**Acquisition, Remission, and Persistence of Eczema, Asthma, and Rhinitis in Children**

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**Keywords (3-10)**

Eczema. Rhinitis. Asthma. Allergic sensitization. Cohort study, Allergic disease, Allergic conditions.

**Abstract**

***Background:***Allergic sensitization is associated with eczema, asthma, and rhinitis. However, it is unknown whether and how allergic sensitization is associated over time with acquisition, remission, and persistence of these diseases and their comorbidity.

***Objective:*** To gain a better understanding of factors including allergic sensitization transitions that influence the temporal pattern of asthma, eczema, and rhinitis and their comorbidity during childhood.

***Methods:*** In the Isle of Wight birth cohort information on allergic sensitization to common allergens was collected at ages 4, 10, and 18 years along with asthma, rhinitis, and eczema status determined by clinical diagnosis. Logistic regressions were used to estimate subsequent and concurrent odds-ratios of diseases transition with allergic sensitization transition status as the main independent variable. Two transition periods were considered, 4 to 10 years of age, and 10 to 18 years of age.

***Results:*** The odds of new diagnosis of allergic disease (no-yes) was increased among subjects with acquired or persistent allergic sensitization to common allergens compared to subjects with no sensitization (acquisition of sensitization odds ratio [OR]=3.22, p <0.0001; persistence of sensitization, OR=6.33, p <0.0001). The odds of remission of allergic diseases (yes-no) was lower among subjects with acquired or sustained allergic sensitization (acquisition, OR=0.18, p =0.0001; persistence, OR=0.085, p <0.0001), compared to subjects not sensitized. Subjects with acquired or persistent allergic sensitization were also had higher odds for persistence of disease (yes-yes) than subjects not sensitized (acquisition, OR=5.49, p =0.0001; persistence, OR=11.79, p <0.0001).

***Conclusion:*** Transition of allergic sensitizations to common allergens is a prognostic factor for subsequent or concurrent transition of eczema, asthma, and rhinitis. Prevention or reduction of allergic sensitization has a potential to lead to remission of these conditions.

**Introduction**

Common childhood conditions associated with allergy include eczema, asthma and rhinitis. These conditions take a variable course, especially during childhood with a remitting and relapsing course. Children may develop one or more of these conditions, which in some persists or goes into remission, while in others, one condition improves only to give way to another. This typical pattern of this latter course is termed the “allergic march” where development of eczema and food allergy in early childhood is followed by respiratory allergic disease i.e. asthma and rhinitis. [[1](#_ENREF_1), [2](#_ENREF_2)] However, recent studies have suggested that in most children, the association among various allergic conditions is better described in terms of comorbidity, i.e. the co-existence of eczema, rhinitis, and asthma. [[3](#_ENREF_3)] Nonetheless, neither concept fully explains the changes in allergic manifestations observed throughout childhood and factors associated with these changes.

Atopy is a personal and/or familial tendency, usually in childhood or adolescence, to become sensitized and produce IgE antibodies in response to ordinary exposure to allergens, usually proteins. As a consequence, such individuals can develop typical symptoms of eczema, asthma, or rhino-conjunctivitis. While allergic sensitization is the common denominator for these conditions, other risk factors are also important. Eczema affects 15 to 30% and 2 to 10% of children and adults, respectively.[[4](#_ENREF_4)] Although allergic sensitization is present in as high as 80% of infants with eczema,[[5](#_ENREF_5)] the major hallmarks of eczema is disrupted epidermal barrier function and dry and itchy skin.[[6](#_ENREF_6)] Asthma is a phenotypically heterogeneous disorder.[[7](#_ENREF_7)] [[8](#_ENREF_8)] Although not all asthma is caused by atopy, the development of asthma during childhood is mostly attributable to allergic sensitization.[[9](#_ENREF_9), [10](#_ENREF_10)] Rhinitis typically begins in childhood or adolescence and continues into adulthood.[[11](#_ENREF_11)] Similarly, allergic sensitization is considered to be the cause in the majority but not in all children with seasonal and perennial allergic rhinitis.[[12](#_ENREF_12)] [[13](#_ENREF_13)] Rhinitis and asthma are often present together [[3](#_ENREF_3)] and rhinitis is considered a risk factor for asthma.[[14](#_ENREF_14), [15](#_ENREF_15)]

Few studies have longitudinally studied the natural history of eczema, asthma, or rhinitis with respect to the transition of these diseases over time and their association with the changes in allergic sensitization status.[[16](#_ENREF_16)] The purpose of this study was to gain a better understanding of factors that influence the temporal pattern of asthma, eczema, and rhinitis and their comorbidity during childhood.

**Material and Methods**

*The Isle of Wight study cohort*

The birth cohort in this study was composed of children born between January 1, 1989 and February 28, 1990 on the Isle of Wight (IoW), UK. It is near the mainland and is semi-rural with no heavy industry. Data collection was done over 18 years on the Isle of Wight birth cohort. Both clinical and survey data were collected. Between January 1, 1989 and February 28, 1990, 1,536 children were born and parents of 1,456 consented for further follow-up. The study was approved by the Isle of Wight Local Research Ethics Committee (06/Q1701/34). The informed consent was written for in person visits. For participants joined by phone, the consent was documented on the face-to-face consent form. The name of the person giving consent and the name and signature of the person taking the form were documented.

*Assessment of allergic diseases and data collection*

 Detailed questionnaires, resembling the questionnaire of the International Study of Asthma and Allergy in Childhood (ISAAC), were given at age of 4 years (before the publication of the ISAAC questionnaire). A participant was determined to have asthma if s/he had experienced recurrent wheezing in the last 12 months and either given a clinical diagnostic of asthma with or without treated with asthma medications. Eczema was defined as chronic or chronically relapsing itchy dermatitis lasting more than 6 weeks with characteristic morphology and distribution.[[17](#_ENREF_17)] Diagnosis of rhinitis required at least two of three recurrent nasal discharge, blockage, sneezing and/or eye symptoms.[[18](#_ENREF_18)]

At the ages of 10 and 18 years, questionnaires including the ISAAC questions were administered. In the case that parents or participants could not attend a follow-up visit to complete the questionnaire, a modified version was given either over the telephone or via postal service. Asthma was defined as “ever had asthma” and “wheezing or whistling in the chest in the last 12 months” or “current treatment for asthma.” Eczema diagnosis was as described for age 4 years. Rhinitis was defined by a positive response to ISAAC questions, “in the past 12 months have you had a problem with sneezing, or a runny or blocked nose when you did not have a cold or the flu?”

The outcome considered in our study was single occurrence or comorbidity of asthma, rhinitis, and/or eczema. The questionnaires were used to determine each subject’s status for each disease at each age, denoted henceforth as allergic diseases. For each of the three outcomes, disease status was treated as a binary variable (yes-no), so at each age, a participant was classified either as disease-free or as experiencing one or more of the diseases.

*Definitions on allergic sensitization and allergic disease transitions*

Allergic sensitization was defined as a positive skin prick test (SPT) (weal size ≥ 3mm larger than negative control) to one or more common allergens at 4, 10 and 18 years. The allergens tested were: indoor allergens (house dust mite, dog, cat, *Cladosporium*, and *Alternaria*), outdoor allergens (grass, tree – tree at ages 10 and 18 only), and food allergens (soy, milk, egg, cod, and peanut).

 Two transition periods were considered, from ages 4 to 10 years, and from 10 to 18 years. In each period, four allergic sensitization transition statuses were considered: acquisition of allergic sensitization (non-atopic to atopic), persistence (atopic at both time points), remission (atopic to non-atopic), and non-atopic at both time points. Transitions of allergic disease status were also defined within these two transition periods (Fig. 1). Acquisition (positive transition) of allergic disease was defined as a previously healthy patient newly diagnosed with one or more disease (asthma, eczema, and/or rhinitis). Persistence referred to an existing diagnosis that continues across a transition point. Remission (negative transition) occurred when a subject who was previously diagnosed with a disease, was disease free at a subsequent follow-up. Participants were measured three times throughout childhood, thus persistence means having a disease at two (or more) consecutive measurements, and remission means having the disease at one follow up age (4 or 10 years) but outgrowing it by the next follow up age (10 or 18, correspondingly) (Figure 1).

*Statistical Analyses*

We calculated attritions at each age (4, 10, and 18 years) for the whole cohort. Descriptive statistics were calculated for allergic disorders and allergic sensitizations including counts and percentages. To assess whether the study samples reasonably represented the samples in the complete cohort at each age, at each age, we assessed the consistency of main characteristics of subjects between subjects in the study and subjects in the whole cohort, including allergic disorders, atopy, and representing covariates including gender, as well as paternal and maternal allergic disorders. One sample proportion tests were applied to assess the consistency.

 We first assessed the association of allergic disorders at each age with allergic sensitization at that age. We also differentiated between different types of allergic sensitizations, specifically, aeroallergen sensitization vs. sensitization against both aero- and food allergens. The number of subjects allergic to food allergens only was extremely small (<2), and thus they were not included in this analyses. Logistic regressions were utilized with allergic disorder status as the dependent variable, and sensitization status as the independent variable, along with covariates and potential confounders. We included factors as covariates and confounders that are potentially associated with allergic disorders: family history of allergic disorders including maternal and paternal disease status for asthma, eczema, and rhinitis, maternal pre- and post-natal smoking exposure (never smoked, smoked after but not during pregnancy, and smoked during pregnancy and thereafter), paternal smoking at birth of the child, sex, birth weight, season of birth, cord IgE measured in *IU/ml*, and starting week of formula feeding.

To examine associations between transitions, logistic regression models with repeated measures were used to assess the association between allergic disorders transition over different periods (4-10 and 10-18) and risk factors. This model was applied to each of the three types of transitions, acquisition, remission, and persistence, noted above. For acquisition, we focused on participants who were disease free at the starting age of the transition, i.e., ages 4 or 10 years; for remission and persistence, data of participants who had experienced at least one of the three diseases (asthma, eczema, or rhinitis) at ages 4 or 10 were included in the analyses (Figure 1). The main independent variable was the transition statuses of allergic sensitization during these two periods (4 to 10, and then 10 to 18 years of age). We included the same covariates and potential confounders described previously. In addition, the transition period was also included in the model as a covariate to assess whether one transition period was more important than the other in the pathway of allergic disease transition.

 We also implemented logistic regressions to examine the association of allergic sensitization transition at an earlier period with allergic disease transition at a later period (time-lagged model). In particular we examined the association of sensitization transition from 4 to 10 years of age with allergic disease transition from 10 to 18 years of age.

 SAS 9.2 PROC GENMOD (SAS Institute Inc., Cary, NC, USA) was used for modeling, with a binomial distribution and a logit link function. Multiple testing was adjusted using the Bonferroni approach with an experiment-wise significance level of 0.05.

**Results**

The retentions of the IoW cohort were high at all follow ups. Specifically, at ages 4, 10, and 18 years of age, the retention percentages were 79%, 89%, and 85%, respectively. Descriptive analysis showed that at age 4, the most common disease was asthma, but at age 10 it was rhinitis and this remained true throughout the remainder of childhood (Table 1). Prevalence of asthma-only, rhinitis-only, asthma and rhinitis, eczema and rhinitis, and all three diseases together increased across childhood. Likewise, the prevalence of allergic sensitization (positive SPT) also increased across childhood in both subjects with allergic diseases as well as those without, though as expected, allergic sensitization was much lower among disease-free children at all ages (Table 2). Given the focus of the study, subjects missing transition status for allergic conditions or for atopy were excluded from subsequent analyses. We compared the subsamples with the complete cohort on main characteristics of interest, including allergic disorders, atopy (being allergic to at least one allergen), and covariates including gender, as well as paternal and maternal allergic disorders. After adjusting for multiple testing, the subsamples did not show any statistically significant differences compared to the cohort (Table 3).

 At each follow up, we examined the association between allergic diseases with atopy status via logistic regressions. We also tested the association for each type of allergic sensitizations (SPT positive for aeroallergens alone, both aeroallergens and food allergens, or any allergens). Compared to children not sensitized to any allergen, the risk of having allergic diseases was higher at all ages among children allergic to one or more allergens, but the risk of allergic diseases for children allergic to both aero and food allergens increased substantially from ages 4 years to 18 years (Figure 2 and Supplemental Tables S1 to S6).

Using logistic regressions with repeated measures, we tested the association of disease transition with the aforementioned covariates. Among children who did not have allergic diseases at ages 4 or 10, the odds of acquisition of any allergic disorder among subjects who experienced allergic sensitization acquisition was 3.27 times the odds (p<0.0001) for those who were not sensitized (Table 4). Among children with persistent allergic sensitization, the odds of new diagnosis (acquisition) was 6.32 times the odds (p<0.0001) of those without allergic sensitization. Children whose mothers reported history of one or more allergic disorders tended to have higher odds of allergic disorder acquisition (OR= 1.55, p=0.038) compared to children whose mothers reported being disease-free, although the finding was not statistically significant after adjusting for multiple testing. On the other hand, it was observed that children whose father had a history of allergic disorder also had higher odds of acquisition (OR=2.02 with p-value 0.0015) (Table 4).

The odds of persistent allergic disease among subjects who acquired allergic sensitization was 5.49 times the odds for those without allergic sensitization (p=0.0001), and the odds of persistent allergic disease was 11.79 times as high among those who had persistent allergic sensitization (p<0.0001; Table 5). Consequently, the odds of remission among children who experienced allergic sensitization acquisition was lower compared to children who were free of allergic sensitization (OR= 0.18, p=0.0001). The odds of remission among children who experienced persistent allergic sensitization was much lower, 0.085 times the odds for children not sensitized (p<0.0001; Table6).

Findings from the time-lagged model revealed similar patterns. In particular, among children who did not have allergic diseases at ages 4 or 10, the odds of acquisition of allergic disorder at a later age (10 or 18 years) among subjects who experienced allergic sensitization acquisition at an earlier age (4 to 10 years) was 5.46 times the odds (p=0.001) for those who were not sensitized. Among children with persistent allergic sensitization, the odds of acquisition was 5.51 times the odds of those with no sensitization (Table 7). Season of birth was potentially associated with transition of allergy-related diseases. In line with what we have previously reported in the cohort,[[19](#_ENREF_19)] compared to children born in autumn, children born in the season of winter had a lower odds of allergic disease acquisition (OR=0.53, p=0.024), while children born in summer tended to have a higher odds (OR=1.66, p=0.031), although both associations did not meet the statistical significance threshold after multiple testing correction (Table 7). Parental history of allergic disorder did not show a statistically significant association with acquisition (Table 7). The odds of persistent allergic diseases from 10 to 18 among subjects who acquired allergic sensitization at 4 or 10 was 4.17 times the odds for those with no sensitization (p=0.008), and the odds of persistent disease from 10 to 18 years was 11.31 times as high among those who had earlier age (4-10 years) persistent allergic sensitization (p<0.0001) (Table 8). Although not statistically significant after adjusting for multiple testing, sex was potentially associated with allergic disease transition. In particular, males tended to be less likely to have persistent allergic disease from 10 to 18 compared to girls (OR=0.43, p=0.029; Table 8), and consequently, more likely to have allergic disease remissions from 10 to 18 years (OR=2.33, p=0.029) compared to girls (Table 9). The odds of remission among children who experienced allergic sensitization acquisition at an earlier age was lower compared to un-sensitized children (OR= 0.23, p=0.008), and the odds of remission among children who had persistent allergic sensitization at an earlier age was much lower, 0.088 times the odds for non-atopic children (p<0.0001) (Table 9).

**Discussion**

Although both the acquisition and remission of allergic diseases occur in a significant proportion of children, overall, both allergic comorbidities (coexistence of asthma, rhinitis and eczema in various combinations) and allergic sensitization increase from early childhood to young adulthood. Findings from our study indicate that maternal and paternal allergic disease, as well as acquisition and persistence of allergic sensitization are common risk factors for acquisition of any allergic disease. Across childhood, acquisition or persistent allergic sensitization is associated with acquisition or persistence of asthma, eczema, and/or rhinitis, and is substantially inversely associated with remission of one or more of these diseases. This finding was consistent under two different statistical modeling frameworks, concurrent longitudinal modeling via logistic regression with repeated measures, and time-lagged logistic regression models.

Previously, the development of allergic disease during childhood and its association with allergic sensitization was considered to progress from food allergy and eczema in early childhood to asthma and rhinitis in later childhood, termed the “atopic or allergic march”.[[20](#_ENREF_20)] However, this concept may be an oversimplification as recent studies using birth cohorts suggest an absence of a typical “atopic march” in the majority of children.[[21](#_ENREF_21), [22](#_ENREF_22)] It is now recognized that at the population level, asthma, rhinitis and eczema occur as allergic comorbidity clusters[[22-24](#_ENREF_22)] with the coexisting allergies becoming increasingly common throughout childhood.[[24](#_ENREF_24)] Using a consortium of birth cohorts, Bousquet *et al.* proposed that sensitization to multiple allergens further increases the risk of allergic comorbidity.[[25](#_ENREF_25)] In this analysis we focused on any allergic sensitization and did not distinguish between subjects sensitized to different allergens.

Asthma, rhinitis and eczema are manifestations of a common underlying immune disorder with T-helper 2 (Th2) dominance resulting in production of IgE to specific allergens.[[25](#_ENREF_25)] Development of allergic sensitization increases the risk of subsequent development of relevant clinical disease.[[26](#_ENREF_26)] However, not all those with allergic sensitization develop allergic conditions and conversely not everyone with asthma, eczema and rhinitis manifest allergic sensitization.[[27](#_ENREF_27)] The natural history does not follow a simple course of acquisition of allergic sensitization followed by allergic disease. A more accurate depiction (as we have demonstrated) is a bi-directional relationship where allergic sensitization and allergic conditions promote or sustain each other with the prevalence of both conditions increasing throughout childhood such that persistence and acquisition outstrip remission. In addition, our time-lagged assessment among children free from allergic diseases at ages 4 or 10 indicated that allergic sensitization acquired at an earlier age confers a much higher risk of allergic disease incidence at a later age, in comparison to un-sensitized individuals. Although this does not conclude causation, the findings of our study suggest a potential for allergic disease preventions with an effort of controlling allergic sensitization.

Genetic factors may underpin both allergic sensitization (positive SPT) and allergic conditions and, hence, we found parental history of allergy as a major risk factor for acquisition or persistence of allergic disease. This is in line with the findings of the German multicenter asthma study, which recently showed that parental allergies predicted the development of allergic multimorbidity throughout childhood.[[24](#_ENREF_24)] Further studies are required to investigate how maternal and paternal allergy and allergic sensitization interact to cause allergic comorbidity from childhood to adulthood. Our study had some limitations. The dynamic associations between allergic sensitization and diseases, we have described during childhood, may not be applicable to adulthood as previous cross-sectional studies indicate that allergic conditions in adults are often non-atopic.[[28](#_ENREF_28), [29](#_ENREF_29)] We used positive SPT to at least one of multiple allergens to assess allergic sensitization, as we do not have specific IgE assessment in all subjects in the cohort to allow a meaningful analysis. Although these two tests reflect the same atopic predisposition and are correlated, epidemiologic studies indicate that there is significant disagreement between the two tests.[[30](#_ENREF_30)] Using specific IgE may reveal different associations, as they may not have the same biological and clinical relevance.[[31](#_ENREF_31)] We did not include infancy in our longitudinal trajectory for two reasons. First, we did not have skin prick tests in all children at the one and two year assessments. Secondly, asthma and rhinitis are impossible to differentiate from respiratory symptoms associated with viral infections. By four years of age, the phenotype is stable enough to make a reasonable assessment, although a later assessment at five or six years would have been more robust. We also did not include food allergy as an allergic condition as the numbers of children with food allergy were small and other studies have looked at the association of individual food allergy with specific food allergic sensitization.[[32](#_ENREF_32)]

In conclusion, our study shows that natural remission and relapse occurs commonly in both allergic sensitization and clinic allergic manifestations and that these phenotypes are closely associated with each other, such that being persistent in allergic sensitization increases the risk of persistent allergic disease and sensitization remission promotes growing out of allergic conditions throughout childhood. Furthermore, this association was confirmed in a time-lagged manner so that remission in allergic sensitization at an earlier age promoted remission in clinical disease at a later time point. This has important implications for allergy prevention, as inducing remission of allergic sensitization, e.g., with allergen immunotherapy (before or after development of clinical disease) will potentially prevent allergic disease or lead to its remission.

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| Table 1. Allergic disorders at ages of 4, 10, and 18 years, %(n). |
| Allergic disorders | **Age 4**  | **Age 10** | **Age 18** |
| Asthma only | 10.2 (123) | 6.3 (84) | 5.5 (71) |
| Eczema only | 7.9 (96) | 8.0 (107) | 5.6 (73) |
| Rhinitis only | 2.5 (30) | 13.4 (181) | 20.4 (265) |
| Asthma & Eczema | 2.4 (29) | 1.0 (14) | 0.5 (7) |
| Eczema & Rhinitis | 0.6 (7) | 2.4 (32) | 3.6 (47) |
| Asthma & Rhinitis | 1.3 (16) | 4.7 (63) | 9.0 (117) |
| Asthma, Eczema, and Rhinitis | 1.0 (12) | 2.4 (32) | 2.6 (34) |

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| Table 2. Allergic sensitizations at ages of 4, 10, and 18 years stratified by status of allergic diseases (Yes/No). |
|  | **Allergic sensitization, % (n)** |  |
| Allergic diseases status  | **Age 4**  |  **Age 10**  | **Age 18**  |
| Yes | 42.8 (62) | 45.54 (102) | 64.55 (173) |
| No | 10.9 (42) | 15.26 (47) | 23.11 (61) |

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| **Table 3. Comparison between the subsamples and the IoW cohort on key characteristics.** |
| **Variable, % (n)** | **Subsample** | **IoW cohort** | **p-value** |
| **Atopy** |  |  |  |
| Age 4 years | 19.9 (106) | 19.7 (193) | 0.97 |
| Age 10 years | 28.0 (149) | 26.9 (279) | 0.60 |
| Age 18 years | 44.2 (235) | 41.4 (353) | 0.14 |
| **Allergic diseases** |  |  |  |
| Age 4 years | 27.3 (145) | 25.9 (313) | 0.51 |
| Age 10 years | 42.1 (224) | 38.1 (513) | 0.05 |
| Age 18 years | 50.4 (268) | 47.3 (614) | 0.12 |
| **Maternal disease (Yes)** | 29.5 (157) | 32.1 (387) | 0.22 |
| **Paternal disease (Yes)** | 28.6 (152) | 24.6 (296) | 0.06 |
| **Sex (Male)** | 45.1 (240) | 51.2 (786) | 0.007 |
| **Notes: Multiple testing-adjusted significance level=0.0027 (Bonferroni).** |

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| **Table 4. Inferences for the acquisition of any allergic diseases (logistic regression with repeated measures).** |
| **Variable** | **Odds Ratio; (95% CI)** | **P-value** |
| **Atopy transition**Atopy no-no | Reference |  |
| Atopy no-yes | 3.27; (1.99, 5.37) | <0.0001\* |
| Atopy yes-no | 1.29; (0.36, 4.60) | 0.6995 |
| Atopy yes-yes | 6.32; (3.44, 11.64) | <0.0001\* |
| **Maternal disease (Yes)** | 1.55; (1.02, 2.35) | 0.0389 |
| **Paternal disease (Yes)** | 2.02; (1.30, 3.12) |  0.0015\* |
| **Postnatal smoking (Yes)** | 1.22; (0.91, 1.65) | 0.1822 |
| **Prenatal smoking during pregnancy (Yes)** | 0.98; (0.68, 1.42) | 0.9331 |
| **Paternal smoking (Yes)** | 0.95; (0.57, 1.58) | 0.8451 |
| **Season of birth** |  |  |
| winter | 0.76; (0.52, 1.10) | 0.1356 |
| spring | 0.89; (0.64, 1.24) | 0.5044 |
| summer | 1.14; (0.84, 1.56) | 0.3854 |
| **Sex (Male)** | 1.09; (0.73, 1.64) | 0.6769 |
| **Birth weight** | 1.06; (0.70, 1.59) | 0.7921 |
| **Formula feeding** | 1.00; (0.98, 1.01) | 0.6876 |
| **Cord blood IgE** | 1.00; (0.69, 1.46) | 0.9851 |
| **Transition period (10-18 years)** | 1.20; (0.83, 1.72) | 0.3422 |
| **Notes:\* denotes significant results after adjusting for multiple testing. Multiple testing-adjusted significance level=0.0016 (Bonferroni).** |

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| **Table 5. Inferences for the persistence of any allergic diseases (logistic regression with repeated measures).** |
| **Variable** | **Odds Ratio; (95% CI)** | **P-value** |
| **Atopy transition**  (no-no is the reference) |  |  |
| Atopy no-yes | 5.49; (2.31, 13.08) |  0.0001\* |
| Atopy yes-no | 1.43; (0.45, 4.55) | 0.5399 |
| Atopy yes-yes | 11.79; (5.56, 25.02) | <0.0001\* |
| **Maternal disease (Yes)** | 1.44; (0.80, 2.59) | 0.2192 |
| **Paternal disease (Yes)** | 0.57; (0.30, 1.07) | 0.0798 |
| **Postnatal smoking (Yes)** | 0.75; (0.48, 1.17) | 0.2072 |
| **Prenatal smoking during pregnancy (Yes)** | 1.23; (0.65, 2.34) | 0.5266 |
| **Paternal smoking (Yes)** | 1.14; (0.49, 2.64) | 0.7622 |
| **Season of birth** |  |  |
| winter | 1.27; (0.78, 2.07) | 0.3366 |
| spring | 0.61; (0.34, 1.09) | 0.0951 |
| summer | 1.53; (0.97, 2.43) | 0.0692 |
| **Sex (Male)** | 0.66; (0.36, 1.20) | 0.1735 |
| **Birth weight** | 0.70; (0.39, 1.24) | 0.2202 |
| **Formula feeding**  | 1.01; (0.98, 1.03) | 0.6981 |
| **Cord blood IgE** | 0.90; (0.46, 1.76) | 0.7541 |
| **Transition period (10-18yrs)** | 0.62; (0.36, 1.08) | 0.0913 |
| **Notes:\* denotes significant results after adjusting for multiple testing. Multiple testing-adjusted significance level=0.0016 (Bonferroni).** |

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| **Table 6. Inferences for the remission of any allergic disease (logistic regression with repeated measures).** |
| **Variable** | **Odds Ratio; (95% CI)** | **P-value** |
| **Atopy transition** (no-no is the reference) |  |  |
| Atopy no-yes | 0.18; (0.08, 0.43) |  0.0001\* |
| Atopy yes-no | 0.70; (0.22, 2.21) | 0.5399 |
| Atopy yes-yes | 0.085; (0.04, 0.18) | <0.0001\* |
| **Maternal disease (Yes)** | 0.69; (0.39, 1.24) | 0.2192 |
| **Paternal disease (Yes)** | 1.76; (0.93, 3.33) | 0.0798 |
| **Postnatal smoking (Yes)** | 1.33; (0.85, 2.07) | 0.2072 |
| **Prenatal smoking during pregnancy (Yes)** | 0.81; (0.43, 1.55) | 0.5266 |
| **Paternal smoking (Yes)** | 0.88; (0.38, 2.03) | 0.7622 |
| **Season of birth** |  |  |
| winter | 0.79; (0.48, 1.28) | 0.3366 |
| spring | 1.65; (0.92, 2.98) | 0.0951 |
| summer | 0.65; (0.41, 1.03) | 0.0692 |
| **Sex (Male)** | 1.52; (0.83, 2.77) | 0.1735 |
| **Birth weight** | 1.44; (0.80, 2.57) | 0.2202 |
| **Formula feeding** | 0.99; (0.97, 1.02) | 0.6981 |
| **Cord blood IgE** | 1.11; (0.57, 2.18) | 0.7541 |
| **Transition period (10-18 years)** | 1.61; (0.93, 2.79) | 0.0913 |
| **Notes:\* denotes significant results after adjusting for multiple testing. Multiple testing-adjusted significance level=0.0016 (Bonferroni).** |

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| **Table 7. Inferences for the acquisition of any allergic disease (time-lagged model via logistic regression).** |
| **Variable** | **Odds Ratio; (95% CI)** | **P-value** |
| **Atopy transition** |  |  |
|  (no-no is the reference) |  |  |
| Atopy no-yes | 5.46; (1.95, 15.25) | 0.001 |
| Atopy yes-no | 2.47; (0.60, 10.21) | 0.213 |
| Atopy yes-yes | 5.51; (1.82, 16.70) | 0.003 |
| **Maternal disease (Yes)** | 1.76; (0.93, 3.32) | 0.083 |
| **Paternal disease (Yes)** | 1.34; (0.69, 2.57) | 0.385 |
| **Postnatal smoking (Yes)** | 1.17; (0.75, 1.80) | 0.493 |
| **Prenatal smoking during pregnancy (Yes)** | 1.26; (0.75, 2.12) | 0.384 |
| **Paternal smoking (Yes)** | 1.04; (0.49, 2.23) | 0.912 |
| **Season of birth** |  |  |
| winter | 0.53; (0.31, 0.92) | 0.024 |
| spring | 1.05; (0.64, 1.73) | 0.842 |
| summer | 1.66; (1.05, 2.61) | 0.031 |
| **Sex (Male)** | 1.15; (0.63, 2.09) | 0.646 |
| **Birth weight** | 1.03; (0.57, 1.87) | 0.92 |
| **Formula feeding** | 0.99; (0.97, 1.02) | 0.655 |
| **Cord blood IgE** | 1.11; (0.57, 2.15) | 0.754 |
| **Notes:\* denotes significant results after adjusting for multiple testing. Multiple testing-adjusted significance level=0.0016 (Bonferroni).** |

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| **Table 8. Inferences for the persistent of any allergic disease (time-lagged model via logistic regression).** |
| **Variable** | **Odds Ratio; (95% CI)** | **P-value** |
| **Atopy transition** |  |  |
|  (no-no is the reference) |  |  |
| Atopy no-yes | 4.17 (1.44, 12.07) | 0.008 |
| Atopy yes-no | 2.04; (0.34, 12.30) | 0.437 |
| Atopy yes-yes | 11.31; (3.90, 32.79) | <0.0001 |
| **Maternal disease (Yes)** | 1.30; (0.61, 2.79)  | 0.494 |
| **Paternal disease (Yes)** | 0.66; (0.31, 1.1) | 0.283 |
| **Postnatal smoking (Yes)** | 0.92; (0.52, 1.63) | 0.766 |
| **Prenatal smoking during pregnancy (Yes)** | 1.61; (0.67, 3.89) | 0.288 |
| **Paternal smoking (Yes)** | 0.45; (0.14, 1.40) | 0.166 |
| **Season of birth** |  |  |
| Season of Birth (winter) | 1.15; (0.60, 2.18) | 0.68 |
| Season of Birth (spring) | 1.31 (0.63, 2.74) | 0.473 |
| Season of Birth (summer) | 1.15; (0.64, 2.06) | 0.643 |
| **Sex (Male)** | 0.43; (0.20, 0.91) | 0.029 |
| **Birth weight** | 0.69; (0.32, 1.50) | 0.349 |
| **Formula feeding** | 0.99; (0.96, 1.03) | 0.7 |
| **Cord blood IgE** | 1.49; (0.51, 4.38) | 0.472 |
| **Notes:\* denotes significant results after adjusting for multiple testing. Multiple testing-adjusted significance level=0.0017 (Bonferroni).** |

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| **Table 9. Inferences for the remission of any allergic disease (time-lagged model via logistic regression).** |
| **Variable** | **Odds Ratio; (95% CI)** | **P-value** |
| **Atopy transition** |  |  |
|  (no-no is the reference) |  |  |
| Atopy no-yes | 0.24; (0.08, 0.69) | 0.008 |
| Atopy yes-no | 0.49; (0.08, 2.96) | 0.438 |
| Atopy yes-yes | 0.09; (0.03, 0.26) | <0.0001 |
| **Maternal disease (Yes)** | 0.77; (0.36, 1.64) | 0.494 |
| **Paternal disease (Yes)** | 1.52; (0.71, 3.24) | 0.283 |
| **Postnatal smoking (Yes)** | 1.09; (0.61, 1.94) | 0.766 |
| **Prenatal smoking during pregnancy (Yes)** | 0.62; (0.26, 1.50) | 0.288 |
| **Paternal smoking (Yes)** | 2.23; (0.72, 6.95) | 0.166 |
| **Season of birth** |  |  |
| winter | 0.87; (0.46, 1.66) | 0.68 |
| spring | 0.76; (0.36, 1.60) | 0.473 |
| summer | 0.87; (0.48, 1.56) | 0.643 |
| **Sex (Male)** | 2.33; (1.09, 4.98) | 0.029 |
| **Birth weight** | 1.44; (0.67, 3.12) | 0.349 |
| **Formula feeding** | 1.01; (0.97, 1.04) | 0.7 |
| **Cord blood IgE** | 0.67; (0.23, 1.98) | 0.472 |
| **Notes:\* denotes significant results after adjusting for multiple testing. Multiple testing-adjusted significance level=0.0017 (Bonferroni).** |

**Figure 1. An illustration of the three transition models.**

**Figure 2. Strength of association of allergic sensitizations with allergic diseases at each age.**

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