

Age-specific associations of early life infections and preterm birth with subsequent atopic diseases

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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 (i.e., daycare, older siblings, and severe airway infection) and developmental adaptations (i.e., preterm birth and overweight 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 overweight gain at 1.5 years, were assessed using multivariable logistic regression with adjustments for potential confounders. Results: A negative association was observed between early life daycare attendance and asthma at 5.5–9 years, which disappeared after 10 years. A negative association was also noted throughout childhood between early life daycare attendance and the presence of older siblings with allergic rhinitis/conjunctivitis. However, the association between early daycare and atopic dermatitis was found to be positive 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 life daycare, severe airway infection, preterm birth, and atopy-related diseases in childhood.

Age-specific associations of early life infections and preterm birth with subsequent atopic diseases

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Results: A negative association was observed between early life daycare attendance and asthma at 5.5–9 years, which disappeared after 10 years. A negative association was also noted throughout childhood between early life daycare attendance and the presence of older siblings with allergic rhinitis/conjunctivitis. However, the association between early daycare and atopic dermatitis was found to be positive 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 life daycare, severe airway infection, preterm birth, and atopy-related diseases in childhood.

Key Words: infection, preterm birth, asthma, allergic rhinitis/conjunctivitis, atopic dermatitis

Key Message: The etiology of atopic diseases such as asthma, allergic rhinitis/conjunctivitis, and atopic dermatitis are 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. This study could potentially help to modify atopic diseases progression by preventing or delaying early life influences.

Abbreviation: OR, odds ratio

Introduction

Investigating the etiology of atopic diseases such as asthma, allergic rhinitis/conjunctivitis, and atopic dermatitis has remained to be 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 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. In this study, we focused on infection and developmental adaptations in infants as the two major influencing factors in the development of diseases related with atopic march.

The effects of infection in early life on atopic diseases, including asthma, are conflicting. The hygiene hypothesis shows that exposure to microbes, through contact with other children or livestock, during immunologic maturation may lower the risk for 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 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 asthma, such as overweight 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 longitudinal studies that have analyzed the age-specific association of the three atopic diseases with the early life factors.

The main aim of this study was to assess the longitudinal phenotype, 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 that were followed from birth.

Methods

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, 3.5, 4.5, 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).

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 common outcomes. The incidence of asthma, allergic rhinitis/conjunctivitis, or atopic dermatitis was based on a positive response to the question, “Has the child visited a physician with the diagnosis of the disease (bronchial asthma, allergic rhinitis/conjunctivitis, or atopic dermatitis) in the last year?”

Early life infection (due to daycare attendance, the presence of older siblings, and severe airway infection) and developmental adaptations (preterm birth and overweight 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 weeks⁹. Infant overweight 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 at 6 months,

breastfeeding, and early atopic dermatitis at 2.5 years were assessed¹⁰. Breastfeeding was defined as feeding [?]4 months¹¹. The evaluated time point of factors was shown in Table S1.

Statistical analysis

Two groups were compared using χ^2 test. The main outcomes were asthma, allergic rhinitis/conjunctivitis, and atopic dermatitis in children. Multivariable logistic regression was used to estimate the adjusted odds ratios with 95% confidence intervals for the following potential factors. 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 overweight gain were analyzed and adjusted for the potential confounders of asthma, including sex, maternal smoking, breastfeeding, and presence of early atopic dermatitis. We used the same factors to analyze allergic rhinitis/conjunctivitis; in addition, to analyze atopic dermatitis, we used the same factors mentioned barring “presence of early atopic dermatitis.” The probability values for the statistical tests were two-tailed, and $P < 0.05$ was regarded as statistically significant. All statistical analyses were performed via JMP system version 15 (SAS Institute Inc., Cary, NC, USA).

Results

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 and Tables S2–6. 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.

Protective and risk factors for the development of atopic diseases: univariable analysis

In the univariable analysis, early daycare attendance between the ages of 5.5 and 8 years resulted in a significant reduction in the risk of developing asthma. Meanwhile, significant risks of developing asthma were noted for those infants who had a history of hospitalization owing to cold/bronchitis/bronchiolitis/pneumonia, preterm birth, and overweight gain (Table 1 and Tables S2–6). Children with rhinitis/conjunctivitis had inverse associations with early daycare attendance and older siblings while having a positive association with overweight gain. Children with atopic dermatitis had a higher frequency of early daycare, older siblings, and history of hospitalization owing to cold/bronchitis/bronchiolitis/pneumonia than those without atopic dermatitis. The results for the confounding factors are shown in Table 1 and Tables S2–6.

Relationship of infection with asthma, allergic rhinitis/conjunctivitis, and atopic dermatitis: multivariable analysis

Multivariable analyses were performed to investigate the effects of early daycare attendance, older siblings, and severe airway infection on asthma development (Table 2a). The strength of the negative 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 (0.74 and 0.83, respectively), and this significant reduction in the risk of asthma disappeared after 10 years (Figure 1A). The association between older siblings and asthma was negative at 10 and 11 years (ORs, 0.90 and 0.90) (Figure S2A). On the contrary, the association between the history of hospitalization due to cold/bronchitis/bronchiolitis/pneumonia and asthma was positive throughout childhood (ORs between 5.5 and 11 years, 1.66–1.82) (Figure 2A).

For allergic rhinitis/conjunctivitis, early daycare attendance (ORs between 5.5 and 11 years, 0.74–0.85) (Figure 1B) and older siblings (ORs between 5.5 and 11 years, 0.66–0.69) (Figure S2B) showed inverse associations with its incidence throughout childhood (Table 2b). The association of a history of hospitalization

due to cold/bronchitis/bronchiolitis/pneumonia with allergic rhinitis/conjunctivitis was found to be positive at the age of 8, 9, 11 years (ORs, 1.17–1.22) (Figure 2B). On the other hand, daycare attendance and older siblings were identified to be risks for the development of atopic dermatitis at the age of 5.5 and 7 years. (Figures 1C and S2C) (Table 2c).

The relationship of developmental adaptations with asthma, allergic rhinitis/conjunctivitis, and atopic dermatitis: multivariable analysis

In the multivariable analysis, preterm birth was positively associated with asthma between 7 and 11 years (ORs, 1.29–1.36) (Figure 3A) (Table 2a). Meanwhile, overweight gain was positively associated with asthma at 9 and 10 years (ORs, 1.17–1.21) (Figure S3A). For allergic rhinitis/conjunctivitis, its positive association with preterm birth and overweight gain was only seen at 8 and 5.5 years, respectively (Figures 3B and S3B) (Table 2b). No significant associations between preterm birth and overweight gain were determined with atopic dermatitis (Figures 3C and S3C) (Table 2c). The results of the confounding factors are shown in Table 2.

Discussion

To the best of our knowledge, this is the first longitudinal study that has highlighted the similarities and differences in the 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 for developing asthma throughout childhood. In addition, preterm birth was a significant risk factor for developing asthma between the ages of 7 and 11 years, with a small effect on allergic rhinitis/conjunctivitis and atopic dermatitis. Overweight gain in infancy did not significantly affect the development of atopy-related diseases.

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 agents¹². In a study comparing the characteristics between Amish and Hutterites¹³, 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 attendance in this study confirmed the result of a previous longitudinal study⁵ that investigated the relationship between airway symptoms and early daycare attendance. On the contrary, early life daycare attendance increased the subsequent risk of developing atopic dermatitis¹⁴. 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 diseases¹⁵. This shows that a number of different mechanisms play a role in the development of allergic airway diseases and skin disease associated with daycare attendance. On the other hand, this current 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 al¹⁶.

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 life¹⁷ 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 airway¹⁸ and gut microbiomes^{19, 20} 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 asthma²¹. A complicated network may be involved in the association between infection and allergic diseases.

This study confirmed the fact that babies born before 37 weeks of gestation are prone to suffer from childhood asthma⁹. 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 childhood⁹. 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 symptoms²², and ongoing respiratory morbidity²³, eventually resulting in lung dysfunction and chronic lung diseases²⁴⁻²⁷ in childhood and adulthood that exhibit hyperreactivity with chemokine and cytokine stimulation²⁸.

Moreover, our study indicated that overweight 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 Japan²⁹.

Our study has some limitations. First, we did not measure the bronchial hyperresponsiveness to diagnose asthma⁵. 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 Japan³⁰. 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.

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. A dynamic interaction is supposed to be involved between the genetic attributes, organ maturation, environmental factors, barrier dysfunction, microbiome abnormalities, and immune system. 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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Author contributions

TN and TT designed the study. TN, HM and KH interpreted the data. TN wrote the manuscript. All authors were involved in the preparation and review of the manuscript and approved the final submitted version.

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Legends to figures

Figure 1. The adjusted odds ratios and 95% confidence intervals of daycare in patients with (A) asthma, (B) allergic rhinitis/conjunctivitis, and (C) atopic dermatitis at different ages.

Figure 2. The adjusted odds ratios and 95% confidence intervals of history of hospitalization due to cold/bronchitis/bronchiolitis/pneumonia in patients with (A) asthma, (B) allergic rhinitis/conjunctivitis, and (C) atopic dermatitis at different ages.

Figure 3. The adjusted odds ratios and 95% confidence intervals of preterm birth in patients with (A) asthma, (B) allergic rhinitis/conjunctivitis, and (C) atopic dermatitis at different ages.

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