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Age-specific associations of early daycare, older siblings, severe airway infection, and preterm birth with subsequent atopic diseases

Tadao Nagasaki¹  | Takahiro Tabuchi² | Hisako Matsumoto³ | Kenta Horimukai⁴

¹Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan

²Department of Cancer Epidemiology, Cancer Control Center, Osaka International Cancer Institute, Osaka, Japan

³Department of Respiratory Medicine & Allergology, Faculty of Medicine, Kindai University, Osaka, Japan

⁴Department of Pediatrics, Jikei University Katsushika Medical Center, Tokyo, Japan

Correspondence

Tadao Nagasaki, Department of Respiratory Medicine, Graduate School of Medicine Kyoto University, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan.
Email: nagasaki@kuhp.kyoto-u.ac.jp

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Abstract

Background: The effects of infection and developmental adaptations in infancy on the prevalence of subsequent atopy-related diseases at different ages during childhood are not fully determined. This study aims to examine the similarities and differences in the age-specific association of asthma, allergic rhinitis/conjunctivitis, and atopic dermatitis with early-life infection-related factors (i.e., daycare, older siblings, and severe airway infection) and developmental adaptations (i.e., preterm birth and rapid weight gain) in children.

Methods: In this longitudinal cohort study ($n = 47,015$), children were followed from 0.5 to 11 years. The potential risks and protective factors, including daycare attendance at 0.5 years, existence of older siblings, history of hospitalization due to cold/bronchitis/bronchiolitis/pneumonia during 0.5–1.5 years, preterm birth, and rapid weight gain in the first 2.5 years, were assessed using multivariable logistic regression with adjustments for potential confounders.

Results: A protective association was observed between early-life daycare attendance and asthma at 5.5–9 years, which disappeared after 10 years. A protective association was also noted throughout childhood between early daycare attendance and older siblings with allergic rhinitis/conjunctivitis. However, the association between early daycare and atopic dermatitis was found to be risky during childhood. In contrast, the early-life history of hospitalization owing to cold/bronchitis/bronchiolitis/pneumonia was identified to be a risk factor for developing both asthma and allergic rhinitis/conjunctivitis. Preterm birth was a significant risk factor for childhood asthma.

Conclusion: Different age-specific patterns were demonstrated in the relationship between early daycare, severe airway infection, preterm birth, and atopy-related diseases in childhood.

KEYWORDS

allergic rhinitis/conjunctivitis, asthma, atopic dermatitis, infection, preterm birth

1 | INTRODUCTION

Investigating the etiology of atopic diseases such as asthma, allergic rhinitis/conjunctivitis, and atopic dermatitis has remained to be a challenge. Reports^{1,2} have indicated that a part of the development of atopic diseases is dictated by the growing organs and immune systems (environmental exposures and host predispositions in early-life), in addition to genetic and epigenetic factors, which can modify the development of atopic diseases. However, the findings that have been reported on the effects of early-life risk and protective factors on subsequent atopic diseases have been noted to be inconsistent. This study focused on infection and developmental adaptations in infants as the two major influencing factors in the development of diseases related with atopic march because these factors were recently shown to play an important role on subsequent asthma as early-life origins.¹

The effects of infection in early-life on atopic diseases, including asthma, are conflicting. The hygiene hypothesis suggests that exposure to microbes, through contact with other children or livestock, during immunologic maturation may lower the risk of the subsequent development of atopic diseases. This hypothesis may explain the increase in the prevalence of atopic diseases over the last few decades: a lower opportunity for airway infection and/or exposure to microbes in early-life due to the improvement in

Key Message

The etiology of atopic diseases such as asthma, allergic rhinitis/conjunctivitis, and atopic dermatitis is not fully understood. Research findings reporting the effects of early-life risk and protective factors on subsequent atopic diseases are inconsistent. This research revealed the similarities and differences of the age-specific associations of several atopic diseases that share the characteristics of atopic manifestations with early-life factors using one cohort. The findings in this study will help to identify strategies to prevent or delay the development of atopic diseases.

hygiene and a decrease in family size. However, the relationship between infection and subsequent atopic diseases remains inconsistent. Severe infection, such as hospitalization with bronchiolitis, has been determined as a risk factor for the development of asthma.³

The relationship between developmental adaptations in infants and subsequent atopic diseases also show inconsistent findings. Recently, it has been shown that the effect of potential factors on

TABLE 1 Patient characteristics of each atopic disease at the age of 5.5 years

	%	n	Children with asthma (n = 3298)	Children without asthma (n = 35,242)	Children with allergic rhinitis/conjunctivitis (n = 5046)	Children without allergic rhinitis/conjunctivitis (n = 33,494)	Children with atopic dermatitis (n = 3022)	Children without atopic dermatitis (n = 35,518)
	%		%	%	%	%	%	%
Sex, male	51.9	20016	62.8***	50.9	60.3***	50.7	52.5	51.9
Preterm birth (<37 weeks)	4.9	1868	5.6*	4.8	5.1	4.8	4.1*	4.9
Maternal smoking after birth, present	14.6	5607	16.3**	14.5	12.7***	14.9	13.8	14.7
Breast feeding (≥4 months)	64.6	24904	66.4*	64.5	66.2*	64.4	69.6***	64.2
Older siblings, present	50.3	19389	50.7	50.3	41.4***	51.7	52.9**	50.1
Daycare attendance, present	18.3	6923	15.6***	18.5	14.7***	18.8	20.5**	18.1
Cold/bronchitis/bronchiolitis/pneumonia, hospitalization, present	6.6	2487	10.4***	6.2	7.0	6.5	7.5*	6.5
Early atopic dermatitis, present	16.1	6126	27.4***	15.1	24.1***	14.9	60.5***	12.4
Overweight gain, present	9.9	3378	11.2*	9.8	11.6***	9.6	9.6	9.9

Note: P values were for comparisons between the 2 groups of population with and without asthma, allergic rhinitis/conjunctivitis, or atopic dermatitis.

* $p < .05$, ** $p < .01$, *** $p < .0001$.

asthma, such as rapid weight gain, may differ at different ages.⁴⁻⁶ The age-dependent pathophysiology involved in the development of atopic diseases could explain the inconsistent relationships. Furthermore, to explore the similarities and differences for asthma, allergic rhinitis/conjunctivitis, and atopic dermatitis could lead to prevent occurrence of each disease by revealing common exposures to the three atopy-related diseases and disease distinct factors. However, there exist no studies that have analyzed the effect of early-life factors on the development of the three atopy-related diseases with repeated measurements of outcomes at different ages using one large cohort.

The main aim of this study was to assess the longitudinal phenotype at 5.5–11 years, defined by the association of the three atopy-related diseases with early-life factors and their time course, using one large cohort. We have investigated the relationships of the characteristics in early-life, including early daycare attendance, existence of older siblings, history of severe airway infection, preterm birth, and overweight gain, with the longitudinal prevalence of atopic diseases in a cohort of children.

2 | METHODS

2.1 | Data

The Longitudinal Surveys of Babies Born in the 21st Century by the Japanese Ministry of Health, Labour and Welfare is a birth cohort that was described previously.^{7,8} Babies born between January 10 and 17, 2001, in Japan were included in this study. The Ministry asked households to participate in the survey by explaining the purpose of obtaining basic data. The first survey was conducted at 6 months. Follow-up surveys were conducted at the ages of 1.5, 2.5, 5.5, 7, 8, 9, 10, and 11 years. We obtained permission from the Japanese Ministry of Health, Labour and Welfare to use the data for this study. The study protocol was approved by the Ethics Committee of Osaka International Cancer Institute (No. 1508119060 and 1508119060–2).

2.2 | Variables

The questionnaires were sent by mail, filled out by a family member, and sent back by mail. Asthma, allergic rhinitis/conjunctivitis, and atopic dermatitis were the outcome variables. The incidence of asthma, allergic rhinitis/conjunctivitis, or atopic dermatitis was based on the medical doctors' diagnosis of the disease with physician visits due to compatible symptoms during the previous year at 5.5, 7, 8, 9, 10, and 11 years, which was reported by a family member repeatedly in the same subjects at different ages.

Early-life infection-related factors (daycare attendance, the presence of older siblings, and severe airway infection) and developmental adaptations (preterm birth and rapid weight gain) were used as the main factors. Information on daycare attendance was obtained when the infant was 6 months of age. The daycare

attendance records were then analyzed based on a positive response to the question, "Does the child attend a childcare?" The data on the existence of older siblings were defined as having one or more older siblings at 6 months. A history of hospitalization owing to cold/bronchitis/bronchiolitis/pneumonia during the last 12 months was evaluated at 1.5 years.³ Preterm birth was defined as delivery at <37 weeks.⁹ Infant rapid weight gain was defined as weight gain above the 90th percentile between the weight at birth and the weight at the age of 2.5 divided by the exact number of months between those two measurements. The 90th percentile is used according to a previous report.⁶ As potential confounding factors, sex, maternal smoking including household smoking at 6 months, breastfeeding at 1.5 years, and early atopic dermatitis at 2.5 years were assessed.¹⁰ Breastfeeding was defined as feeding ≥ 4 months.¹¹ The evaluated time point of each potential factor was decided based on previous studies (Table S1).

2.3 | Statistical analysis

Two groups were compared using χ^2 test. The main outcomes were asthma, allergic rhinitis/conjunctivitis, and atopic dermatitis in children. Generalized estimating equations were used to estimate logistic regression models for the repeated measurements of asthma, allergic rhinitis/conjunctivitis, and atopic dermatitis from 5.5 to 11 years using SPSS 18 (SPSS Inc.). Age was adjusted as dummy variables and interaction terms with potential factors were included. Age-specific adjusted odds ratios (ORs) calculated from the combinations of estimated regression coefficients of these potential factors and interaction terms have been reported. The standard errors and the Wald 95% confidence intervals were obtained through the standard variance formula (for the sum of two random variables) using the sandwich variance-covariance matrix.

This study investigated the effect of the early occurrence of atopic dermatitis on the subsequent asthma and allergic rhinitis/conjunctivitis, because multiple longitudinal studies have provided evidence supporting the atopic march between early atopic dermatitis and subsequent allergies.^{12,13} Based on previous reports, the factors related to the incidence of asthma, including daycare attendance, existence of older siblings, a history of hospitalization owing to cold/bronchitis/bronchiolitis/pneumonia, preterm birth, and rapid weight gain were analyzed and adjusted for the potential confounders of asthma, including sex, maternal smoking, breastfeeding, the presence of early atopic dermatitis, and allergic rhinitis/conjunctivitis at 5.5–11 years (Table S2). The confounders were also selected based on previous studies. To analyze allergic rhinitis/conjunctivitis, we used the same factors mentioned barring "the presence of allergic rhinitis/conjunctivitis" and asthma. To analyze asthma with allergic rhinitis/conjunctivitis, we used the following factors: daycare, older siblings, severe airway infections, preterm birth, rapid weight gain, sex, maternal smoking, breastfeeding, and early atopic dermatitis (Table S2). To analyze atopic dermatitis, we used the same factors mentioned barring the "presence of early atopic dermatitis" and

asthma. The probability values for the statistical tests were two-tailed, and $p < .05$ was regarded as statistically significant.

3 | RESULTS

3.1 | Study characteristics and prevalence of atopic diseases

Of the 47,015 children born in 2001 in the cohort, the data on the factors were available in 38,540; 36,798; 36,151; 35,275; 34,145; and 32,913 children at the ages of 5.5, 7, 8, 9, 10, and 11 years, respectively. The clinical characteristics of the study subjects were determined to be similar between the ages of 5.5 and 11 years and are presented in Table 1. The prevalence of asthma was reported to be 8.6% at 5.5 years and showed a linear decrease to 5.4% at 11 years (Figure S1). Atopic dermatitis showed a similar trend: 7.8% at 5.5 years and 5.9% at 11 years. On the contrary, the prevalence of allergic rhinitis/conjunctivitis showed a linear increase, with 13% at 5.5 years and 24% at 11 years.

3.2 | Relationship of early-life infection-related factors and developmental adaptations with asthma, allergic rhinitis/conjunctivitis, and atopic dermatitis: multivariable analysis

The strength of the protective association between daycare attendance and asthma has been noted to decrease with increasing age; the adjusted odds ratio (OR) of daycare attendance showed a significant

inverse association with asthma between 5.5 and 9 years, and this significant reduction in the risk of asthma disappeared after 10 years (Figure 1). The association between older siblings and asthma was not observed (Figure 2). On the contrary, the association between the history of hospitalization due to cold/bronchitis/bronchiolitis/pneumonia and asthma was risky throughout childhood (Figure 3). Preterm birth was a risk factor for asthma between 7 and 11 years (Figure 4). Meanwhile, rapid weight gain was a risk factor for asthma at 9 years (Figure 5).

For allergic rhinitis/conjunctivitis, early daycare and older siblings showed protective associations with its incidence throughout childhood. The association of a history of hospitalization due to cold/bronchitis/bronchiolitis/pneumonia with allergic rhinitis/conjunctivitis was found to be risky at the age of 8, 9, 11 years. Its risky association with preterm birth and rapid weight gain was only seen at 8 and 5.5 years, respectively.

For asthma with allergic rhinitis/conjunctivitis, early daycare and older siblings were found to be protective at the age of 5.5, 7, 8, 9, and 11 years, while a history of hospitalization due to cold/bronchitis/bronchiolitis/pneumonia was found to be a risky association throughout childhood. Preterm birth was risky at the age of 7 years, and rapid weight gain was risky at the age of 8 and 10 years.

On the other hand, daycare and older siblings were identified to be risk factors for the development of atopic dermatitis at the age of 5.5, 7, 8, 10 years. The results of the confounding factors are shown in Table S3.

4 | DISCUSSION

To the best of our knowledge, this is the first longitudinal study that has highlighted the similarities and differences in the

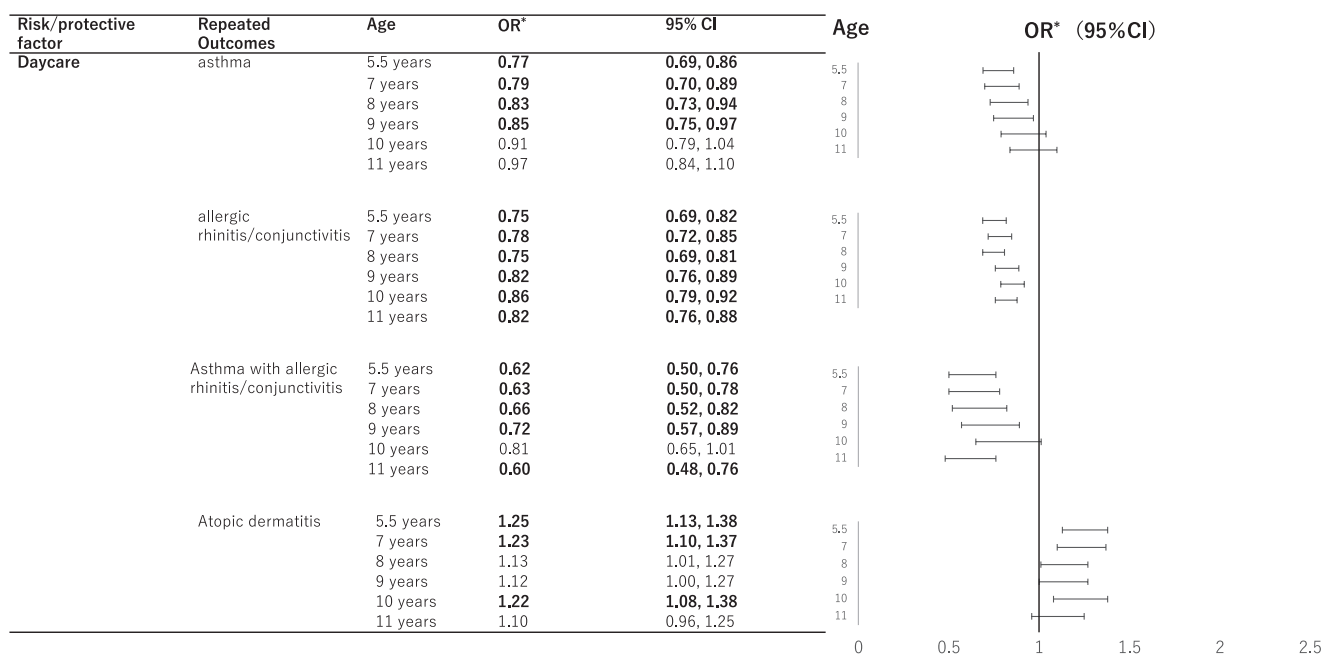


FIGURE 1 The adjusted odds ratios and 95% confidence intervals of daycare in patients with asthma, allergic rhinitis/conjunctivitis, and atopic dermatitis at different ages

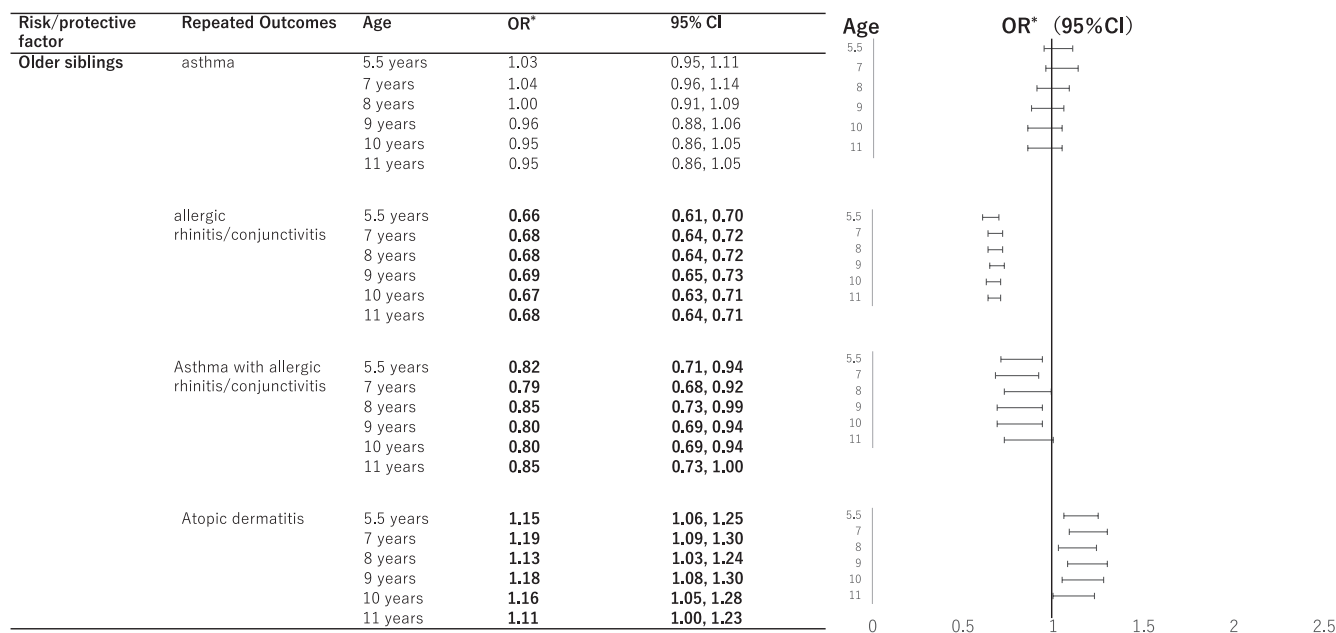


FIGURE 2 The adjusted odds ratios and 95% confidence intervals of older siblings in patients with asthma, allergic rhinitis/conjunctivitis, and atopic dermatitis at different ages

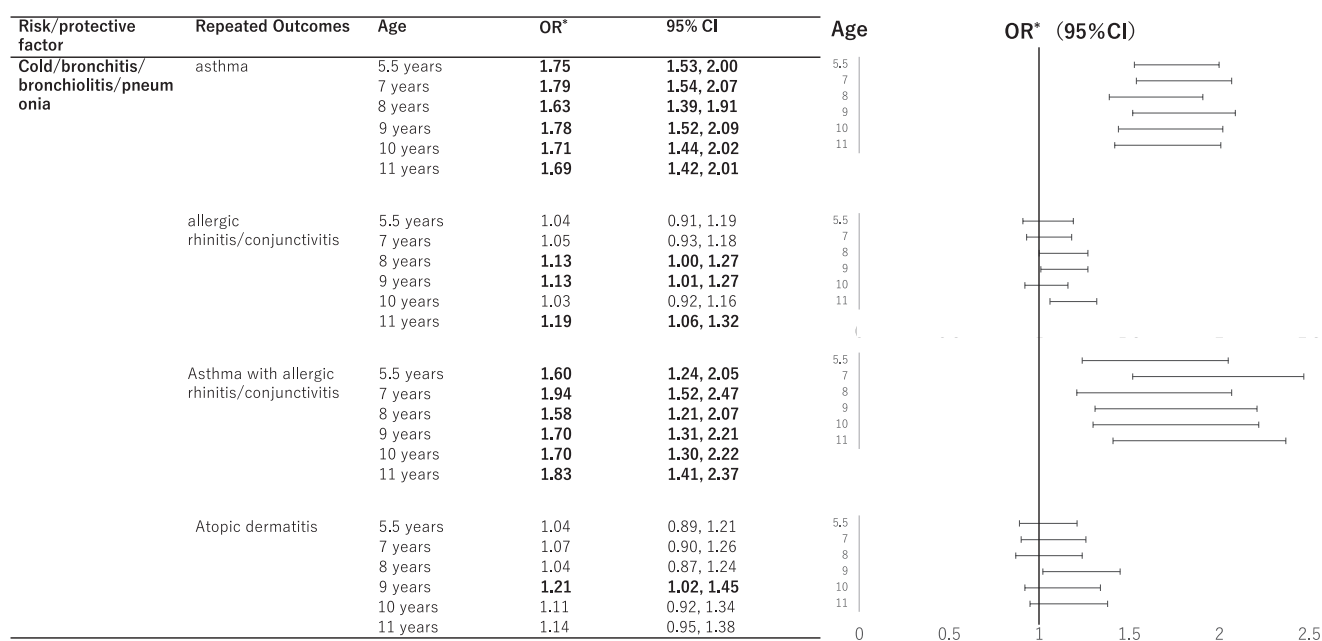


FIGURE 3 The adjusted odds ratios and 95% confidence intervals of history of hospitalization due to cold/bronchitis/bronchiolitis/pneumonia in patients with asthma, allergic rhinitis/conjunctivitis, and atopic dermatitis at different ages

age-specific associations of the three atopy-related diseases with early-life factors using a large and a long-term cohort. The protective effect of daycare attendance during infancy in preventing the development of childhood asthma attenuated after 10 years old, while the protective effect of exposure to infectious agents in preventing the development of allergic rhinitis/conjunctivitis remained throughout childhood. This effect was not observed in

atopic dermatitis. In contrast, a history of severe airway infection showed an increased risk of developing asthma throughout childhood. In addition, preterm birth was a significant risk factor for developing asthma throughout childhood, with a small effect on allergic rhinitis/conjunctivitis and atopic dermatitis. Rapid weight gain in infancy did not significantly affect the development of atopy-related diseases.

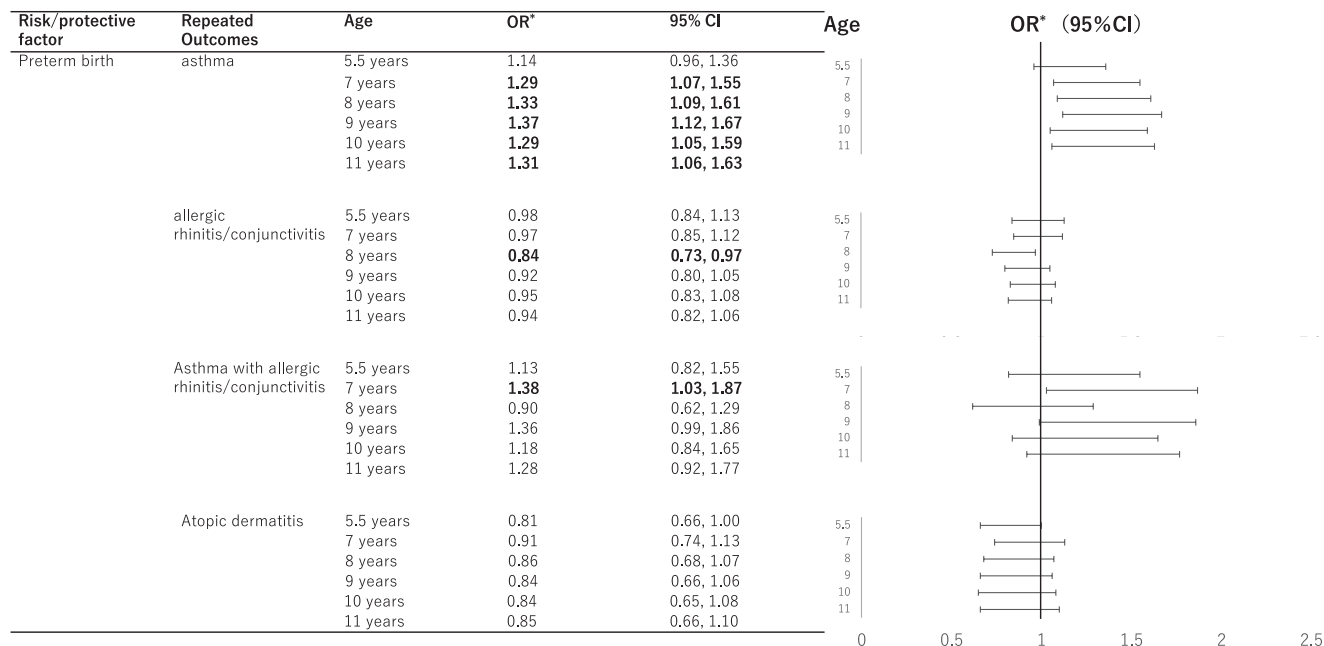


FIGURE 4 The adjusted odds ratios and 95% confidence intervals of preterm birth in patients with asthma, allergic rhinitis/conjunctivitis, and atopic dermatitis at different ages

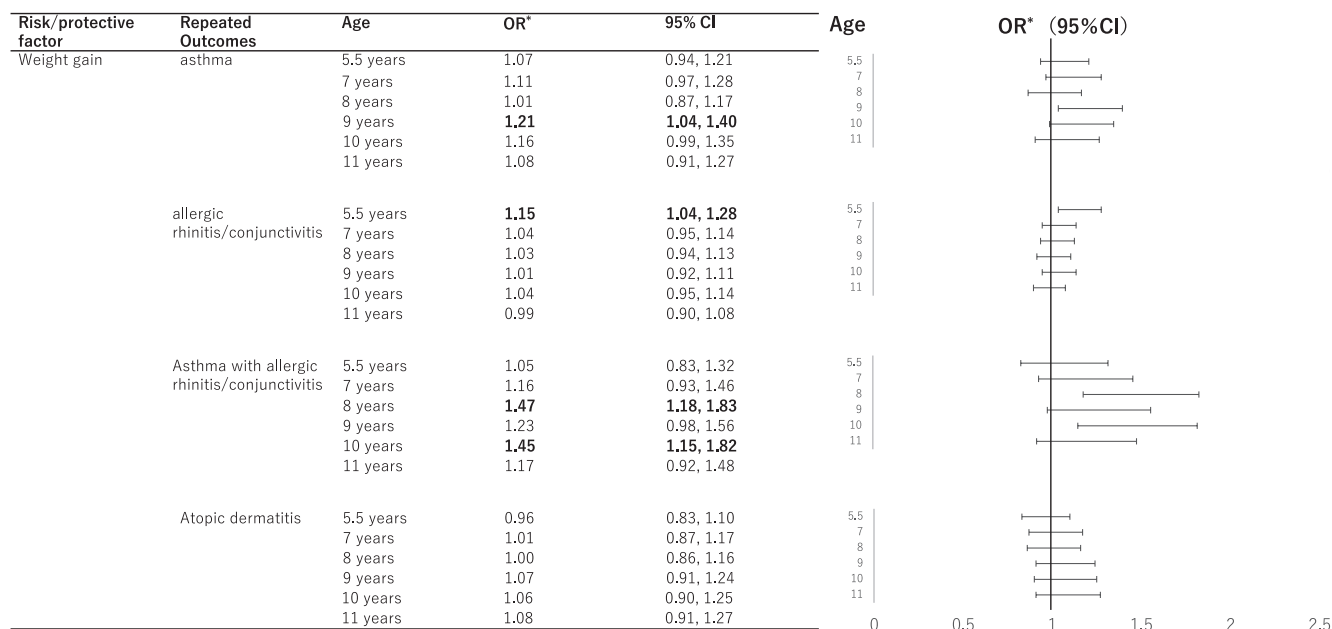


FIGURE 5 The adjusted odds ratios and 95% confidence intervals of rapid weight gain in patients with asthma, allergic rhinitis/conjunctivitis, and atopic dermatitis at different age

Daycare attendance has prevented the development of asthma in selected age groups, and its protective effect remained throughout childhood in allergic rhinitis/conjunctivitis, whereas the opposite was seen in atopic dermatitis. Contact with other infants in daycare or siblings at home reflects frequent exposure to infectious agents.¹⁴ In a study comparing the characteristics between

Amish and Hutterites,¹⁵ the mechanism of protection against asthma has been determined to be related with innate immunity mediated by microbes in dust. The transient protective effect of daycare in this study confirmed the result of a previous longitudinal study⁵ that investigated the relationship between airway symptoms and early daycare. On the contrary, early-life daycare

increased the subsequent risk of developing atopic dermatitis.¹⁶ This inverse relationship could be related to the differences of barrier intensity and indigenous microbiota between the airway and the skin. A previous study reported that early-life daycare attendance may cause non-atopic eczema with a different pathogenesis from that of atopic diseases.¹⁷ This shows that a number of different mechanisms play a role in the development of allergic airway diseases and skin disease associated with daycare. On the other hand, this study did not indicate an association between older siblings and the prevention of developing of asthma in children, which is in line with a report by Nicolaou et al.¹⁸

The effect of an episode of severe airway infection on the subsequent development of asthma and allergic rhinitis/conjunctivitis was harmful. Some patients may have early colonization of pathogenic bacteria in the airways, which may then predispose them to bronchiolitis with symptoms severe enough to warrant hospitalization resulting in an increased susceptibility to developing childhood asthma. This was opposite to the protective effect of exposure to microbes when attending daycare. The mechanisms of the inverse association of severe airway infection and daycare with allergic airway diseases remain unknown. However, a highly variable microbial composition in early-life¹⁹ that is induced by commensal and pathogenic bacteria and environmental microbes could be the difference on whether the immune system becomes susceptible or resistant to allergic airway diseases. The airway²⁰ and gut microbiomes^{21,22} were also suggested to be one of the features which may potentially alter the phenotype of immune responses. In addition, Illi et al. suggested that the number and sites of infections early in life may determine the risk of subsequent asthma.²³ A complicated network may be involved in the association between infection and allergic diseases.

This study showed the fact that babies born before 37 weeks of gestation are prone to suffer from childhood asthma as has been demonstrated in a previous study.⁹ A meta-analysis of European children pointed out that preterm birth in infants was associated with asthma and that preterm birth mainly explains the association between a lower birth weight and asthma in childhood.⁹ It has been regarded that patients with immature lung growth in early-life experience altered lung structure such as bronchial wall thickening, sub-pleural opacities and fibrosis, increased respiratory symptoms,²⁴ and ongoing respiratory morbidity,²⁵ eventually resulting in lung dysfunction and chronic lung diseases^{26,27} in childhood and adulthood that exhibit hyperreactivity with chemokine and cytokine stimulation.²⁸

Moreover, our study indicated that rapid weight gain did not seem to be as relevant to the development of asthma in children, although the cause of obesity-related asthma in children was shown to occur in infancy in a European birth cohort study. This might be explained by the small number of obese children and adults in Japan.²⁹

Our study has some limitations. First, we did not measure the bronchial hyperresponsiveness to diagnose asthma.⁵ The prevalence of asthma in this study was similar to that of asthma in another survey

in 2002 that assessed children with asthma across 11 prefectures in Japan.³⁰ Second, we did not have a replication population. Instead, we assessed 3 atopic diseases with allergic manifestations using different age groups. Furthermore, we used a cohort study that covers a large population. Third, patients' statements may have been biased due to recall memory. However, repeated measurements with a large longitudinal study could reduce the risk of misclassification of atopy-related diseases.

In conclusion, we have demonstrated markedly different patterns in the relationship of the potent factors in infancy and the development of atopy-related diseases in childhood. Further cohort studies are required to determine whether preventing or delaying early-life influences in growing years could modify atopy-related diseases progression.

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CONFLICT OF INTEREST

The authors have no relevant conflicts of interests to declare.

AUTHOR CONTRIBUTION

Tadao Nagasaki: Conceptualization (lead); Formal analysis (equal); Methodology (equal); Writing – original draft (lead). **Takahiro Tabuchi:** Conceptualization (supporting); Data curation (supporting); Formal analysis (equal); Methodology (equal); Project administration (lead); Resources (lead); Writing – review & editing (supporting). **Hisako Matsumoto:** Conceptualization (supporting); Methodology (supporting); Supervision (equal); Writing – review & editing (supporting). **Kenta Horimukai:** Conceptualization (supporting); Methodology (supporting); Supervision (equal); Writing – review & editing (supporting).

PEER REVIEW

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ORCID

Tadao Nagasaki  <https://orcid.org/0000-0002-3231-7841>

REFERENCES

- Martinez FD, Guerra S. Early origins of asthma. Role of microbial dysbiosis and metabolic dysfunction. *Am J Respir Crit Care Med*. 2018;197(5):573-579.
- Pincus M, Keil T, Rucke M, et al. Fetal origin of atopic dermatitis. *J Allergy Clin Immunol*. 2010;125(1):273-275.e4.
- Sigurs N, Gustafsson PM, Bjarnason R, et al. Severe respiratory syncytial virus bronchiolitis in infancy and asthma and allergy at age 13. *Am J Respir Crit Care Med*. 2005;171:137-141.
- Simpson A, Brough HA, Haider S, Belgrave D, Murray CS, Custovic A. Early-life inhalant allergen exposure, filaggrin genotype, and the development of sensitization from infancy to adolescence. *J Allergy Clin Immunol*. 2020;145:993-1001.

5. Caudri D, Wijga A, Scholtens S, et al. Early daycare is associated with an increase in airway symptoms in early childhood but is no protection against asthma or atopy at 8 years. *Am J Respir Crit Care Med*. 2009;180:491-498.
6. Rzehak P, Wijga AH, Keil T, et al. Body mass index trajectory classes and incident asthma in childhood: results from 8 European Birth Cohorts—a Global Allergy and Asthma European Network initiative. *J Allergy Clin Immunol*. 2013;131(6):1528-1536.e13.
7. Fujiwara T, Ito J, Kawachi I. Income inequality, parental socioeconomic status, and birth outcomes in Japan. *Am J Epidemiol*. 2013;177:1042-1052.
8. Kanoh M, Kaneita Y, Hara M, et al. Longitudinal study of parental smoking habits and development of asthma in early childhood. *Prev Med*. 2012;54:94-96.
9. Sonnenschein-Van Der Voort AM, Arends LR, de Jongste JC, et al. Preterm birth, infant weight gain, and childhood asthma risk: a meta-analysis of 147,000 European children. *J Allergy Clin Immunol*. 2014;133:1317-1329.
10. Roduit C, Frei R, Depner M, et al. Phenotypes of atopic dermatitis depending on the timing of onset and progression in childhood. *JAMA Pediatr*. 2017;171:655-662.
11. Kull I, Almqvist C, Lilja G, Pershagen G, Wickman M. Breast-feeding reduces the risk of asthma during the first 4 years of life. *J Allergy Clin Immunol*. 2004;114:755-760.
12. Burgess JA, Dharmage SC, Byrnes GB, et al. Childhood eczema and asthma incidence and persistence: a cohort study from childhood to middle age. *J Allergy Clin Immunol*. 2008;122:280-285.
13. Carlsten C, Dimich-Ward H, Ferguson A, et al. Atopic dermatitis in a high-risk cohort: natural history, associated allergic outcomes, and risk factors. *Ann Allergy Asthma Immunol*. 2013;110:24-28.
14. Ball TM, Castro-Rodriguez JA, Griffith KA, Holberg CJ, Martinez FD, Wright AL. Siblings, day-care attendance, and the risk of asthma and wheezing during childhood. *N Engl J Med*. 2000;343:538-543.
15. Stein MM, Hrusch CL, Gozdz J, et al. Innate immunity and asthma risk in Amish and Hutterite farm children. *N Engl J Med*. 2016;375:411-421.
16. Pekkanen J, Remes S, Kajosaari M, Husman T, Soininen L. Infections in early childhood and risk of atopic disease. *Acta Paediatr*. 1999;88:710-714.
17. Kusel MM, Holt PG, De Klerk N, Sly PD. Support for 2 variants of eczema. *J Allergy Clin Immunol*. 2005;116:1067-1072.
18. Nicolaou NC, Simpson A, Lowe LA, Murray CS, Woodcock A, Custovic A. Day-care attendance, position in sibship, and early childhood wheezing: a population-based birth cohort study. *J Allergy Clin Immunol*. 2008;122(3):500-506.e5.
19. Man WH, de Steenhuijsen Piters WA, Bogaert D. The microbiota of the respiratory tract: gatekeeper to respiratory health. *Nat Rev Microbiol*. 2017;15:259-270.
20. Bisgaard H, Hermansen MN, Buchvald F, et al. Childhood asthma after bacterial colonization of the airway in neonates. *N Engl J Med*. 2007;357:1487-1495.
21. Stokholm J, Blaser MJ, Thorsen J, et al. Maturation of the gut microbiome and risk of asthma in childhood. *Nat Commun*. 2018;9:1-10.
22. Fujimura KE, Sitarik AR, Havstad S, et al. Neonatal gut microbiota associates with childhood multisensitized atopy and T cell differentiation. *Nat Med*. 2016;22:1187-1191.
23. Illi S, von Mutius E, Lau S, et al. Early childhood infectious diseases and the development of asthma up to school age: a birth cohort study. *BMJ*. 2001;322:390-395.
24. Been JV, Lugtenberg MJ, Smets E, et al. Preterm birth and childhood wheezing disorders: a systematic review and meta-analysis. *PLoS Medicine*. 2014;11:e1001596.
25. Hennessy EM, Bracewell M, Wood N, et al. Respiratory health in pre-school and school age children following extremely preterm birth. *Arch Dis Child*. 2008;93:1037-1043.
26. Fawke J, Lum S, Kirkby J, et al. Lung function and respiratory symptoms at 11 years in children born extremely preterm: the EPICure study. *Am J Respir Crit Care Med*. 2010;182:237-245.
27. Martinez FD. Early-life origins of chronic obstructive pulmonary disease. *N Engl J Med*. 2016;375:871-878.
28. Matías V, San Feliciano L, Fernández JE, et al. Host and environmental factors influencing respiratory secretion of pro-wheezing biomarkers in preterm children. *Pediatr Allergy Immunol*. 2012;23:441-447.
29. Nagasaki T, Matsumoto H, Kanemitsu Y, et al. Integrating longitudinal information on pulmonary function and inflammation using asthma phenotypes. *J Allergy Clin Immunol*. 2014;133(5):1474-1477.e2.
30. Nishima S, Chisaka H, Fujiwara T, et al. Surveys on the prevalence of pediatric bronchial asthma in Japan: a comparison between the 1982, 1992, and 2002 surveys conducted in the same region using the same methodology. *Allergol Int*. 2009;58:37-53.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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