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Patterns of allergic sensitization and atopic dermatitis from 1 to 3 years: effects on allergic diseases

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Abstract

Background

While allergic sensitization and atopic dermatitis (AD) are known to increase the risk for allergic diseases, the impact of different temporal and clinical patterns of sensitization and AD is less well defined.

Objective

We investigated patterns of sensitization and AD from early infancy to age 3, and the differential risk for developing allergic diseases within each pattern in a general cohort.

Methods

Children (n=2629) from the Canadian Healthy Infant Longitudinal Development (CHILD) Study underwent skin prick tests and were assessed clinically for AD at ages 1 and 3 years. We applied an unsupervised latent class analysis (LCA) to the following 5 factors at these ages: AD, food sensitization, inhalant sensitization, poly-sensitization to foods, and poly-sensitization to inhalants. The risks for developing asthma, allergic rhinitis and food allergy at 3 years were evaluated for each identified group.

Results

Five distinct classes were revealed by LCA: healthy (81.8%), atopic dermatitis (7.6%), inhalant sensitization (3.5%), transient sensitization (4.1%), and persistent sensitization (3.2%). Using healthy children as the baseline, children in the "atopic dermatitis" group had the next lowest risk for all allergic outcomes at 3 years; those in the "inhalant sensitization" group had the highest risk for allergic rhinitis; children in the "transient sensitization" group were at an increased risk for food allergy; while children in the "persistent sensitization" group had the highest risk for all allergic diseases.

Conclusion and Clinical Relevance

There is substantial heterogeneity among allergen-sensitized children. Researchers and clinicians need to be aware of the non-specificity associated with labelling children simply as "atopic" and "non-atopic" without considering the timing of their atopic history, type of sensitization, and AD status. Children with AD who were poly-sensitized to foods at an early age appear to be at greatest risk of developing other allergic diseases.

Introduction

Understanding the temporal and clinical patterns of allergic sensitization and atopic dermatitis (AD) from a young age is crucial in identifying children most vulnerable for serious allergic diseases at later ages. Previous prospective cohorts have illustrated that from birth to age one, children are usually only mono-sensitized (sensitized to one allergen), primarily to food. Between ages one to four years, inhalant sensitization becomes more frequent, concurrent with a decline in food sensitization (1–3); more children also start to exhibit poly-sensitization (sensitization to multiple allergens) (4,5).

Using various machine learning techniques (such as latent class analysis and cluster analysis), several population cohorts have deciphered various patterns of sensitization from childhood to adolescents and their differential risks for various allergic outcomes at later ages (6–10). While strong associations between AD and food sensitization are known, fewer studies have examined how manifestations of AD co-occur with these various sensitization patterns, especially at a younger age. One such study clearly showed that early AD, especially if associated with early food sensitization was highly associated with subsequent allergic disease, supporting the 'atopic march' hypothesis (3). However, latent class analysis of data from the Manchester Asthma and Allergy Study (MAAS) suggested not all allergy leads to the atopic march, and that the atopic march may not be causal in subsequent development of allergic diseases (11).

The heterogeneity of methods used in past cross sectional and cohort studies examining sensitization and AD as risk factors for allergic diseases make interpretation difficult. Some examined only incident cases of AD (12,13), others assessed the risk of AD among all children, and some did not distinguish between different types of sensitization (1,12–18). Ignoring the heterogeneity in the type of allergic sensitization (food, inhalant, food

and inhalant, mono-sensitization and poly-sensitization), time of manifestation (persistent or transient) and AD status by simply categorizing children as "atopic" and "non-atopic" may obscure differential impacts of these risk factors (6–10). For instance, an increased risk for hospitalizations due to asthma were only found among children who were poly-sensitized at an early age, but not among those sensitized at a later age (10). A recently reported unsupervised cluster analysis of data from the Copenhagen at-risk cohort from 6 months to 6 years of age identified 7 age- and allergen-specific patterns. Asthma was associated solely with the allergen pattern of dog/cat/horse, whereas AD was associated with all food and inhalant allergen clusters apart from house dust mite and allergic rhinitis with 5 of the 7 patterns (9).

Machine learning techniques provide opportunities to explore the heterogeneity inherent in longitudinal patterns of development of symptoms of allergic diseases and of biological markers such as food and inhalant sensitization. We have applied latent class analysis to data from the Canadian Healthy Infant Longitudinal Development (CHILD) Study to examine the relationships between changes in AD and patterns of allergic sensitization from birth to age 3 years and the development of allergic diseases by that age, to better elucidate these patterns at an earlier age.

Materials and methods

Data collection

The CHILD Study recruited 3,623 pregnant women from the general population across 4 Canadian provinces (Edmonton (Alberta), Toronto (Ontario), Vancouver (British Columbia) and Winnipeg (Manitoba)). Excluding 83 children who were ineligible at birth and 45 families who failed to begin the study (19), we are following 3,495 infants from pregnancy to age 5 years. The current analysis is based on 2,629 children who completed skin

prick tests (SPT) to common food and inhalant allergens at both 1 year and 3 years of age, and whose AD status was ascertained by clinical assessment by CHILD Study physicians at both ages. Food allergens tested included peanut, milk, egg white and soy. At 1 year and 3 years, inhalant allergens tested included alternaria tenuis, cat hair, dog epithelium, house dust mites (Der.pt and Der.f) and cockroach. Additional inhalants, namely cladosporium, penicillium, aspergillus fumigatus, trees, grass, weeds and ragweed were tested only at 3 years of age. At 3 months, 6 months, 1 year, 18 months, 2 years, 2.5 years, and 3 years, parents were asked to complete questionnaires that inquired about the children's skin rashes, allergic histories, medication and if the child had been diagnosed with eczema or atopic dermatitis by a health care professional during each time period. We accepted the terms eczema and atopic dermatitis as equivalent. Parents were also asked to report their own allergic history and completed similar skin prick tests (SPT). Full details on recruitment and procedures can be found in previous publications (19).

Definitions

Atopic status was determined by wheal size from SPTs, calculated as the average of the diameter and its perpendicular measured at the mid-point of the maximum length, from which was subtracted any wheal size produced by a negative control (glycerin) (Appendix 1). A child or parent was considered atopic if they produced a wheal $\geq$ 2 mm to at least one allergen (20). In the very rare cases (n = 3) where skin testing to a specific allergen was declined due to previous reactions, external test results when available were used to determine sensitization status.

To reduce the child's apprehension and because infants' arms were small, some children had skin tests performed on the back rather than on the arms. Mean histamine wheal sizes on the back were consistently larger at both ages necessitating application of a correction factor of 0.82 to all wheals measured on the back (see details in Appendix 1).

During the clinic visits at 1 and 3 years, children were assessed for AD, asthma, allergic rhinitis, and food allergy by interviewing parents about symptoms in the past year. Interviews were conducted by CHILD Study physicians (ABB, PJM, PS, SET; all experienced pediatricians specializing in allergy and asthma) or highly trained healthcare professionals under the guidance of these CHILD Study physicians. Diagnoses were recorded as "definite", "possible" or "no" for each allergic condition. In the current analysis, only "definite" cases were considered positive. The methods by which these diagnoses were established can be found in Appendix 2.

To ensure that the diagnosis of AD by 1 year of age was inclusive, we combined multiple sources of reporting (14). Based on the questionnaires, itchy wet or red rashes reported on the face, inside of elbows, wrist / hands, or back of knees which were treated with corticosteroid creams were considered as definite AD. A child was also considered to have definite AD if parents reported a diagnosis made by a health care professional. Finally, definite AD was also recorded if the child was so diagnosed by our experienced study personnel during the clinical assessment visits, based on criteria from the UK Working Party (21). This required that children must have an itchy skin condition, together with one of the following three criteria: a history of involvement of the skin creases of elbows, behind the knees, front of ankles or around the neck; a history of general dry skin in the last year; or visible flexural eczema or eczema involving the cheeks/foreheads and outer limbs.

A parental history of allergic diseases was defined as at least one parent reporting a history of food allergies, eczema, asthma, or allergic rhinitis (or hay fever). More details on definitions of variables can be found in Appendix 3.

Statistical analysis

Latent class analysis

First, we examined the changes in sensitization patterns from age 1 to 3 years for each allergen tested at both ages using McNemar's test for paired data. To understand the overall patterns of sensitization and AD within the data, we employed an exploratory, unsupervised latent class analysis (LCA), with no preconceived hypothesis. Ten factors which were assessed at 1 and 3 years of age were evaluated to reveal distinct patterns of sensitization and AD. These factors were: AD at 1 year and 3 years, food sensitization at 1 year and 3 years, inhalant sensitization at 1 year and 3 years, poly-sensitization to foods at 1 year and 3 years, and poly-sensitization to inhalants at 1 year and 3 years. In performing the LCA, we considered models ranging from one to six classes; we selected the optimum number of classes using the Bayesian Information Criterion (BIC) and Akaike Information Criterion (AIC), as well as considering the model that was most interpretable (22,23). The model then generated a posterior probability of membership in each identified class for each child. Subsequently, each child was assigned to the class that yielded the highest posterior probability among all the available classes. The "poLCA" (24) package in R 3.3.2 (25) was used to perform the LCA.

Risk for allergic diseases due to trajectories in sensitization patterns and AD

Following results from our LCA model, the identified groups were assessed for differences in the following sociodemographic factors: sex, parental sensitization (SPT-based), parental history of allergic diseases, pet ownership, ethnicity, smoking in the house, breastfeeding, presence of older siblings, household income, parental education, and study center using a chi-square test (or Fisher's exact test where appropriate) (12,13). To account for uncertainties in group assignment based on LCA, frequencies were weighted by the

child's posterior probability of belonging to each group, rather than directly counting the number of children belonging in each group (26,27). These weights were calculated and rounded to the nearest whole number (28). Demographic variables garnering significant chi-square results were followed with a post-hoc comparison with the reference group ("healthy"); p-values were adjusted using the Holm-Bonferroni correction (29).

Finally, we evaluated the risks for demonstrating allergic diseases (allergic rhinitis, food allergy, and asthma) at 3 years for each of the identified LCA groups compared to the "healthy" group. Odds ratios were obtained from multivariable logistic regression models with robust variance to account for the strong clustering effects of study center (30). To reduce bias, regression models were also weighted for each individual probability of group assignment (26,27). For example, a child with a 0.7 probability of belonging to group 1 and 0.3 probability of belonging to group 2 was considered as two observations in the regression model, contributing to the count in both groups, and weighted accordingly. Sensitivity analysis was conducted to determine if results differed when these regression weights were not accounted for and each child was only assigned to the group with the highest membership probability.

Using a more relaxed threshold of $p < 0.2$, demographic factors that were associated with both outcomes and predictor variables were included as adjustment variables, while ensuring that enough events were observed given the number of covariates (31). To calculate the robust variance while accounting for the regression weights, the software STATA 13 was used for this analysis (32).

After groups were determined, we conducted post-hoc analyses to determine whether an increased risk for food allergy might be explained through food avoidance by children who were food-sensitized at age 1 year.

Results

Study population

Of the 2,629 children eligible for this analysis, the majority had a white Caucasian mother (74.3%) with a tertiary education (58.3%) and middle to upper socioeconomic status (57.1%). The majority of parents reported a history of ever having allergies and atopic diseases (77.0 %); and more than half (57.5%) of mothers tested positive to at least one allergen (Table 1). There were no significant differences in the characteristics of children included in the study to the full cohort (Appendix 4). However, among those excluded from this analysis, we noted a lower prevalence of AD at 1 year, fewer fathers with asthma and fewer mothers with AD.

Prevalence of AD and allergic sensitization

At one year, 20.0% of children had AD and 13.5% were sensitized to at least one allergen; at three years, 22.1% had AD and 14.4% were sensitized. The majority of allergic sensitization at 1 year was to a single food; very few children were sensitized to inhalants. Conversely, at 3 years, more children were sensitized to inhalants; many were poly-sensitized and fewer children were sensitized to food (Table 2).

The most common food sensitization at one year was to egg white, which decreased significantly at age 3 (7.2% to 2.5%, $p < 0.001$). At 3 years, peanut allergy was the most common food sensitization, although the rate had decreased significantly since age 1 year (4.9% to 3.9%; $p < 0.04$). Sensitization to cow milk also decreased significantly between age 1 to 3 years (1.8% to 1.1%, $p < 0.03$) but not soybean, which was the least common food sensitization at both ages (0.8% to 0.5%, $p < 0.29$).

The most common inhalant sensitization at both ages was to cat hair, which also demonstrated the largest increase with age (1.7% to 5.0%, $p < 0.001$). Sensitizations to both house dust mites were also common at both ages and increased significantly at age 3 (Der.pt: 0.4% to 1.5%, $p < 0.001$; Der.f: 0.6% to 1.6%; $p < 0.001$). Sensitization to alternia tenuis was the least common at age 3 with no discernable changes between the two ages (0.7% to 0.6%; $p = 0.61$). Between age 1 to 3 years, more children were sensitized to dog epithelium (0.7% to 1.1%; $p = 0.11$) and cockroach (0.6% to 1.0%, $p = 0.09$); these differences were approaching significance. The changes in rates of sensitization for each allergen are shown in Figure 1.

Trajectory of sensitization patterns and AD from LCA

A five-class structure yielded the lowest BIC among all models considered; a six-class structure gives a slightly smaller AIC, however this difference is negligible (Appendix 5). After considering the interpretability of four, five and six classes models, as well as recognizing BIC as the preferred model diagnostic criteria (23), a five class structure was selected as the optimum model; there was an excellent separation of classes, with entropy of 0.91 (33). These five classes were:

[1] *Healthy:* Of all eligible children, 81.8% clustered into a "healthy" group; these children demonstrated very little AD or sensitization at either age.

[2] *Atopic Dermatitis:* The group accounts for 7.6% of the children. This group displayed very little sensitization at either age, but at both ages, a large number had AD (1Y: 100%; 3Y: 85.2%).

[3] *Inhalant sensitization:* The group accounts for 3.5% of children in the study. This group is characterized by little sensitization of any type at age 1, but substantial inhalant sensitization

at age 3 years. They demonstrated a moderate level of AD at both ages (1Y: 30.0%; 3Y: 41.3%). Sensitization at age 1 tended to be mono-sensitization, whereas the surge of inhalant sensitization at age 3 was primarily poly-sensitization (65.0%); food sensitization remained low at age 3.

[4] *Transient sensitization:* This group accounts for 4.1% of the children. They displayed a unique pattern where 100% were sensitized to food with few inhalant sensitizations at age 1 year; as they aged, food sensitization decreased significantly (to 30.8%) and inhalant sensitization remained low (11.4%). Food sensitization at age 1 was primarily mono-sensitization (74.0%), and the level of AD was moderate (1Y: 28.7%; 3Y: 38.4%). Since most did not retain sensitization at age 3, this was termed the "Transient Sensitization" group.

[5] *Persistent sensitization:* The last group identified was the smallest, accounting for 3.2% of children. Almost all in this group (87.5%) were food sensitized at age 1 year, with little inhalant sensitization, but unlike the "transient sensitization" group, 100% were food sensitized at age 3; they were also largely poly-sensitized to food at both ages (1Y: 56.7%; 3Y: 62.8%). This group was characterized by higher prevalence of AD at both ages compared to other groups (1Y: 77.1%, 3Y: 67.6%). Many of them also acquired inhalant sensitization at age 3 years (72.2%), primarily mono-sensitization (61.0%). Given the persistence of their food sensitizations, this group is referred to as "persistent sensitization". Figure 2 illustrates the probability distribution of the 10 key variables within the identified LCA groups (more details in Appendix 6).

Demographic factors related to latent class group memberships

Sex, parental sensitization, pet ownership at 1 year, ethnicity, and study center were all significantly associated with the patterns of allergic sensitization and AD that emerged from the LCA (overall $p < 0.01$). However, having an older sibling, reported allergies in

parents, income, smoking in the home, any breastfeeding at 1 year and parental education were not significantly associated with the patterns of AD and sensitization (Table 3).

Post hoc analysis revealed the direction of these observed differences. Males were more likely to be in the "inhalant sensitization" group ($p = 0.02$) and especially the "persistent sensitization" group ($p = 0.02$), with twice as many males as females in this group. Similarly, a strong difference in parental sensitization was found in the "persistent sensitization" group, where 90.7% of children had at least one parent with a positive skin prick test ($p < 0.01$). Children in the persistent sensitization group were less likely to have lived with pets by age one year compared to children in the healthy group ($p = 0.03$). Compared to the "healthy" group, children in the other four groups were more likely to be non-white ($p < 0.05$ for all). Although the cohort sample's composition was primarily white Caucasian, 66.3% of those in the "persistent sensitization" group were non-white, indicating a strong effect of ethnicity ($p < 0.001$). Compared to healthy children, a higher proportion of "persistent sensitization" children came from Edmonton and Vancouver, while Winnipeg had a lowest proportion of "persistent sensitization" children. On the other hand, children living in Edmonton and Winnipeg represented the smallest proportion in the "inhalant sensitization" group, whereas the children living in Vancouver represented a higher proportion of this group.

After considering the association with allergic diseases presenting at 3 years, the following factors were retained as potential confounders for subsequent analyses: sex, parental sensitization, reported parental allergies, any breastfeeding, ethnicity, and any pets.

Risks for allergic diseases at 3 years by latent class memberships

Asthma

Compared to healthy children, children in the ”persistent sensitization” group had the greatest risk of having asthma at 3 years, with an almost 12-fold increased risk (aOR: 11.44; 95% CI: 5.60, 23.37). Risk was also increased among children in the “transient sensitization” group despite no longer being sensitized at 3 years of age, as well as in the “inhalant sensitization” group; albeit risks in these groups were much lower than the ”persistent sensitization” group (aOR: 3.84, 95% CI: 2.94, 5.00; aOR: 2.90, 95% CI: 1.45, 5.78 respectively). The risk of having asthma at 3 years among children in the “atopic dermatitis” group was also increased, albeit the lowest among all other groups (aOR: 1.65; 95% CI: 1.05, 2.57). When groups were not weighted according to their posterior probability, the risk for asthma in the “atopic dermatitis” group was no longer significant (Appendix 7).

Allergic rhinitis

Children in the “persistent sensitization” group were six times more likely to develop allergic rhinitis at age 3 compared to children in the “healthy” group (aOR: 6.37, 95% CI: 2.56, 15.84). However, unlike asthma, the odds for developing rhinitis among children in the “inhalant sensitization” group were just as high as in the “persistent sensitization” group (aOR: 7.45; 95% CI: 3.98, 13.94). Children in the “transient sensitization” and “atopic dermatitis” groups were also at increased but somewhat lower risk of developing rhinitis, (aOR: 2.71; 95% CI: 1.26, 5.83; aOR: 2.36; 95% CI: 2.13, 2.62 respectively).

Food allergy

The risk for having reported food allergy was most elevated for those in the “persistent sensitization” group (aOR: 110.74, 95% CI: 38.33, 319.97). Although the “transient sensitization” children were no longer exhibiting food sensitization at 3 years, they

were still at high risk of having food allergy at 3 years compared with healthy children (aOR: 22.35, 95% CI: 13.06, 38.24). In spite of low rates of food sensitization at ages 1 and 3, children in the "atopic dermatitis" and "inhalant sensitization" groups also exhibited increased risks for developing reported food allergies compared to healthy children (aOR: 5.16, 95% CI: 3.03, 8.78; aOR: 7.37, 95% CI: 3.50, 15.54 respectively). Additional post-hoc analysis supported the possibility that the increased risk of food allergy among children in the "persistent sensitization" group may have been related to children avoiding foods to which they were sensitized at 1 year; children in the "persistent sensitization" group were more likely to have avoided common food allergens in the past year than any other groups, including "transient sensitization" (Table 5).

Adjusted and unadjusted risks for all group memberships are summarized in Table 4. Results from sensitivity analysis ignoring the posterior probability weighting of each group memberships can be found in Appendix 7.

Discussion

This study has identified almost 20% of children in a general Canadian population exhibiting four distinct patterns of allergic sensitization and AD, resulting in differential risks for important allergic outcomes at 3 years including asthma, allergic rhinitis, and food allergy. Children with persistent poly-sensitization to foods from 1 to 3 years of age concomitant with AD were at the highest risk for all the studied allergic diseases. Children with AD only were at risk for rhinitis and food allergy.(16,17) On the other hand, although children who demonstrated monosensitization to foods at 1 year tended to have transient sensitization that disappeared by 3 years, they were still at an increased risk for allergic outcomes, especially reported food allergy. Finally, as well reported in past studies (1,4,34),

some children who were non-sensitized at 1 year developed inhalant sensitization by 3 years. The risk of reported food allergy among these children was less than in other groups, although their risk for developing allergic rhinitis was equal to that of the "persistent sensitization" children.

The term 'atopic march' has been used to refer to the progression of atopic dermatitis to asthma and allergic rhinitis. However we and others have noted that 'atopic dermatitis' is often a misnomer as quite frequently AD is diagnosed in the absence of allergic sensitization. In another publication from this population-based, longitudinal birth cohort, we reported that AD without evidence of allergic sensitization was not associated with an increased risk of subsequent asthma (35), whereas the combination of AD and allergic sensitization at age 1 year was associated with increased risks for both asthma and food allergy at 3 years. The combined effect of diagnosed AD and allergic sensitization was greater than the sum of their individual effects on these risks.

Our results have confirmed past studies that found similar sensitization patterns among children and their associated risks with allergic diseases at age 3 years. Roduit and colleagues undertook latent class analysis in 1038 children in the PASTURE cohort, reporting that while both early transient and early persistent AD were associated with food allergy, persistent AD increased the risk of asthma almost 3-fold, food allergy 7-fold, and allergic rhinitis 4-fold (36). Lee and colleagues reported that early presentation of AD, associated with a high prevalence of atopy, was the strongest risk factor for subsequent asthma and increased airway responsiveness (37). Similarly, Matricardi and colleagues found in the Multicentre Allergy Study (MAS) that AD occurring before age 2 years in association

with wheezing before age 3 years gave a Positive Predictive Value of 41.4 for wheezing in early adolescence (38). In the GUSTO cohort in Singapore, AD occurring before 18 months of age was associated with a 3-fold increased risk of new allergic sensitization; a similar 3-fold increase in risk of new sensitization was found for wheeze before 18 months (13).

Strengths of the present study are its longitudinal design, large sample size and recruitment from a general-population cohort that allows stronger inferences of causality for all children. Furthermore, the use of LCA allows us to examine the distinct effects of timing, sensitization types and AD on the development of allergic diseases, rather than simply combining effects of any sensitization and AD.

There are limitations to the study. First, misclassification may have occurred. There are no validated instruments for diagnosis of AD in children younger than 2 years of age (12). We used the UK Working Party criteria (21), which may have underestimated the number of children with AD, since milder cases may not be diagnosed (12). To address this, we included reported rashes that met accepted clinical criteria for atopic dermatitis and were treated with corticosteroid creams. Similarly, food allergy was not identified by the gold standard of an oral food challenge, but rather relied on parent-reported symptoms of food allergy, which may be subject to bias. Secondly, we have not used specific IgE measurements as have some other studies, which may have identified sensitization to food or inhalant allergens over and above those detected by our panel of skin tests. Of necessity, we tested a limited number of allergens in determining the atopic status of the children. As reported by parents, some children reacted to other allergens not tested in this current study (such as kiwi, banana, and sesame). For consistency, if these children did not have a positive reaction to the panel of allergens tested and did not provide external test results, they were classified as non-sensitized. Given that we tested the most common food allergens, we believe we have identified at least 90% of sensitized children. Finally, while our cohort was taken from the

general population, there was an unintentional recruitment bias where the proportion of parents with a history of allergic diseases is somewhat higher than in the general population, which may limit generalizability.

The differences in food avoidance between "persistent sensitization" and "transient sensitization" is worth noting, in light of recent literature indicating that food avoidance can exacerbate the risk for food allergy (39,40). Whenever mothers requested their children's skin test results at 1 year, we were careful to inform them that these results indicated food sensitization, not food allergy. However, our data do suggest children who were food sensitized at age 1 year were more likely to avoid common food allergens than the other groups. This may explain why children in the "transient sensitization" group were still at an increased risk of food allergy although their food sensitization had disappeared at age 3 years. Given the possibility of confounding by food avoidance, findings regarding food allergy in the current study should be interpreted with caution.

To our knowledge, this is the first general population-based prospective longitudinal birth cohort study that uniquely identifies trajectories of both AD and sensitization among 1 to 3 year old children and assesses their effects on subsequent development of allergic diseases. These classes should be validated in an independent cohort, preferably with a more precise diagnosis of food allergy to assess the effect of transient sensitization on the development of food allergy. Further studies are required to identify interventions that could help prevent allergic diseases. Longitudinal data will also help determine whether these patterns persist, disappear or even reemerge after remitting at 3 years, to confirm results from past retrospective or cross sectional studies (4,34). The CHILD Study is currently collecting follow-up data at 5 years which will allow us to examine this further.

In conclusion, our findings suggest that children with persistent food poly-sensitization with AD by age 3 years may require the most clinical attention in order to reduce the risk of subsequent development of allergic diseases. This study adds to the evidence of substantial heterogeneity within groups of "atopic" and "non-atopic" children (6,9,10). Researchers and clinicians need to be cognizant of the problems associated with labelling children simply as "atopic" and "non-atopic" without considering timing of their atopic history, type of sensitization, and AD status. These enhanced research practices will lead to more clinically relevant findings which could assist in early identification of modifiable risk factors for acquiring allergic diseases.

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Table 1. Demographic of Participants

Demographics	**N (%) = 2629**	
Sex		
Female	1232 (46.9)	
Male	1397 (53.1)	
Study Center		
Edmonton	560 (21.2)	
Toronto	544 (20.7)	
Vancouver	620 (23.6)	
Manitoba	905 (34.4)	
Parental Information*		
Family Income	**N (%)**	
$0 to 49,999	311 (11.9)	
$50,000 to 99,999	828 (31.6)	
$100,000 to 149,999	667 (25.5)	
> $150,000	563 (21.5)	
Prefer not say	248 (9.5)	
Any parental history (ever)	**Mother**	**Father**
Eczema or Atopic Dermatitis	1606 (62.4)	1020 (45.6)
Allergic Rhinitis (Hay Fever)	1281 (49.7)	1082 (48.3)
Asthma	577 (22.4)	449 (20.1)
Food Allergies	571 (22.3)	387 (17.5)
Any history of allergic disease	1986 (77.0)	1525 (68.1)
Sensitized (≥ 1 positive skin test)	1496 (57.5)	1422 (67.9)
Parental Ethnicity		
First Nation	101 (3.9)	101 (3.8)
South East Asian	334 (12.8)	265 (10.1)
South Asian	75 (2.9)	93 (3.6)
Black	48 (1.8)	80 (3.1)
White	1941 (74.3)	1958 (74.8)
Other	112 (4.3)	108 (4.1)
Unknown	2 (0.1)	14 (0.5)

Highest Parental Education		
Graduate degree or higher	486 (19.1)	393 (15.5)
Post-secondary graduation	1485 (58.2)	1364 (53.9)
Some post-secondary	376 (14.7)	412 (16.3)
Secondary graduation (no post-secondary) or less	203 (8.0)	364 (14.4)

*May not sum to 2629 due to missing data

Table 2. Pattern of Sensitizations and Atopic Dermatitis at 1 Year and 3 Years old (N = 2629)

	1 Year	**3 Year**
Any food sensitization	284 (10.8)	155 (5.9)
Peanut	130 (5.0)	106 (4.0)
Cow's milk	47 (1.8)	33 (1.3)
Egg white	190 (7.2)	66 (2.5)
Soybean	21 (0.8)	14 (0.5)
Any inhalant sensitization	104 (4.0)	305 (11.6)
Alternaria Tenuis	19 (0.7)	16 (0.6)
Cat Hair	44 (1.7)	133 (5.1)
Dog Epithelium	19 (0.7)	29 (1.1)
D. Pteronyssinus	11 (0.4)	41 (1.6)
D. Farinae	14 (0.5)	42 (1.6)
Cockroach	16 (0.6)	27 (1.0)
Cladosporium	-	29 (1.1)
Penicillium Mixed	-	9 (0.3)
Aspergillus fumigatus	-	13 (0.5)
Trees Midwest	-	42 (1.6)
Grass Mix	-	53 (2.0)
Weeds	-	26 (1.0)
Ragweed mixed	-	22 (0.8)
Any sensitization (food or inhalant)	355 (13.5)	378 (14.4)
Polysensitization (food or inhalant)	109 (4.2)	166 (6.3)
Polysensitization to food	81 (3.1)	54 (2.1)
Polysensitization to inhalant	15 (0.6)	105 (4.0)
Number of Positive Skin Tests (≥ 2mm wheal)		
None	2274 (86.5)	2251 (85.6)
1 allergen	246 (9.4)	212 (8.1)
2 allergens	74 (2.8)	88 (3.4)
3 or more allergens	35 (1.3)	78 (3.0)
Reported or diagnosed with AD or eczema	527 (20.0)	582 (22.1)

Table 3. Association between demographic characteristics with patterns of sensitization and atopic dermatitis (N = 2629)

	N (row %)[+]		**p-value**[++]
Characteristics	**Sex**		
Groups (from LCA)	**Females**	**Males**	**< 0.001**
Healthy	1037 (48.7)	1094 (51.3)	-
Atopic Dermatitis	80 (40.8)	116 (59.2)	0.07
Inhalant Sensitization	38 (34.9)	71 (65.1)	0.02
Transient Sensitization	49 (45.8)	58 (54.2)	0.62
Persistent Sensitization	28 (32.6)	58 (67.4)	0.02
χ^2	19.1		
Characteristics	**Parental Sensitization (SPT)**		
Groups (from LCA)	**No**	**Yes**	**< 0.001**
Healthy	471 (22.2)	1653 (77.8)	-
Atopic Dermatitis	32 (16.3)	164 (83.7)	0.08
Inhalant Sensitization	15 (13.9)	93 (86.1)	0.08
Transient Sensitization	13 (12.1)	94 (87.9)	0.03
Persistent Sensitization	8 (9.3)	78 (90.7)	0.01
χ^2	19.8		
Characteristics	**Parental Reported Allergic Disease**		
Groups (from LCA)	**No**	**Yes**	**0.52**
Healthy	216 (10.3)	1890 (89.7)	-
Atopic Dermatitis	14 (7.1)	183 (92.9)	-
Inhalant Sensitization	9 (8.4)	98 (91.6)	-
Transient Sensitization	8 (7.5)	98 (92.5)	-
Persistent Sensitization	7 (8.2)	79 (91.9)	-
χ^2	3.2		
Characteristics	**Pet Ownership at 1 Year**		
Groups (from LCA)	**No**	**Yes**	**0.02**
Healthy	1065 (50.3)	1051 (49.7)	-
Atopic Dermatitis	104 (54.4)	91 (45.6)	0.54

Inhalant Sensitization	55 (59.3)	36 (40.7)	0.23
Transient Sensitization	63 (56.2)	45 (43.8)	0.54
Persistent Sensitization	56 (65.1)	29 (34.9)	0.03
χ^2	11.7		
Characteristics	**Ethnicity**		
Groups (from LCA)	**Non-White**	**White**	**< 0.001**
Healthy	688 (32.4)	1436 (67.6)	-
Atopic Dermatitis	85 (43.1)	112 (56.9)	0.008
Inhalant Sensitization	49 (45.4)	59 (54.6)	0.01
Transient Sensitization	48 (45.3)	58 (54.7)	0.01
Persistent Sensitization	57 (66.3)	29 (33.7)	< 0.001
χ^2	58.7		
Characteristics	**Smoking in the Home 1Y**		
Groups (from LCA)	**No**	**Yes**	**0.32**
Healthy	1718 (81.2)	397 (18.8)	-
Atopic Dermatitis	162 (83.9)	31 (16.1)	-
Inhalant Sensitization	94 (86.2)	15 (13.8)	-
Transient Sensitization	91 (86.7)	14 (13.3)	-
Persistent Sensitization	73 (84.8)	13 (15.1)	-
χ^2	4.7		
Characteristics	**Any Breastfeeding at 1 Y**		
Groups (from LCA)	**No**	**Yes**	**0.14**
Healthy	1028 (51.2)	978 (48.8)	-
Atopic Dermatitis	116 (60.7)	75 (39.3)	-
Inhalant Sensitization	52 (51.5)	49 (48.5)	-
Transient Sensitization	48 (49.0)	50 (51.0)	-
Persistent Sensitization	39 (48.8)	41 (51.3)	-
χ^2	7.0		
Characteristics	**Older Sibling**		
Groups (from LCA)	**No**	**Yes**	**0.65**
Healthy	1403 (65.9)	725 (34.1)	-

Atopic Dermatitis	139 (70.6)	58 (29.4)	-
Inhalant Sensitization	75 (68.8)	34 (31.2)	-
Transient Sensitization	71 (67.0)	35 (33.0)	-
Persistent Sensitization	60 (69.8)	26 (30.2)	-
χ^2	2.4		

Characteristics	**Study Center**				
Groups (from LCA)	**Edmonton**	**Toronto**	**Vancouver**	**Winnipeg**	**< 0.001**
Healthy	452 (21.2)	420 (19.7)	477 (22.4)	782 (36.7)	-
Atopic Dermatitis	38 (19.3)	48 (24.6)	47 (23.9)	64 (32.5)	0.35
Inhalant Sensitization	14 (16.8)	31 (29.0)	41 (38.3)	17 (15.9)	< 0.001
Transient Sensitization	27 (25.5)	29 (27.4)	28 (26.4)	22 (20.8)	0.02
Persistent Sensitization	25 (29.1)	15 (17.4)	27 (31.4)	19 (22.1)	0.03
χ^2	50.6				

Characteristics	**Income**					
Groups (from LCA)	**$0 - 49,999**	**$50,000 – 99,999**	**$100,000 – 149,999**	**>$150,000**	**Prefer not say**	**0.59**
Healthy	267 (12.6)	675 (31.8)	525 (24.8)	456 (21.5)	197 (9.3)	-
Atopic Dermatitis	17 (8.6)	68 (34.5)	57 (28.9)	36 (18.3)	19 (9.6)	-
Inhalant Sensitization	11 (10.0)	30 (27.5)	32 (29.4)	28 (25.7)	8 (7.3)	-
Transient Sensitization	9 (8.5)	28 (26.4)	31 (29.2)	25 (23.6)	13 (12.3)	-
Persistent Sensitization	8 (8.1)	28 (32.6)	22 (25.6)	18 (20.9)	11 (12.8)	-
χ^2	14.2					

Characteristics	**Highest Education of Either Parents**				
Groups (from LCA)	**Secondary graduation or less**	**Some post-secondary**	**Post-secondary graduation**	**Graduate degree or higher**	**0.53**
Healthy	121 (5.8)	210 (10.1)	1197 (57.6)	549 (26.4)	-
Atopic Dermatitis	8 (4.1)	19 (9.8)	128 (64.4)	42 (21.6)	-
Inhalant Sensitization	2 (2.8)	11 (10.2)	60 (55.5)	34 (31.5)	-
Transient Sensitization	3 (2.8)	11 (10.5)	64 (61.0)	27 (25.7)	-
Persistent Sensitization	3 (3.7)	5 (6.1)	48 (58.5)	26 (31.7)	-
χ^2	11.0				

+Frequencies are weighted for the posterior probabilities of each child belonging in each group

++All pairwise p-values were presented in comparison to the "healthy". Pairwise comparisons were conducted only when an overall significance was detected. Pairwise comparison p-values were adjusted using the Fifer package in R

*significant at 0.05 level

$\chi 2$ are the chi square values for each categorical variabl

Table 4. Odds for asthma, allergic rhinitis and reported food allergies at age 3 years within each identified pattern

	OR (N = 2616)	**aOR[+] (N = 2419)**
Asthma at 3Y	**(N = 89)**	**(N = 82)**
Healthy	1.00 (Ref)	1.00 (Ref)
Atopic Dermatitis	2.03 (1.44, 2.87)	1.65 (1.05, 2.57)
Inhalant Sensitization	2.54 (1.06, 6.09)	2.90 (1.46, 5.78)
Transient Sensitization	3.58 (2.67, 4.80)	3.84 (2.94, 5.00)
Persistent Sensitization	9.57 (4.24, 21.58)	11.44 (5.60, 23.37)
Allergic Rhinitis at 3Y	**(N = 63)**	**(N = 56)**
Healthy	1.00 (Ref)	1.00 (Ref)
Atopic Dermatitis	2.32 (2.13, 2.54)	2.36 (2.13, 2.62)
Inhalant Sensitization	7.59 (2.84, 20.27)	7.45 (3.98, 13.94)
Transient Sensitization	3.00 (1.42, 6.36)	2.71 (1.26, 5.83)
Persistent Sensitization	6.07 (2.71, 13.56)	6.37 (2.56, 15.84)
Reported Food Allergy at 3Y	**(N = 112)**	**(N =104)**
Healthy	1.00 (Ref)	1.00 (Ref)
Atopic Dermatitis	5.70 (3.39, 9.57)	5.16 (3.03, 8.78)
Inhalant Sensitization	7.27 (3.24, 16.31)	7.37 (3.50, 15.54)
Transient Sensitization	22.42 (11.32, 44.38)	22.35 (13.06, 38.24)
Persistent Sensitization	128.51 (36.8, 451.50)	110.74 (38.33, 319.97)

+ adjusted for sex, parental sensitization, parental reported allergies, any breastfeeding at 1 year, ethnicity, sex, and any pets. Confidence intervals take into account the clustering effects of study centers. OR: unadjusted odds ratio; aOR: adjusted odds ratio. Observations differ due to missing data on outcomes or covariates

* significant at 0.05 level

Table 5. Class memberships and food avoidance in the past year (between 2 to 3 years)

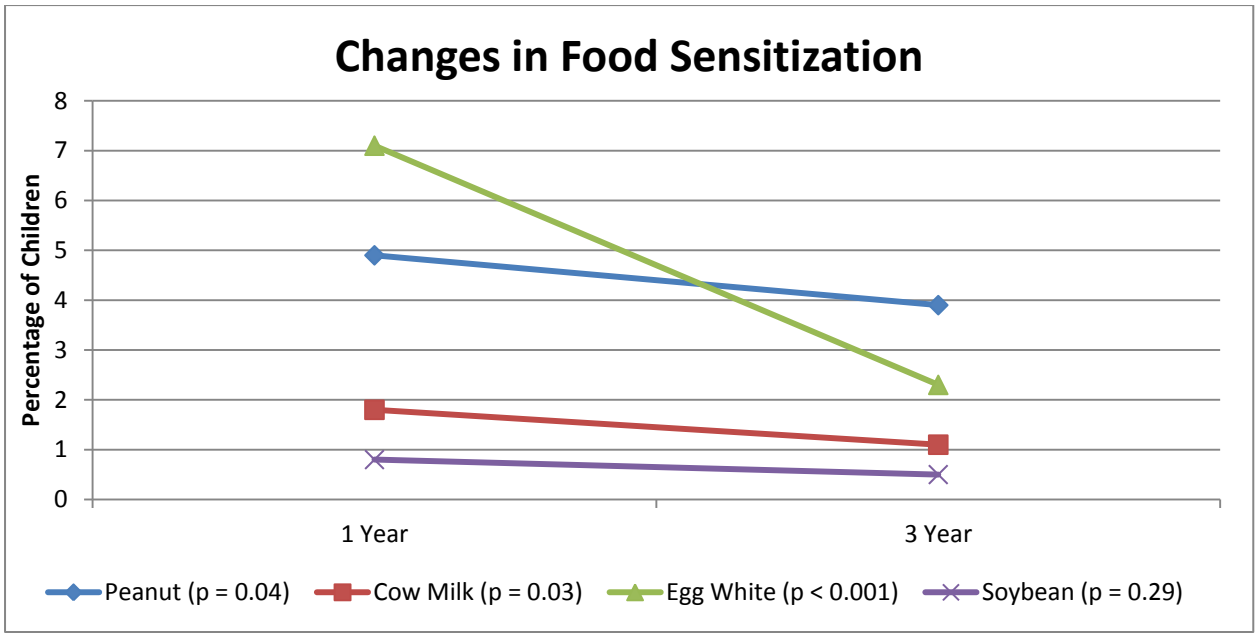
	N (% column) *					
Group	**Healthy**	**Atopic Dermatitis**	**Inhalant Sensitization**	**Transient Sensitization**	**Persistent Sensitization**	**p-value**
Consume milk	1833 (97.45)	181 (97.84)	70 (94.59)	92 (97.87)	62 (88.57)	< 0.001
Avoid milk	48 (2.55)	4 (2.16)	4 (5.41)	2 (2.13)	8 (11.43)	

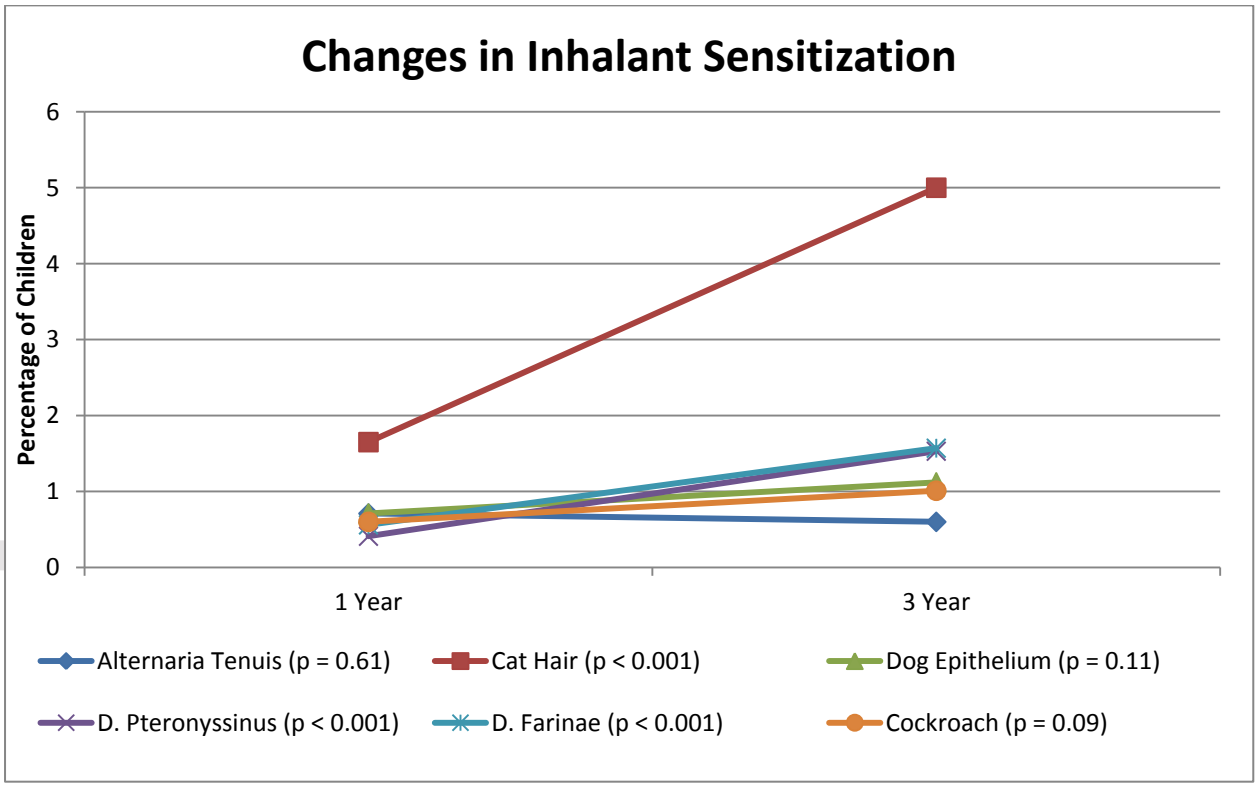
	N (% column) *					
Group	**Healthy**	**Atopic Dermatitis**	**Inhalant Sensitization**	**Transient Sensitization**	**Persistent Sensitization**	**p-value**
Consume peanut	1760 (95.39)	169 (92.35)	65 (92.86)	71 (84.52)	29 (50.00)	< 0.001
Avoid peanut	85 (4.06)	14 (7.65)	5 (7.14)	13 (15.48)	29 (50.00)	

	N (% column) *					
Group	**Healthy**	**Atopic Dermatitis**	**Inhalant Sensitization**	**Transient Sensitization**	**Persistent Sensitization**	**p-value**
Consume egg	1816 (97.06)	176 (95.14)	73 (97.33)	72 (81.82)	44 (70.97)	< 0.001
Avoid egg	55 (2.94)	9 (4.86)	2 (2.67)	16 (18.18)	18 (29.03)	

*Does not sum to 2629 due to missing food avoidance data

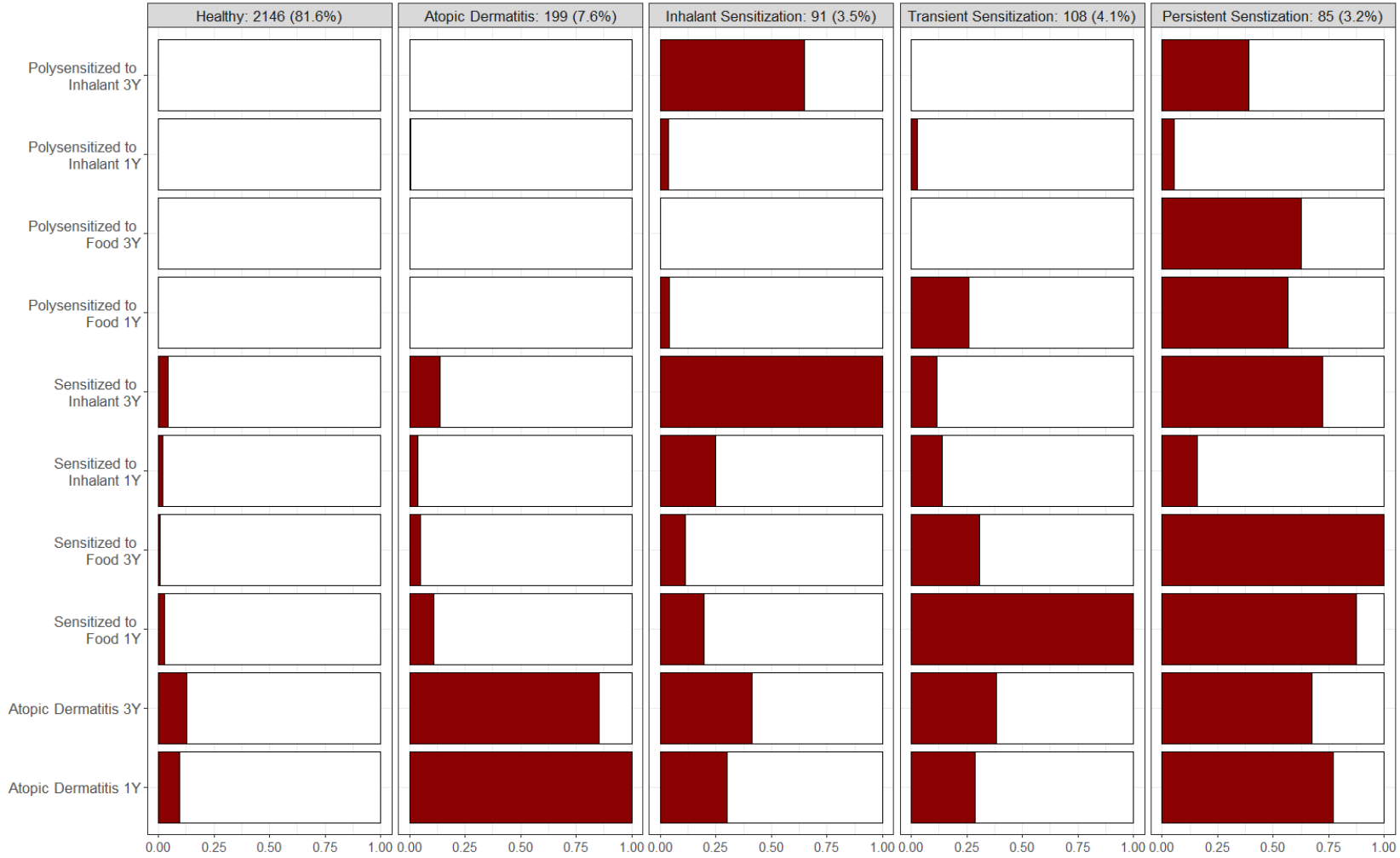
Figure 1 Changes in sensitization patterns from 1 year to 3 year*





*p-values were obtained by McNemar's test of proportions

Figure 2 Probability of atopic dermatitis and allergic sensitization conditional on latent class memberships



*Actual frequencies for each group and diagnostic of model fits from LCA can be found in the Supplementary Materials

Legend: Probability of exhibiting the associated characteristics