases, contradictory findings have been observed recently.

Objective: To investigate the cumulative prevalence of allergic diseases in Japanese university students and to identify explanatory variables including breastfeeding.

Methods: From March 18, 2003, through March 29, 2005, a total of 9,615 students newly enrolled at the University of Tokyo responded to a written questionnaire on allergic diseases.

Results: Cumulative prevalence of allergic rhinitis, atopic dermatitis, and asthma was 47.2%, 17.4%, and 9.3%, respectively. These data were closely correlated, and prevalence of any 1 of the 3 diseases significantly increased the odds for historical prevalence of the other 2 ($P < .001$). Male sex (odds ratio [OR], 1.5; 95% confidence interval [CI], 1.4–1.7) and maternal (OR, 2.2; 95% CI, 2.0–2.5) or paternal (OR, 1.6; 95% CI, 1.4–1.8) history of allergic rhinitis were significant correlates of increased odds for allergic rhinitis. Maternal (OR, 2.7; 95% CI, 1.6–4.5), paternal (OR, 3.8; 95% CI, 2.2–6.6), or sibling (OR, 1.9; 95% CI, 1.5–2.4) history of atopic dermatitis was a significant correlate of increased odds for atopic dermatitis. As for asthma, maternal (OR, 4.9; 95% CI, 3.0–7.9), paternal (OR, 4.0; 95% CI, 2.3–7.0), or sibling (OR, 3.3; 95% CI, 2.4–4.5) history of asthma was a significant correlate of increased odds. Logistic regression analysis showed no consistent evidence of the effects of breastfeeding on the cumulative prevalence.

Conclusion: The cumulative prevalence of these diseases among young adults revealed that the effect of breastfeeding is negligible when compared with genetic factors.

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INTRODUCTION

Some investigators have supported the concept that breastfeeding is protective against allergic diseases,^{1–3} whereas others suggest that breastfeeding is associated with increased odds for allergic diseases.^{4–9} However, no comprehensive study has tracked their cumulative prevalence after puberty in a large population of young adults. The aim of the present study was to investigate the cumulative prevalence and the factors associated with increased prevalence of allergic diseases in a university student population, specifically whether breastfeeding causes a difference in the prevalence of allergic rhinitis (AR), atopic dermatitis (AD), and asthma among students newly enrolled at the University of Tokyo.

METHODS

Participants and Procedures

A series of questionnaires, designed with ethical considerations by the Health Service Centre at the University of

Tokyo, were filled out by students who were going to enter the university from March 18, 2003, through March 29, 2005. The questionnaires (Table 1) were mailed to the students in advance, filled out by them with their families at home, and collected on the day of their physical checkup performed at the Health Service Centre. In total, 9,615 freshmen students responded to the questionnaires, of whom 7,688 were male and 1,927 were female (Table 2). The response rate was 100.0%, 98.7%, and 99.7% in 2003, 2004, and 2005, respectively. The aim and method of this study were described in the questionnaire, and informed consent was obtained on using the data for clinical investigation as well as promoting health care for the students. The study was approved by the ethnics committee of clinical research in the Health Service Centre.

Statistical Analyses

Statistical analyses were performed by using Dr. SPSS II 11.0.1 J (SPSS Japan Inc, Tokyo, Japan). We used “cumulative prevalence of each disease” to mean a history of disease being prevalent at any time during a student’s life up until the time of completing the questionnaire. A step-forward approach was used to build a logistic regression model with potential explanatory variables such as sex and parental history of allergic diseases entered one at a time in order of statistical importance. A likelihood ratio test was used at each entry step to verify how well the logistic regression equation

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Table 1. Study Questions

1. Do you have a history of allergic rhinitis (including hay fever)?
 - Yes
 - Age of onset, y
 - Present status: persistent, remedied, or unknown
 - Dominant season (multiple answers allowed): spring, summer, fall, winter, throughout the year, or other
 - Diagnosed by physician? Yes/no
 - No
2. Do you have a history of atopic dermatitis?
 - Yes
 - Age of onset, y
 - Present status: persistent, remedied, or unknown
 - Dominant season (multiple answers allowed): spring, summer, fall, winter, throughout the year, or other
 - No
3. Do you have a history of asthma?
 - Yes
 - Age of onset, y
 - Present status: persistent, remedied, unknown
 - Dominant season (multiple answers allowed): spring, summer, fall, winter, throughout the year, or other
 - No
4. Do you have any family member who has experienced allergic diseases?
 - Yes
 - Who and what kind of allergic disease
 - No
 - Unknown
5. Were you breastfed or fed with formula?
 - Breastfeeding only, formula only, both, or unknown
 - Duration of breastfeeding, wk

Table 2. Number of Students Who Responded to the Surveys Between 2003 and 2005^a

Year	2003	2004	2005
Total	3,335 (3,261)	3,122 (3,069)	3,158 (3,094)
Male	2,685 (2,623)	2,468 (2,423)	2,535 (2,484)
Female	650 (638)	654 (646)	623 (610)

^a Numbers of students younger than 21 years are shown in parentheses.

fit our data by summing the squares of the deviance residuals. The level of significance used to decide whether a potential explanatory variable should enter the model was .1. $P < .05$ denoted the presence of a statistically significant effect of a factor. Odds ratios (ORs) are the outcome of the logistic regression analyses. The variables evaluated in the analysis were male sex; maternal, paternal, and sibling history of each allergic disease; nutrition in infancy; duration of breastfeeding; and history of other allergic diseases. Two kinds of classification were used for nutrition in infancy: nutrition 1 indicates exclusive formula vs mixed nutrition (both breastfeeding and formula) vs exclusive breastfeeding as the reference category, and nutrition 2 indicates breastfeeding vs exclusive formula as the reference. The exclusive-breastfeeding group and the mixed-nutrition group were combined.

Because previous studies have adopted various kinds of classifications for the duration of breastfeeding,^{1-3,7-11} 4 kinds of classification were tried for our analyses: duration 1 indicates that 4 categories (up to 4 weeks, 4–12 weeks, 12–24 weeks, and 24 weeks) were studied with no breastfeeding as the reference; duration 2, the duration of more than 4 weeks vs the group of up to 4 weeks as the reference; duration 3, the duration of more than 12 weeks vs the group of 12 weeks or less as the reference; and duration 4, the duration of more than 24 weeks vs the group of 24 weeks or less as the reference. The terms *asthma*, *allergic rhinitis*, and *atopic dermatitis* were not defined in the questionnaires.

RESULTS

Most of the students enrolled in this study were 18, 19, or 20 years of age. The median age (interquartile range) of the participants was 18 years (18–19 years) throughout the 3 years of the study. To minimize the variance of age, only students younger than 21 years were enrolled in the following statistical analyses (Table 2). The percentage of participants younger than 21 years was 97.8%, 98.3%, and 98.0% in 2003, 2004, and 2005, respectively. Because differences in data among the 3 years were very small in general, we pooled them to simplify the analyses and presentation, whereas the results of logistic regression analyses were compared with those of similar analyses in single years.

Table 3 lists the cumulative prevalence of the 3 allergic diseases. Almost half of the participants answered that they had a history of AR, and 75.4% of those who answered positively (35.6% of all freshmen) reported persistent disease. A total of 66.2% of those who answered “yes” had their condition diagnosed by a physician; thus, the cumulative prevalence of AR diagnosed by a physician was 31.3%. A total of 17.4% of the participants answered that they had a history of AD, and 51.5% of the cases (affecting 9.0% of all freshmen) were persistent. A total of 9.3% of the participants answered that they had asthma, and 21.1% of the cases (affecting 2.0% of all freshmen) were persistent. A total of 31.9% of the participants with a history of AR had AD and/or asthma. A total of 70.0% of those with a history of AD had AR and/or asthma. A total of 82.2% of those with a history of asthma had AR and/or AD. Multiple allergic diseases (2 or 3 of the 3 diseases in an individual) were found in 16.0% of all the participants, whereas the proportion of participants who had at least 1 of the 3 diseases was 55.1%. Figure 1 demonstrates the distributions of onset age for the allergic diseases. The peak onset age of AR was 10 years in the total population; however, a clear contrast exists between the onset age of perennial cases and that of seasonal cases. A prominent peak of AD and asthma onset was found at younger than 1 year and at 4 years of age, respectively.

The proportion of exclusive breastfeeding, exclusive formula feeding, mixed nutrition, and “unknown” was 31.2%, 6.2%, 47.3%, and 10.5%, respectively. The percentage of missing values was 4.8%. The percentage of students who responded to the questions concerning the duration of breastfeeding was 62.9% in the exclusive-breastfeeding group and

Table 3. Descriptive Statistics on Allergic Diseases (in Students Younger Than 21 Years)^a

Allergic disease	No. (%) of students [% with disease]
AR	
Yes	4,452 (47.2)
Yes, persistent	3,355 (35.6)
Yes, remedied	189 (2.0)
Yes, unknown	744 (7.9)
Yes, spring	2,330 [52.3]
Yes, summer	96 [2.2]
Yes, fall	332 [7.5]
Yes, winter	227 [5.1]
Yes, throughout the year	1,319 [29.6]
Yes, other	285 [6.4]
Yes, diagnosed by a physician	2,945 [66.2]
Cumulative prevalence of diagnosed disease, %	31.3
Yes, not diagnosed	1,356 [30.5]
AR with AD and/or asthma	1,422 [31.9]
No	4,961 (52.6)
AD	
Yes	1,644 (17.4)
Yes, persistent	847 (9.0)
Yes, remedied	547 (5.8)
Yes, unknown	249 (2.6)
AD with AR and/or asthma	1,150 [70.0]
No	7,775 (82.5)
Asthma	
Yes	876 (9.3)
Yes, persistent	185 (2.0)
Yes, remedied	494 (5.2)
Yes, unknown	192 (2.0)
Asthma with AR and/or AD	720 [82.2]
No	8,545 (90.7)
Family history	
Yes	4,073 (43.2)
AR	
Mother	1,752 (18.6)
Father	1,365 (14.5)
Sibling	1,107 (11.7)
AD	
Mother	90 (1.0)
Father	80 (0.8)
Sibling	642 (6.8)
Asthma	
Mother	90 (1.0)
Father	66 (0.7)
Sibling	238 (2.5)
No	4,855 (51.5)
Unknown	4,85 (5.1)
Multiple allergic diseases	1,509 (16.0)

Abbreviations: AD, atopic dermatitis; AR, allergic rhinitis.

^a Percentages of all participants (younger than 21 years) in each year are shown in parentheses. Percentages of students with the disease are shown in brackets.

58.9% in the mixed-nutrition group, respectively. This finding means that approximately 40% of the breast-fed respondents had no idea how long the duration was.

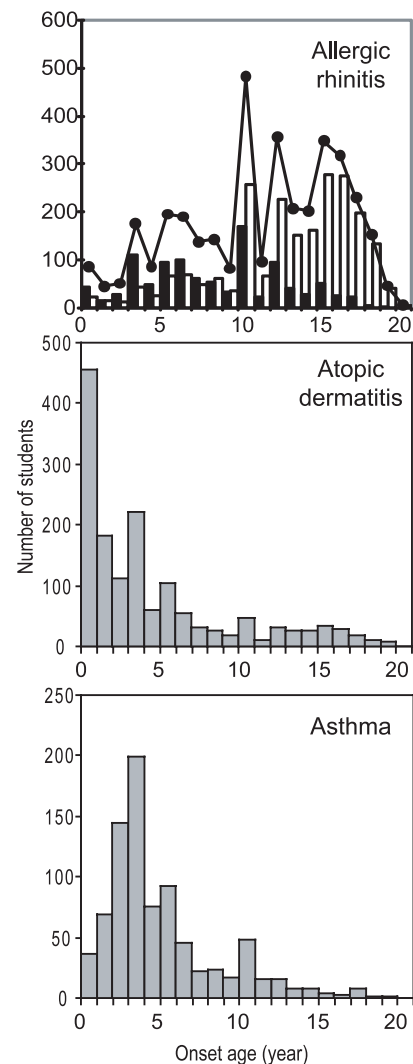


Figure 1. Distributions of onset age for allergic rhinitis (upper panel), atopic dermatitis (middle panel), and asthma (lower panel) in students younger than 21 years. In the upper panel, age distributions in perennial cases, seasonal cases, and the total are represented by black bars, white bars, and thick line, respectively.

Figure 2 demonstrates distributions of the duration. In the exclusive-breastfeeding group, the peak is approximately the same as the mean (SD) value: 47.7 (19.5) weeks. In the mixed-nutrition group, the configuration of the distribution is deviated: A high peak is found at approximately 14 weeks, which is a much shorter length of time than the mean (SD) value: 21.4 (16.6) weeks.

Logistic regression analysis using a single explanatory variable was executed to overview individual effects of variables on the cumulative prevalence. In the analysis on AR, male sex; maternal, paternal, or sibling history of AR; and a patient's positive history of AD or asthma were significant correlates of increased odds. As for the effects of nutrition in

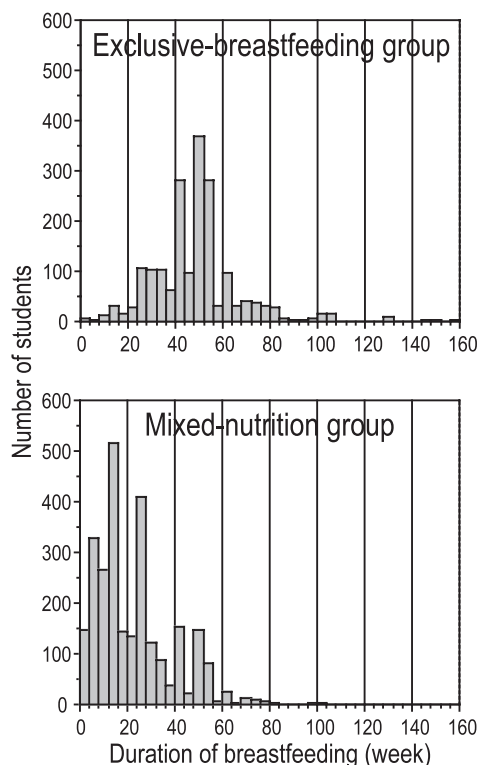


Figure 2. Distributions of the duration of breastfeeding in exclusive-breastfeeding (upper panel) and mixed-nutrition (lower panel) groups in students younger than 21 years.

infancy, no result showed any significant difference between the groups in each of the 2 classifications. The duration of breastfeeding showed no significant effect in each of the 4 classifications. Next, logistic regression analysis with multiple explanatory variables was used to investigate the effects of combinations of variables (Table 4). All of the 6 significant variables mentioned herein were used as possible variables. Nutrition 1 was added arbitrarily as a possible confounding factor. A final logistic regression model in the pooled data included 6 variables: male sex, maternal history, paternal history, sibling history, the patient's history of AD, and the patient's history of asthma. However, when we repeated the same analysis using data in single years, sibling history was significant only in 2005 ($P < .001$). We considered the other 5 factors as significant because they were significant in any of the 3 years. We tried another analysis in which prevalence of AR was considered positive only when it was diagnosed by a physician. This analysis of a limited group in the pooled data or in single years, however, revealed the same 5 significant factors.

Male sex was not a significant correlate of increased or decreased odds as a single explanatory variable for AD. Maternal, paternal, or sibling history of AD and the patient's positive history of AR or asthma were significant correlates of increased odds. Nutrition in infancy caused no significant

difference between the groups in each of the 2 classifications. As for the duration of breastfeeding, longer durations were significant correlates of increased odds for AD. However, ORs showed that the effect was very weak. The OR for the duration of more than 24 weeks in duration 1 was 1.3 ($P = .03$). The OR in duration 2, duration 3, and duration 4 was 1.2 ($P = .03$), 1.3 ($P = .001$), and 1.2 ($P = .007$), respectively. Besides the 5 significant variables, duration 3 was used as a potential explanatory variable for logistic regression analysis with multiple variables (Table 4). Male sex was added as a potential confounding factor. A final logistic regression model in the pooled data included 7 variables: male sex, maternal history, paternal history, sibling history, the patient's history of AR, the patient's history of asthma, and duration 3. However, when we repeated the same analysis using data in single years, duration 3 was not significant in any of the 3 years. Male sex was a significant correlate of decreased odds only in 2005 ($P = .02$). Consequently, we considered the other 5 factors as significant because they were significant in any of the 3 years.

In the logistic regression analysis using a single explanatory variable for asthma, male sex; maternal, paternal, or sibling history of asthma; and the patient's positive history of AR or AD were significant correlates of increased odds. As for nutrition, we found no significant difference between the groups in each of the 2 classifications. Similarly, the duration of breastfeeding showed no significant effect in each of the 4 classifications. All of the 6 significant variables were used as potential variables for analysis with multiple variables (Table 4). Nutrition 1 was arbitrarily added as a potential confounding factor. A final logistic regression model in the pooled data included 6 variables: male sex; maternal, paternal, and sibling history; the patient's history of AR; and the patient's history of AD. However, when we repeated the same analysis using data in single years, male sex was significant only in 2003 ($P = .02$) and 2005 ($P = .03$). Consequently, we considered the other 5 factors as significant because they were significant in any of the 3 years.

We applied a 2-way analysis of variance, adopting family history of the allergic disease (any positive history of mother, father, or siblings vs no such history) and multiple allergic diseases (2 or more of the 3 diseases vs only 1) as potential factors, to evaluate these effects on the age at onset. For AR, family history had no significant main effect. However, the main effect of multiple allergic diseases was significant ($F_{1,1} = 254.31$, $P < .001$), and the onset age of participants with multiple allergic diseases (mean [SD], 9.0 [5.0]) was significantly younger than that of participants with AR only (11.8 [4.5]). We found no significant interaction between family history and multiple diseases. For AD, family history had no significant main effect. However, the main effect of multiple allergic diseases was significant ($F_{1,1} = 7.89$, $P = .005$), and the onset age of participants with multiple allergic diseases (mean [SD], 3.8 [4.6]) was significantly younger than that of participants with AD only (4.5 [5.2]). We found no significant interaction between family history and multiple diseases.

Table 4. Logistic Regression Analyses of the Pooled Data^a

Factors	AR			AD			Asthma		
	Rate, %	<i>P</i> value	OR (95% CI)	Rate, %	<i>P</i> value	OR (95% CI)	Rate, %	<i>P</i> value	OR (95% CI)
Sex									
Male	49.1	<.001	1.5 (1.4–1.7)	17.1	.006	0.8 (0.7–0.9)	9.8	.001	1.4 (1.2–1.7)
Female	40.1			18.7			7.3		
Maternal history									
No	42.9			17.2			8.9		
Yes	66.4	<.001	2.2 (2.0–2.5)	48.9	<.001	2.7 (1.6–4.5)	38.5	<.001	4.9 (3.0–7.9)
Paternal history									
No	44.6			17.1			9.1		
Yes	63.1	<.001	1.6 (1.4–1.8)	55.0	<.001	3.8 (2.2–6.6)	32.8	<.001	4.0 (2.3–7.0)
Sibling history									
No	45.4			16.3			8.7		
Yes	61.9	<.001	1.4 (1.2–1.6)	33.3	<.001	1.9 (1.5–2.4)	28.9	<.001	3.3 (2.4–4.5)
Nutrition 1									
Exclusive breastfeeding	47.0			19.1			9.9		
Exclusive formula	51.1			17.1			11.4		
Mixed	48.7			18.0			9.8		
Nutrition 2 (breastfeeding, yes or no)									
No	51.1			17.1			11.4		
Yes	48.0			18.5			9.8		
Duration 1, wk									
0	51.1			17.4			11.4		
<0 to ≤4	50.5			17.5			12.2		
<4 to ≤12	48.5			17.6			9.5		
<12 to ≤24	51.3			20.7			10.0		
<24	50.5			21.5			11.8		
Duration 2, wk									
≤0 to ≤4	50.9			17.4			11.7		
<4	50.3			20.6			11.0		
Duration 3, wk									
≤0 to ≤12	49.8			17.5			10.7		
<12	50.7			21.3	.013	1.2 (1.0–1.4)	11.4		
Duration 4, wk									
≤0 to ≤24	50.3			18.5			10.5		
<24	50.5			21.5			11.8		
Other allergic disease 1									
No history	43.7			11.7			4.8		
History	64.7	<.001	2.0 (1.8–2.3)	23.9	<.001	2.1 (1.8–2.4)	14.2	<.001	2.7 (2.3–3.2)
Other allergic disease 2									
No history	44.8			15.0			6.5		
History	72.3	<.001	2.6 (2.2–3.1)	41.3	<.001	3.2 (2.7–3.9)	21.9	<.001	3.3 (2.9–3.9)

Abbreviations: AD, atopic dermatitis; AR, allergic rhinitis; CI, confidence interval; OR, odds ratio.

^a Factors not included in logistic regression analyses with multiple explanatory variables are indicated in italics with neither *P* value nor OR. Nutrition 1 was added as a potential confounding factor for AR and asthma, but it was not approved in step-forward model building.

For asthma, neither family history nor multiple diseases had a significant main effect. We also found no significant interaction between the 2 factors.

DISCUSSION

A number of prospective birth cohort studies^{5–9} have recently suggested that breastfeeding might be a risk factor for allergic diseases. The reasons that some studies of breastfeeding show protection and others show increased risk might relate to the duration of a follow-up period and the ages at which out-

comes are evaluated. Studies in which early childhood outcomes were evaluated show protection from prolonged or exclusive breastfeeding, whereas studies in which outcomes were evaluated later in childhood show increased allergic diseases associated with prolonged or exclusive breastfeeding, especially in those genetically at risk.^{4,5,12} Our investigation might have avoided the effect of age, since the cumulative prevalence in young adults should reap data that reflect both the early and late effects. It has been pointed out that infants with a strong family history of atopic disease or early

signs such as infantile eczema might be breastfed longer in the hope that breastfeeding might reduce the risk.^{13–15} To decrease the bias introduced by mothers' breastfeeding choices, we evenly adopted both genetic factors and nutritional factors in step-forward model-building as potential confounding factors. Although breastfeeding longer than 12 weeks was a significant correlate of increased odds for AD in the pooled data (Table 4), the OR of 1.2 was very weak. No increased OR was found in any single years, and we could not find any other convincing evidence of the effects of breastfeeding. This is consistent with recent reports.^{11,16,17} In a recent study of Japanese junior high school students ages 12 to 15 years, half of the students had been mixed milk feeders, whereas only 8% had consumed artificial milk exclusively.¹⁰ The proportion is close to our results, and this consistency supports the accuracy of our data.

The atopic march is the natural history of atopic manifestations, characterized by a typical progression of the clinical signs of atopic disease, with some signs becoming more prominent and others subsiding. We confirmed that in the case of any combination of AR, AD, and asthma, there was a significantly higher prevalence of one allergic disease when a positive history of the others coexisted.

The present study examined the cumulative prevalence of 3 allergic diseases in the Japanese adolescent population, which has rarely been studied. Our results revealed a high rate of AR because almost half of the participants had AR. One clear reason is that our study used cumulative prevalence, which is the percentage of people who have ever had a condition, whereas previous studies^{18,19} used mostly current prevalence, which is the percentage with symptoms during the previous 12 months. Few studies that use criteria similar to ours reported values close to our results.²⁰ One concern about AR is the possibility that there are many subjects whose conditions were not diagnosed by physicians. However, our cumulative prevalence of diagnosed AR was 31.3%, consistent with previous studies.^{20–22} A family history of allergy, and especially a family history of AR, is the most established risk factor for AR.^{23–25}

A total of 9.0% of the freshmen had AD at the time of our study. This prevalence rate is consistent with data of 13- and 14-year-olds in recent multicountry cross-sectional surveys²⁶ and with a study that used skin examinations to ascertain the prevalence of AD²⁷; the Japanese study reported that 11% of adolescents between 16 and 18 years of age had AD. As revealed in our logistic regression analysis, most patients with AD have a personal or familial aggregation of AD, AR, and allergic asthma,²⁸ and twin studies have provided strong support for the heritability of AD.²⁹

In 1998, Takemura et al³⁰ investigated asthma in Japanese children ages 6 to 15 years by questionnaires and reported that the cumulative prevalence of the disease was approximately 10%. The participants of our study in 2003 to 2005 belong to a similar population, and 9.3% of them reported that they had asthma. The factors that were significant cor-

relates of increased odds in our logistic regression analysis are consistent with previous reports on asthma.^{31,32}

Our findings must be viewed in conjunction with several limitations of the study design, mainly methodologic drawbacks.³³ Diagnosis in our study was based on questionnaire data alone, with no gold standard for the definition of the diseases. In a methodologic study by Kilpeläinen et al,³⁴ questions on reported "asthma" and "physician-diagnosed asthma" throughout life had good positive predictive value and were highly specific. In contrast, questions referring to "allergic" nasal symptoms throughout life worked well in screening and diagnosing, but the most exact diagnosis was obtained only by a further question: "Has the disease been diagnosed by a physician?" Recollection after a long period could have affected the accuracy of our data in the questionnaire method. For example, a high peak at 10 years for AR in Figure 1 might be related to the fact that 10 is a convenient number for a recall questionnaire. It is a drawback that we did not investigate several factors found to be significant in previous studies, such as maternal or family smoking status, birth order, and maternal age.¹⁸ Furthermore, the great disparity in the male-to-female ratio, which is unique to our university and uncommon in others, might influence the results. Our participants had enough time to answer the questions at home in consultation with their family, and the response rate was nearly 100%. The large number and homogenous nature of our patient group make our analysis more reliable. All of the patients were freshmen in a university, so they had a similar age and educational level. The selection of university students might introduce a selection bias due to socioeconomic status, as indicated in old data.¹⁸ However, at least to some extent, our patients appear to represent the adolescent population of Japan. These advantages are reflected by the fact that our observations were highly reproducible through 3 years and consequently consistent with previous reports as mentioned herein. In conclusion, the cumulative prevalence of allergic diseases among young adults revealed that the effect of breastfeeding is negligible when compared with genetic factors.

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