Development of allergic rhinitis in early life: A prospective cohort study in high-risk infants

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Abstract

Background: Allergic rhinitis (AR) is the most common allergic disease in children and is closely associated with asthma in the context of atopic march. The development process of AR in early childhood, however, is not well understood due to the absence of definitive diagnostic criteria. We prospectively investigated the process in regard to not only the nasal symptoms and sensitization, but also the nasal cytology, in relation to asthma in a high-risk cohort. Methods: Infants under 2 years of age with atopic dermatitis (AD) and/or food allergy (FA) without a diagnosis of asthma were recruited and followed prospectively for 2 years. The phenotype of perennial AR was classified based on the presence/absence of 1) persistent nasal symptoms, 2) nasal eosinophils and 3) HDM sensitization, the most common allergen for perennial AR in Japan. AR-like phenotypes were defined as positive for at least 2 of those 3 categories. Results: A total of 304 children were enrolled, and 242 subjects (80%) completed the 2-year observation. The prevalence of eosinophilia in nasal secretions increased from 18.5% to 69.9%, while HDM-specific IgE >0.35 kUA/L increased from 30.6% to 74.8%. AR-like phenotypes increased from 18.4% to 65.0%. The cumulative incidence of physician-diagnosed asthma during the 2-year follow-up was significantly higher in the subjects with an AR-like phenotype at 1 year than in those with a non-AR phenotypes. Conclusions: The prevalence of an HDM-related AR-like phenotype was markedly increased during infancy in high-risk infants with AD/FA and was associated with asthma.

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Methods: Infants under 2 years of age with atopic dermatitis (AD) and/or food allergy (FA) without a diagnosis of asthma were recruited and followed prospectively for 2 years. The phenotype of perennial AR was classified based on the presence/absence of 1) persistent nasal symptoms, 2) nasal eosinophils and 3) HDM sensitization, the most common allergen for perennial AR in Japan. AR-like phenotypes were defined as positive for at least 2 of those 3 categories.

Results: A total of 304 children were enrolled, and 242 subjects (80%) completed the 2-year observation. The prevalence of eosinophilia in nasal secretions increased from 18.5% to 69.9%, while HDM-specific IgE >0.35 kUA/L increased from 30.6% to 74.8%. AR-like phenotypes increased from 18.4% to 65.0%. The cumulative incidence of physician-diagnosed asthma during the 2-year follow-up was significantly higher in the subjects with an AR-like phenotype at 1 year than in those with a non-AR phenotypes.

Conclusions: The prevalence of an HDM-related AR-like phenotype was markedly increased during infancy in high-risk infants with AD/FA and was associated with asthma.

(245 words)

Keywords

Rhinitis, allergic, perennial, asthma, infant, child, cell count, eosinophils

ABBREVIATIONS

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Key Message

Allergic rhinitis (AR) is a cardinal disease in the atopic march. However, the precise course of AR's development has remained unclear, partly due to the absence of diagnostic criteria for early AR. We investigated AR development in a cohort of high-risk infants with atopic dermatitis and/or food allergy by prospectively observing them for symptoms and sensitization and also their nasal cytology. We found that the prevalence of AR increased markedly between 1 and 3 years of age and was associated with onset of asthma.

INTRODUCTION

Allergic rhinitis (AR) is a common allergic disease in childhood, and its prevalence is increasing worldwide.[1-3] AR significantly impacts the quality of life by causing various problems, such as sleep disturbance, emotional stress and impairment of school activities.[4] More importantly, AR is a risk factor for asthma as "one airway, one disease".[5-7] The International Study of Asthma and Allergies in Childhood (ISAAC) employed standardized methodology and showed clearly that the prevalence of AR increased during childhood, i.e., from 6-7 y.o. to 13-14 y.o.[8]

However, the onset of AR in children is not well understood due to the absence of definitive diagnostic criteria. We previously reported that, in school children with asthma, AR started even before 3 years of age.[9] In the PARIS birth cohort study, the prevalence of AR-like symptoms was 9.1% at 18 months of age.[10]However, in the above studies, diagnosis of AR was based only on the parents' recall in the former and a symptom questionnaire in the latter. In addition, those reports did not provide a good description of the development process.

With the aim of improving our understanding of the onset of AR, we designed and carried out a high-risk infant cohort study, the Impact of Allergic Rhinitis on Atopic March (IRAM) in children. Infants less than 2 years of age who had food allergy or atopic dermatitis were recruited into the study. We prospectively followed up not only their nasal symptoms, but also their nasal cytology and allergic sensitization for 2 years. The ARIA guidelines classify AR as intermittent or persistent, not seasonal or perennial.[11] However, Japan is characterized by sole high morbidity of seasonal AR due to Japanese cedar pollen and a high prevalence of perennial AR due to house dust mite (HDM). Accordingly, the Japanese guidelines include classifications for seasonal AR and perennial AR.[12] Here, in light of the relatively late development of pollen sensitization in young children,[13] we focused on development of HDM-sensitized perennial AR in infancy.

METHODS

Study design and subjects

This is a multicenter observational prospective cohort study named IRAM (Impact of Rhinitis on Atopic March; UMIN000004157). Children aged 6–23 months with physician-diagnosed atopic dermatitis (AD), food allergy (FA) and/or AR were recruited from 30 sites in the central region of Japan in 2011 by investigators of the IRAM study group in Kinki Hokuriku Airway Disease Conference (KiHAC).[14] The IRAM study aimed to delineate atopic march in high-risk infants, focusing especially on development of AR and asthma. Children who had been diagnosed with asthma were not enrolled. In the on-going follow-up of the IRAM cohort, the first part consisted of 5 visits—at 6-month intervals—in the first 2 years.[13] At enrollment, the following background factors were surveyed: the family history of allergic diseases, history of wheezing not diagnosed as asthma, history of lower respiratory infections, number of siblings, environmental factors such as pets and passive smoking at home, and other medical information. Every 6 months, the study physicians diagnosed asthma based on the Japanese guidelines for pediatric asthma.[15]Blood and nasal secretion samples were collected at enrollment, 1 year and 2 years.

The study was approved by the Ethics Committee of Mie National Hospital, (#21-9). The parents/guardians of all participants gave written informed consent.

Assessment of respiratory symptoms

A questionnaire regarding respiratory symptoms was developed by making minor modifications of the questionnaire of the International Study of Asthma and Allergies in Childhood.[16] The parents/guardians completed the questionnaire at 6-month intervals. For perennial AR, the following question was used: "In the past 6 months, has your child consistently had a problem with sneezing, or a runny or blocked nose, even when he/she DID NOT have a cold or flu?" If the answer was "yes", the parents further indicated each symptom, i.e., sneezing, runny nose, and/or blocked nose. For asthma, the core question was: "Has your child had wheezing or whistling in the chest in the last 6 months?"

Examination of nasal secretions

Cytological examination of nasal secretions was performed when children had no signs of an acute respiratory infection. Nasal secretions were sampled by swabbing the bilateral inferior turbinates with cotton swabs. The samples were spread onto a slide glass, air-dried, fixed and stained with Hansel solution (Eosinostein®; Torii Pharmaceutical, Tokyo, Japan). The specimens were examined by light microscopy for eosinophils, neutrophils and bacteria by a single well-trained laboratory technician. Nasal eosinophilia was defined as the presence of more than a few eosinophils in the whole field. The percentage of eosinophils compared with neutrophils was also determined, and >10% was defined as significant nasal eosinophilia.[17]

Sensitization to common allergens

Serum samples were analyzed for total IgE and specific IgE antibodies using the ImmunoCAP® system according to the manufacturer's guidelines (Phadia AB, Uppsala, Sweden). The tested allergens were as reported elsewhere.[13] In this study, we focused on house dust mite (HDM) sensitization (positive = HDM-sIgE >0.34 U_A/ml).

Classification ofHDM-sensitized perennial AR in young children

AR is IgE-mediated inflammation of the nasal mucosa. It is diagnosed based on the presence of typical allergic symptoms and nasal eosinophilia, and identification of the causative allergen(s).[18,19] AR in children, however, is often undiagnosed, or misdiagnosed because of the multitude of causes for rhinitis.[18] Thus, we tentatively classified the phenotypes of the nasal condition in young children in relation to HDM-sensitized perennial AR based on 3 clinical criteria: persistent nasal symptoms, nasal eosinophilia and HDM sensitization. The various combinations of those 3 criteria make up 8 phenotypes, as shown in Table 1. We defined the subtype that was positive for all 3 criteria as "classical AR", and the subtypes that were positive for 2 of the 3 criteria as "eosinophilic rhinitis", "AR without nasal eosinophilia" and "subclinical AR", respectively. We classified those 4 subtypes as "AR-like phenotypes" (Table 1). Four subtypes that met only one, or none, of the 3 criteria were classified as "non-AR phenotypes" (Table 1).

Statistical analysis

The chi-square test for trend was used to compare the distribution of the prevalence of various factors at each of the yearly visits. The Kaplan-Meier method was applied to estimate the probability of asthma onset, and the log-rank test was used to compare the probability between AR phenotypes. All reported P values are 2-tailed, with a P value of <.05 considered to be statistically significant. Statistical analyses were performed with GraphPad Prism 8 (GraphPad Software; La Jolla, California) and SPSS (version 26; SPSS; Chicago, Illinois).

RESULTS

Study population

A total of 304 children were screened, and 299 were enrolled in the study. Of them, 269 (90%) were retained at the 1styear, and 237 (79%) were retained at the 2nd year (Figure S1). Table 2 presents the characteristics of the study population. The mean age in months was 13.3, and 51% of the children were less than 12 months. Figure S2 shows the age distribution. More boys (64.5%) than girls were enrolled. Most (86.3%) of the children had food allergies, including to egg (77%), milk (43%), wheat (25%) and other foods (17%). Those rates correspond with the reported prevalences of food allergies in Japan.[20] Atopic dermatitis was diagnosed in 70.2% of the children. A history of wheezing that was not diagnosed as asthma was found in 17.3%, and a history of lower respiratory infection was found in 10.0%. Table 2 also shows the prevalences of various environmental factors such as pet keeping, presence of siblings, daycare use and passive smoking, and a parental history of asthma and allergic rhinitis.

Prevalence of persistent nasal symptoms

Table 3 summarizes the changes in the prevalences of the nasal symptoms, nasal cytology findings and HDM sensitization during the 2-year observation period. The prevalence of each of sneezing, runny nose, nasal eosinophils and positive HDM-specific IgE increased significantly from enrollment to the 2nd-year visit.

Although the high initial prevalence of neutrophils in the nasal secretions increased even further over the 2 years, the eosinophil/neutrophil ratio also increased, indicating that nasal eosinophilia became progressively prevalent in early childhood.

Prevalence of phenotypes related to perennial AR

Figure 1 shows the changes in the prevalence of the 8 phenotypes related to early AR. The prevalence of "classical AR" that met all 3 criteria was 2.9% at enrollment, 17.1% at the 1st-year visit and 29.5% at the 2nd-year visit. The prevalence of "subclinical AR"—in which nasal eosinophilia and HDM sensitization were present even when there were no nasal symptoms—also increased from 3.3% at entry to 11.7 % and 26.6 %, respectively, at the 2 later time-points. In contrast, the prevalence of the "no rhinitis" phenotype, which met none of the 3 criteria, decreased from 33.1% to 15.2% and 8.4%, respectively (Fig. 1).

Since the presence/absence of each criterion individually had the potential to have changed at each visit, a positive finding did not always persist throughout the study. Figure 2 shows the actual numbers of subjects classified as 3+ criteria and 2+ criteria (AR-like phenotypes), HDM-sensitization-only, and other non-AR phenotypes at each visit. Overall, it can be seen that the AR-like phenotypes increased during the observation period, whereas the HDM-sensitization-only phenotype population remained small, and the other non-AR phenotypes decreased markedly (Fig. 2).

Association of AR-like phenotypes with asthma during the study

Figure 3 shows the cumulative prevalence of physician-diagnosed asthma. The subjects who were classified as AR-like phenotypes at 1 year and 2 years had significantly higher prevalences of asthma compared with those who were classified as non-AR phenotypes (Fig. 3B and 3C). The cumulative prevalence of asthma did not differ between patients who were classified as an AR-phenotype at enrollment and those who were classified as a non-AR phenotype (Fig. 3A).

DISCUSSION

This study aimed to elucidate and characterize the development of allergic rhinitis (AR) in young children below 2 y.o. who had atopic dermatitis and/or food allergy. Those children are regarded as a high-risk population for atopic march leading to respiratory allergies, including asthma and AR, in later life. Since there are no definitive diagnostic criteria for AR in young children, we tentatively defined 8 subgroups based on 3 major clinical features of HDM-related AR, which is the most prevalent type of AR in Japanese children below the age of 6 years.[12] We found that the prevalence of AR-like phenotypes, which meet 2 or more of the 3 clinical criteria (i.e., persistent nasalsymptoms, nasal eosinophilia and HDM sensitization), increased significantly during the 2-year follow-up, from an average age of 13 months to 27 months, and was associated with the cumulative prevalence of physician-diagnosed asthma.

Several papers have reported on the prevalence of AR in infants and young children. The PARIS birth cohort study found that 9.1% of infants at age 18 months had AR-like symptoms (runny nose, blocked nose, sneezing; apart from a cold).[10] Positive associations of AR-like symptoms with inhalant allergen sensitization, HDM sensitization and a blood eosinophil count [?]400/mL were described, with adjusted odds ratios of 2.2, 2.9 and 1.5, respectively. Osawa et al.[21] reported that general health examinations at age 18 months found that 8 (2%) of 408 infants had both inhalant allergen sensitization and nasal eosinophils, and 6 (1.5%) infants also had rhinorrhea. Zeiger et al.[22] investigated nasal basophilic cells and eosinophils in a cohort of high-risk infants with atopic parents who participated in an intervention study of maternal allergenic food avoidance for allergy prevention. They found that the prevalence of nasal eosinophils increased from 0.7% at age 4 months to 38.2% at 48 months, and the prevalence was higher in infants with an allergic disease such as FA. In the MAS birth cohort, the prevalence of AR (based on the ISAAC questionnaire) was investigated from age 3 years to 13 years.[23] The prevalence of symptom-based AR increased continuously from 6% at age 3 to 24% at age 13 in children with no parental history of allergy and from 13% to 44% in those with parental allergy. Sensitization to aeroallergens was a significant risk for AR, with an odds ratio of 18.9. Collectively, AR starts in infancy and becomes more common as children grow older, especially in those with a genetic

predisposition to allergy and/or aeroallergen sensitization.

Our present results from a high-risk cohort of infants with AD and/or FA were in accord with those earlier findings. An added strength of our study is that we prospectively investigated AR development in regard to not only the nasal symptoms but also nasal eosinophilia and sensitization during a critical 2-year period of infancy (up to 37.3 months of age).

AR is a Th2-type inflammatory disease of the upper airways.[24,25] It is diagnosed on the basis of the pathogenesis, i.e, IgE antibody to an aeroallergen, IgE-mediated mast cell activation leading to mucosal symptoms such as rhinorrhea, nose itching, sneezing, blocked nose, and eosinophilic inflammation of the nasal mucosa leading to nasal hyper-reactivity. Positive findings for the "triad" of AR criteria, i.e., 1) "allergic" nasal symptoms, 2) aeroallergen sensitization and 3) nasal eosinophilia, can establish the diagnosis. However, in the early stage of AR development, the triad may not be present due to the non-specific nature of symptoms and variable nasal mucosal pathology. Moreover, in preschool children, viral upper respiratory infections are common and symptom-recognition relies on a mother's observation, not the perception or complaints of the child him/herself. To circumvent those problems, we employed a classification system of AR-like phenotypes that allows for fluctuation of AR manifestations in children. We found that our classifications corresponded well with previous observations in several birth cohort studies and, importantly, correlated positively with the prevalence of asthma.

Nasal eosinophilia has been variously defined. In adults, more than 10%[17] or 20%[26] eosinophils in inflammatory cells were regarded to be eosinophilia. In 11- to 15-year-old children, more than 10 eosinophils per high-power field was defined as nasal eosinophilia, with a diagnostic specificity of 96% and a sensitivity of 62% for AR.[27] We defined nasal eosinophilia in young children as when more than a few eosinophils were present in the whole field, which may be a lower cut-off level for nasal eosinophilia compared with those in adults and older children. Because the number of eosinophils in nasal smears was reported to be much lower in young children with rhinorrhea and no signs of acute infection,[28] we employed our above definition. Yet, we found that a higher cut-off of [?]10% for the eosinophil/neutrophil ratio yielded similar results, although the prevalence of eosinophilia with this definition was lower than that with the former definition. Overall, we believe that our definition of positive nasal eosinophilia may be optimal due to its higher sensitivity.

Multimorbidity is a characteristic feature of allergies in children.[25] The MeDALL (Mechanisms of the development of ALLergy) study, involving 12 cohort studies, reported that coexistence of asthma, rhinitis and eczema in the same child was more prevalent than would be expected by chance.[29] An important aspect of multimorbidity is development of asthma, because it places the largest burden on children. We previously reported that 78% of children younger than 10 years old with asthma had AR, and onset of AR preceded asthma onset in one-third of them.[9] In a German MAS birth cohort, AR at 2 years and 5 years of age predicted later development of wheeze.[6] Our present study, in which we focused on "multimorbid" infants with AD and/or FA, confirmed those earlier findings.

This study has several limitations. First, the number of subjects was relatively small compared with large birth cohort studies. However, prospective investigation of the development of AR relied on not only the nasal symptoms but also HDM sensitization and nasal eosinophilia, which we believe enhanced the reliability of our findings. Second, definitive diagnosis of asthma at an early age is difficult, and the asthma outcome findings of this study may not be accurate. For that reason, we continue to follow the subjects for development of school-age asthma and will confirm our results by using more objective findings, such as lung function. Third, our cohort was high-risk infants with AD/FA, and we may not be able to extrapolate the findings to natural history in the general population. However, because of the focused population, we were able to describe the clinical course of early AR in our relatively small number of subjects.

In conclusion, we described the early phase of AR development in a high-risk cohort of children and proposed practical diagnostic criteria for AR in young children. Our findings show that AR increased markedly during 1 to 3 years of age, and that increase was positively associated with the prevalence of asthma. Additional studies will be needed to clarify the natural history of AR in children in the context of atopic march.

Authors' contributions

SM, TF and MN conceived the idea and designed this study. SM, SU, MN, and TF collected the data, and MN and SM performed the statistical analyses. All co-authors gave input and agreed to the final submitted version. All authors read and approved the final manuscript.

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References

1. Moyes CD, Clayton T, Pearce N, et al. Time trends and risk factors for rhinoconjunctivitis in New Zealand children: an International Study of Asthma and Allergies in Childhood (ISAAC) survey. *J Paediatr Child Health.* 2012;48(10):913-920.

2. Bjorksten B, Clayton T, Ellwood P, Stewart A, Strachan D, Group IPIS. Worldwide time trends for symptoms of rhinitis and conjunctivitis: Phase III of the International Study of Asthma and Allergies in Childhood.*Pediatr Allergy Immunol.* 2008;19(2):110-124.

3. Sasaki M, Morikawa E, Yoshida K, Adachi Y, Odajima H, Akasawa A. The change in the prevalence of wheeze, eczema and rhino-conjunctivitis among Japanese children: Findings from 3 nationwide cross-sectional surveys between 2005 and 2015. *Allergy.* 2019;74(8):1572-1575.

4. Sih T, Mion O. Allergic rhinitis in the child and associated comorbidities. *Pediatr Allergy Immunol.* 2010;21(1 Pt 2):e107-113.

5. Grossman J. One airway, one disease. *Chest.* 1997;111(2 Suppl):11S-16S.

6. Rochat MK, Illi S, Ege MJ, et al. Allergic rhinitis as a predictor for wheezing onset in school-aged children. *J Allergy Clin Immunol.* 2010;126(6):1170-1175 e1172.

7. Burgess JA, Walters EH, Byrnes GB, et al. Childhood allergic rhinitis predicts asthma incidence and persistence to middle age: a longitudinal study. *J Allergy Clin Immunol.* 2007;120(4):863-869.

8. Asher MI, Montefort S, Bjorksten B, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet.* 2006;368(9537):733-743.

9. Masuda S, Fujisawa T, Katsumata H, Atsuta J, Iguchi K. High prevalence and young onset of allergic rhinitis in children with bronchial asthma. *Pediatr Allergy Immunol.* 2008;19:517–522.

10. Herr M, Clarisse B, Nikasinovic L, et al. Does allergic rhinitis exist in infancy? Findings from the PARIS birth cohort. *Allergy.*2011;66(2):214-221.

11. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy.* 2008;63 Suppl 86:8-160.

12. Okubo K, Kurono Y, Ichimura K, et al. Japanese guidelines for allergic rhinitis 2020. *Allergol Int.* 2020;69(3):331-345.

13. Nagao M, Borres MP, Sugimoto M, et al. Sensitization to secretoglobin and lipocalins in a group of young children with risk of developing respiratory allergy. *Clin Mol Allergy.* 2017;15:4.

14. Iwanaga T, Tohda Y. Importance of clinical epidemiology research in studies on respiratory diseases. *Respir Investig.*2013;51(4):217-223.

15. Arakawa H, Hamasaki Y, Kohno Y, et al. Japanese guidelines for childhood asthma 2017. *Allergol Int.* 2017;66(2):190-204.

16. Asher MI, Keil U, Anderson HR, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J.* 1995;8(3):483-491.

17. Lee HS, Majima Y, Sakakura Y, Shinogi J, Kawaguchi S, Kim BW. Quantitative cytology of nasal secretions under various conditions.*Laryngoscope.* 1993;103(5):533-537.

18. Skoner DP. Allergic rhinitis: definition, epidemiology, pathophysiology, detection, and diagnosis. *J Allergy Clin Immunol.* 2001;108(1 Suppl):S2-8.

19. Okubo K, Kurono Y, Ichimura K, et al. Japanese guidelines for allergic rhinitis 2017. *Allergol Int.* 2017;66(2):205-219.

20. Ebisawa M, Ito K, Fujisawa T. Japanese guidelines for food allergy 2017. *Allergol Int.* 2017;66(2):248-264.

21. Osawa Y, Suzuki D, Ito Y, et al. Prevalence of inhaled antigen sensitization and nasal eosinophils in Japanese children under two years old. *Int J Pediatr Otorhinolaryngol.* 2012;76(2):189-193.

22. Zeiger RS, Heller S. Development of nasal basophilic cells and nasal eosinophils from age 4 months through 4 years in children of atopic parents. *J Allergy Clin Immunol.* 1993;91(3):723-734.

23. Keil T, Bockelbrink A, Reich A, et al. The natural history of allergic rhinitis in childhood. *Pediatr Allergy Immunol.*2010;21(6):962-969.

24. Ciprandi G, Tosca MA. House dust mites-driven allergic rhinitis: could its natural history be modified? *Expert Rev Clin Immunol.*2021;17(2):109-114.

25. Papadopoulos NG, Aggelides X, Stamataki S, Prokopakis E, Katotomichelakis M, Xepapadaki P. New concepts in pediatric rhinitis.*Pediatr Allergy Immunol.* 2021;32(4):635-646.

26. Jankowski R, Persoons M, Foliguet B, Coffinet L, Thomas C, Verient-Montaut B. Eosinophil count in nasal secretions of subjects with and without nasal symptoms. *Rhinology.* 2000;38(1):23-32.

27. Miri S, Farid R, Akbari H, Amin R. Prevalence of allergic rhinitis and nasal smear eosinophilia in 11- to 15 yr-old children in Shiraz.*Pediatr Allergy Immunol.* 2006;17(7):519-523.

28. Otsuka H, Otsuka K, Matsune S, Okubo K. Assessing the onset of allergic rhinitis by nasal cytology and immunoglobulin E antibody levels in children. *Am J Rhinol Allergy.* 2018;32(1):16-22.

29. Pinart M, Benet M, Annesi-Maesano I, et al. Comorbidity of eczema, rhinitis, and asthma in IgE-sensitised and non-IgE-sensitised children in MeDALL: a population-based cohort study. *Lancet Respir Med.*2014;2(2):131-140.

Figure legends

FIGURE 1

Prevalence of 8 rhinitis-related phenotypes (Table 1) classified based on the 3 features of allergic rhinitis (AR), i.e., nasal symptoms, nasal eosinophilia and HDM-sensitization at entry (open bar), 1 year (dot-shaded bar) and 2 years (cross-shaded bar).

FIGURE 2

Transition of phenotypes during 2-year follow-up. The numerical values are the number of subjects, and the size of each circle reflects the numerical value.

FIGURE 3

Cumulative percentage of subjects with physician-diagnosed asthma in AR-like phenotypes (solid line) and non-AR-like phenotypes (dotted line) diagnosed at entry (A), 1 year (B) and 2 years (C). The children with AR-like phenotypes at entry (hazard ratio: 1.5 (95% CI: 0.75–3.0); P = 0.26), at 1 year (hazard ratio: 2.0 (95% CI: 1.2–3.5); *P =0.02) and at 2 years (hazard ratio: 2.0 (95% CI: 1.2–3.5); *P =0.04) had higher cumulative percentages of asthma than children with the non-AR-like phenotypes.

Legends for supplemental figures

FIGURE S1

Flow-diagram showing enrollment and retention of subjects.

FIGURE S2

Age-distribution of subjects at enrollment.

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