

Atopic dermatitis trajectories to age 8 years in the GUSTO cohort

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Abstract

Background: The heterogeneity of childhood atopic dermatitis (AD) underscores the need to understand latent phenotypes that may inform risk stratification and disease prognostication.

Objective: To identify AD trajectories across the first 8 years of life and investigate risk factors associated with each trajectory and their relationships with other comorbidities.

Methods: Data were collected prospectively from 1152 mother-offspring dyads in the Growing Up in Singapore Towards healthy Outcomes (GUSTO) cohort from ages 3 months to 8 years. AD was defined based on parent-reported doctor's diagnosis. An unsupervised machine learning technique was used to determine AD trajectories.

Results: Three AD trajectories were identified as follows: early-onset transient (6.3%), late-onset persistent (6.3%) and early-onset persistent (2.1%), alongside a no AD/reference group (85.2%). Early-onset transient AD was positively associated with male gender, family history of atopy, house dust mite sensitization and some measures of wheezing. Early-onset persistent AD was associated with antenatal/intrapartum antibiotic use, food sensitization and some measures of wheezing. Late-onset persistent

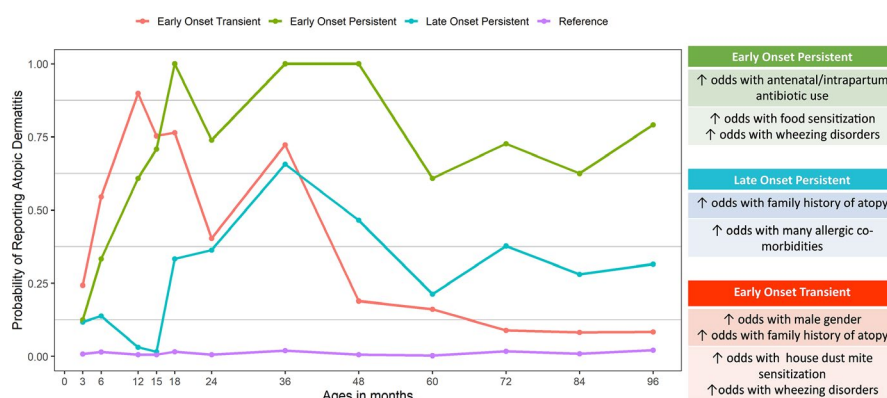
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AD was associated with a family history of atopy, some measures of house dust mite sensitization and some measures of allergic rhinitis and wheezing.

Conclusion and Clinical Relevance: Three AD trajectories were identified in this birth cohort, with different risk factors and prognostic implications. Further work is needed to understand the molecular and immunological origins of these phenotypes.

KEYWORDS

atopic dermatitis, machine learning, rhinitis, trajectories, wheezing



GRAPHICAL ABSTRACT

Three AD trajectories—early transient, early persistent and late persistent were generated from the unsupervised machine learning approach. Early transient AD was associated with non-modifiable risk factors (male gender and family history of atopy) and increased wheezing while, persistent AD was associated with maternal antibiotic use, breastfeeding and increased food sensitization. Late persistent AD was the strongest phenotype associated with allergic disorders.

1 | INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory condition characterized by itchy, dry and red skin, which often develops early in life, and can have debilitating effects. AD in infancy is a precursor of food allergy, asthma and allergic rhinitis later in childhood.¹ Mechanistically, defects in the skin epithelial barrier are postulated to promote allergen entry through the skin, inducing epicutaneous sensitization and food allergy, followed by allergic airway disorders such as allergic rhinitis and asthma.^{2,3}

This progression of atopic manifestations is often termed the “allergic march” or “atopic march.” At an individual level, this pathway has been observed in about 3.1% of children, but more than 90% of children with symptoms do not follow the classical atopic march trajectory.⁴ Current literature has also shown that these allergic diseases share some common genetic risk markers and pathogenic pathways.^{5–7} Nonetheless, the atopic march may be an oversimplification of more complex and multifactorial processes involved in allergic disease progression.⁸

Given its heterogeneity and complex aetiology,^{9,10} there are likely to be several endotypes of AD, which may not be captured solely based on classical diagnostic tools measuring the severity and epidermal barrier function, such as scoring of atopic dermatitis (SCORAD) and trans-epidermal water loss (TEWL).¹¹ There has been

Key Message

1. We used machine learning to characterise atopic dermatitis phenotypes in a birth cohort study.
2. Three AD trajectories were identified—early transient, early persistent and late persistent AD.
3. Molecular and immunological work is needed to understand the origins of these distinct phenotypes.

a recent shift towards the use of machine learning approaches to classify latent classes of AD and other allergic diseases. Machine-learning techniques represent an unbiased and hypothesis-free approach in explaining clinical outcomes by generating clusters of phenotypes based on a set of variables added to the model.^{12,13} Since they are not based on a pre-determined hypothesis, results from data-driven analyses may better reflect underlying biological mechanisms of action.¹⁴ Although hypothesis-driven techniques are preferred in investigating an existing phenomenon/theory, they aim to pursue and address a different set of research questions, which was not the main aim of the present study.

While there have been several studies exploring latent AD phenotypes, these were predominantly in Caucasian populations and

not in ethnically Asian populations. Fewer studies have investigated the development of wheeze and allergic rhinitis in relation to AD phenotypes over time. This study was, therefore, designed to identify latent AD trajectories in the first 8 years of life, elucidate risk factors and characterize their relationships with other comorbidities such as wheezing, allergic sensitization and rhinitis in a multi-ethnic Asian population.

2 | METHODS

2.1 | Study cohort

This study was conducted in the Growing Up in Singapore Towards healthy Outcomes (GUSTO) mother-offspring cohort. The GUSTO cohort has previously been described in detail.¹⁵ In brief, GUSTO recruited women of Chinese, Malay and Indian ethnicity in their first trimester of pregnancy. Detailed information on demographic characteristics, family history of allergy and lifestyle factors was collected prospectively. Data on allergic outcomes were obtained from questionnaires administered at 3, 6, 12, 15, 18 and 24 months and 3, 4, 5, 6, 7 and 8 years, based on the International Study of Asthma and Allergies in Childhood (ISAAC) modified questionnaire, which has been extensively validated for epidemiological studies worldwide.^{16–19} All mothers gave written informed consent, and ethics approval was obtained from the Domain Specific Review Board of Singapore National Healthcare Group (D/2009/021; 26/02/2009) and the Centralised Institutional Review Board of SingHealth (2018/2767; 02/03/2009).

2.2 | Definition of main outcome

2.2.1 | Atopic dermatitis

From months 3 to 18 and at month 36, this was defined as an affirmative response to the question “Has your child ever been diagnosed with eczema?” From month 24 onwards, this was defined as an affirmative response to the question “Has your child ever been diagnosed with eczema since the (previous time-point)/last visit?” All other definitions of allergic diseases can be found in the Supporting Information.

2.3 | Statistical analysis

2.3.1 | Unsupervised machine learning

The AD trajectories analysis was performed on doctor-diagnosed AD data from 1152 participants over twelve total time-points from 3 months to 8 years of age (at 3, 6, 12, 15, 18 and 24 months, 3, 4, 5, 6, 7 and 8 years). The expectation-maximization (EM) method in conjunction with 10-fold cross-validation was used to identify and

determine the appropriate number of AD trajectories within the dataset. Only the AD variables over the 12 time-points were included in the EM method. The EM method also accounts for missing data in its calculations, and therefore, all participants remained in the model. Detailed information on the EM method is provided in the Supporting Information.

2.3.2 | Association analyses

Statistical comparisons for the demographic characteristics and allergic outcomes between the trajectories were obtained using Pearson's chi-square or Fisher's exact test with Bonferroni correction. Multinomial logistic regressions were used to examine associations between trajectories and three sets of variables: prenatal risk factors, environmental risk factors and comorbidities which we hypothesized to modulate AD pathogenesis. Odds ratios and 95% confidence intervals with statistical significance of $p < .05$ were used.

The EM unsupervised machine learning method was carried out in Weka, version 3.8.4 (Machine Learning Group, University of Waikato, Hamilton, New Zealand²⁰), while other analyses were carried out using IBM SPSS version 24 (Armonk, NK).

3 | RESULTS

3.1 | Study participants

Of the 1237 GUSTO mothers recruited, 1152 children conceived naturally were included in the analysis. The point prevalence of AD steadily increased from 3.7% at 3 months to 9.3% at 12 months. Thereafter, the prevalence at each time-point fluctuated from 8.7% at 15 months to 7.3% at 8 years (12.5% at 18 months, 8.3% at 24 months, 15.1% at 3 years, 8.3% at 4 years, 4.8% at 5 years, 6.8% at 6 years and 5.2% at 7 years), with 22.8% of our study population having AD at any time-point ($n = 258/1152$). Figure 1 shows the flow diagram of participants with AD at each time-point. Complete data at all time-points were available on 448 children, and their trajectories shown in Figures S1 and S2.

Three AD trajectories were identified—which we termed early-onset transient (EOT; $n = 73$, 6.3%), early-onset persistent (EOP; $n = 24$, 2.1%) and late-onset persistent (LOP; $n = 73$, 6.3%) based on the trajectory patterns over time (Figure 2). The group of children with low calculated probability of AD throughout all the time-points were designated as the reference group ($n = 982$, 85.2%). The demographics of participants in each cluster are also provided in Table 1.

3.2 | Early-onset transient (EOT) AD

This trajectory ($n = 73$, 6.3%) was characterized by a sharp increase in the probability of AD in the first 12 months of life, which

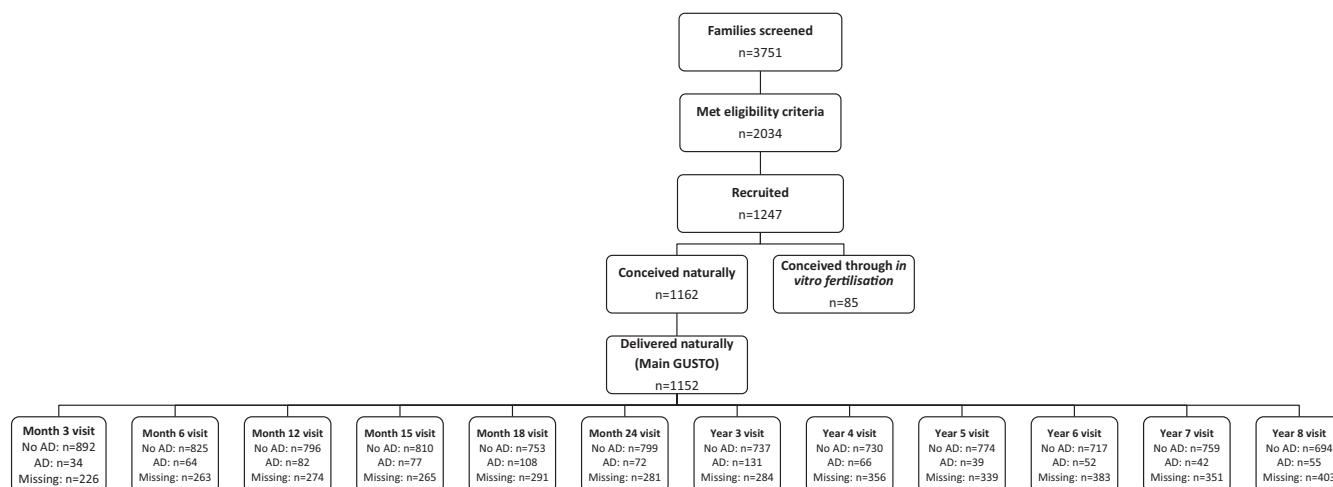


FIGURE 1 Flow diagram of participants with and without AD at each time-point

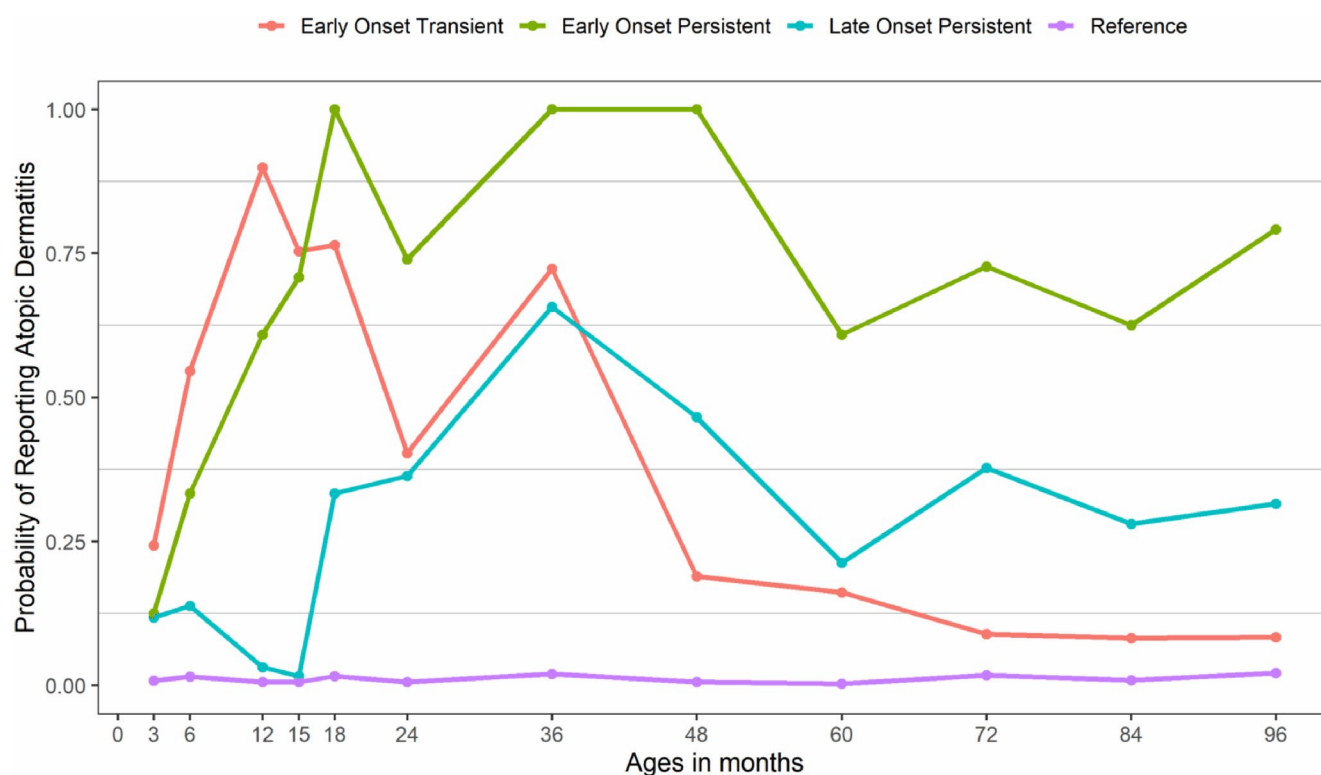


FIGURE 2 Three atopic dermatitis (AD) and one reference trajectory generated from the unsupervised machine learning approach. The unsupervised machine learning method identified four atopic dermatitis trajectories. Early-onset transient (EOT) was made up of children with the high probability of reporting AD in the first 12 months of life and this subsequently decreased up till year 8. The early-onset persistent (EOP) AD trajectory was marked by a gradual increase in the probability of AD from month 3 to month 18, and this remained high throughout till year 8. In the late-onset persistent (LOP) trajectory, the probability of AD was low in the first year of life, peaking at 3 years and stabilized thereafter up till year 8. Those with low probability of reporting atopic dermatitis were classified in the reference group

subsequently decreased until year 8 (Figure 2). More children in this trajectory were male (65.8%), had a family history of atopy (69%) and owned pets in the first 12 months of life (14.3%) compared with the reference group (Table 1). A higher proportion of children in this

trajectory had current allergic rhinitis, persistent allergic rhinitis with or without sensitization, current wheezing with or without sensitization and any allergen sensitization compared with the reference group (Table 2).

TABLE 1 Demographics of study participants in each trajectory

	Reference group (<i>n</i> = 982) <i>N</i> (%)	Early-onset transient (<i>n</i> = 73) <i>N</i> (%)	Early-onset persistent (<i>n</i> = 24) <i>N</i> (%)	Late-onset persistent (<i>n</i> = 73) <i>N</i> (%)
Male	468 (51)	48 (65.8)	15 (62.5)	40 (54.8)
Family history of atopy	410 (51.3)	49 (69)	17 (70.8)	49 (72.1)
Household income >USD 4000	232 (25.4)	26 (36.6)	11 (47.8)	21 (30)
Ethnicity				
Chinese	520 (53)	43 (58.9)	16 (66.7)	47 (64.4)
Malay	267 (27.2)	24 (32.9)	7 (29.2)	16 (21.9)
Indian	193 (19.7)	6 (8.2)	1 (4.2)	10 (13.7)
Others	2 (0.2)	0 (0)	0 (0)	0 (0)
Presence of siblings	533 (58.1)	37 (50.7)	12 (50)	38 (52.1)
Antenatal and intrapartum antibiotics	404 (44)	33 (45.8)	16 (66.7)	30 (41.1)
Caesarean delivery	270 (29.4)	26 (36.1)	4 (16.7)	22 (30.1)
Breastfeeding level				
Low	381 (47.7)	26 (36.6)	5 (21.7)	27 (39.7)
Mid	319 (40)	36 (50.7)	14 (60.9)	39 (57.4)
High	98 (12.3)	9 (12.7)	4 (17.4)	2 (2.9)
Pet ownership in first year of life	47 (6.1)	10 (14.3)	4 (16.7)	5 (7.5)
Household exposure to tobacco smoke	226 (38.7)	27 (42.9)	3 (15.8)	20 (35.1)
Childcare attendance in first year of life	53 (8.3)	11 (16.9)	5 (25)	3 (5.1)
Infant antibiotic use in first year of life	287 (46.1)	33 (50)	12 (57.1)	19 (34.5)

Note: Cells in bold and italics indicate significance at *p* value ≤.05 compared with reference group in univariate analysis after Bonferroni correction.

In the multinomial regression analyses, male gender [aOR 1.98 (95% CI 1.16–3.39) *p* = .012] and a family history of atopy [aOR 1.85 (95% CI 1.08–3.18) *p* = .025] were associated with increased odds of EOT AD. Additionally, being of Indian ancestry was protective for EOT AD [aOR 0.38 (95% CI 0.14–0.98) *p* = .046] (Figure 3).

EOT AD was also associated with HDM sensitization at 3 years and wheezing at several time-points (Table 3). Of note, this trajectory was not associated with any risk of food sensitization or rhinitis.

3.3 | Early-onset persistent (EOP) AD

The EOP AD trajectory (*n* = 24, 2.1%) was marked by a steady increase in the probability of AD from month 3 to month 18 and remained high up till year 8 (Figure 2). More children in this trajectory were from households earning >\$4000 USD (47.8%) compared with the reference group (25.4%) (Table 1).

Antenatal and intrapartum antibiotic use [aOR 2.71 (95% CI 1.12–6.58) *p* = .027] and breastfeeding were associated with increased odds of EOP AD [aOR 5.14 (95% CI 1.04–25.4) *p* = .045] (Figure 3).

EOP AD was the only AD phenotype associated with food sensitization. Apart from current wheezing at 8 years, there were no associations with any other comorbidities (Table 3). Food allergy

prevalence is known to be very low in the GUSTO cohort²¹; thus, the inclusion of food allergy outcomes in the multinomial analyses was not possible. Of note, the use of topical steroids, as a proxy of eczema severity, was the highest in this group compared with other trajectories (55.6% at 18 months, 40.9% at 5 years and 38.1% at 8 years).

3.4 | Late-onset persistent (LOP) AD

In this trajectory (*n* = 73, 6.3%), the probability of AD was the lowest among the three AD trajectories in the first year of life, increased only after the 15-month time-point and peaked at 3 years before stabilizing thereafter up till year 8, but remained lower than the EOP trajectory (Figure 2). The majority of the children with LOP AD were from atopic families (72.1%) (Table 1). Frequencies of the various comorbidities observed in this trajectory are presented in Table 2.

In multinomial analyses, family history of atopy was associated with increased odds of LOP AD [aOR 2.56 (95% CI 1.45–4.52) *p* = .001], while breastfeeding was associated with reduced odds of LOP AD [aOR 0.21 (95% CI 0.04–0.97) *p* = .046] (Figure 3). LOP AD was also associated with increased odds of almost all of the

TABLE 2 Prevalence of comorbidities at 8 years in each AD trajectory

	Reference group (n = 982)		Early-onset transient (n = 73)		Early-onset persistent (n = 24)		Late-onset persistent (n = 73)	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
AR diagnosis (n = 744)	604	27 (4.5)	59	4 (6.8)	24	5 (20.8)	57	9 (15.8)
Current AR (n = 744)	604	101 (16.7)	59	18 (30.5)	24	9 (37.5)	57	22 (38.6)
Current AR + sensitization (n = 734)	599	73 (12.2)	58	11 (19)	22	6 (27.3)	55	18 (32.7)
Persistent AR (n = 483)	385	32 (8.3)	49	10 (20.4)	17	4 (23.5)	32	11 (34.4)
Persistent AR + sensitization (n = 483)	385	19 (4.9)	49	7 (14.3)	17	2 (11.8)	32	8 (25)
Current wheezing (n = 722)	586	24 (4.1)	59	10 (16.9)	24	8 (33.3)	53	6 (11.3)
Current wheezing + sensitization (n = 350)	301	15 (5)	21	9 (42.9)	8	5 (62.5)	20	4 (20)
Food allergic (n = 736)	600	3 (0.5)	58	0 (0)	22	1 (4.5)	56	0 (0)
Food sensitized tolerant (n = 736)	600	13 (2.2)	58	5 (8.6)	22	3 (13.6)	56	4 (7.1)
Any sensitization (n = 716)	586	287 (49.1)	57	44 (77.2)	20	16 (80)	53	36 (67.9)
Any HDM sensitization (n = 716)	586	284 (48.5)	57	44 (77.2)	20	16 (80)	53	36 (67.9)
Any food sensitization (n = 716)	585	36 (6.2)	57	10 (17.5)	20	4 (20)	54	6 (11.1)

Note: Any sensitization: positive skin prick test result to any of the house dust mite allergens (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae* and *Blomia tropicalis*), food allergens (egg, peanut, cow's milk, shrimp and crab) or aeroallergens (*Blatella germanica* and *Periplaneta Americana*). Cells in bold and italics indicate significance at p value $\leq .05$ compared with reference group in univariate analysis after Bonferroni correction.

Abbreviations: AR, allergic rhinitis; HDM, house dust mite.

comorbidities assessed at 8 years as well as HDM sensitization at 3 and 5 years, and wheezing at 3 years (Table 3).

3.5 | Sensitivity analyses

To demonstrate reproducibility and robustness of our results, we performed sensitivity analyses based on a different definition of AD, AD symptoms of itchy rash with topical steroid use and parent-reported doctor's diagnosis in the full cohort.

The AD trajectories generated from the two sensitivity analyses were similar to the original trajectories (Figures S3 and S4). Risk factors identified in the sensitivity analyses remained the same in both sensitivity analyses. In the multinomial analyses for associations with allergic comorbidities, both analyses using the definition of a "doctor's diagnosis of AD" demonstrated similar findings (Table S1), while the analyses using the "itchy rash with steroid use" definition were similar, but not statistically significant for HDM sensitization and current allergic rhinitis in late-onset persistent AD (Table S2).

We also assessed the sensitivity and specificity of both AD definitions against SCORAD, which is the standard for measurement of AD severity. SCORAD was carried out at 18 months in a subset of

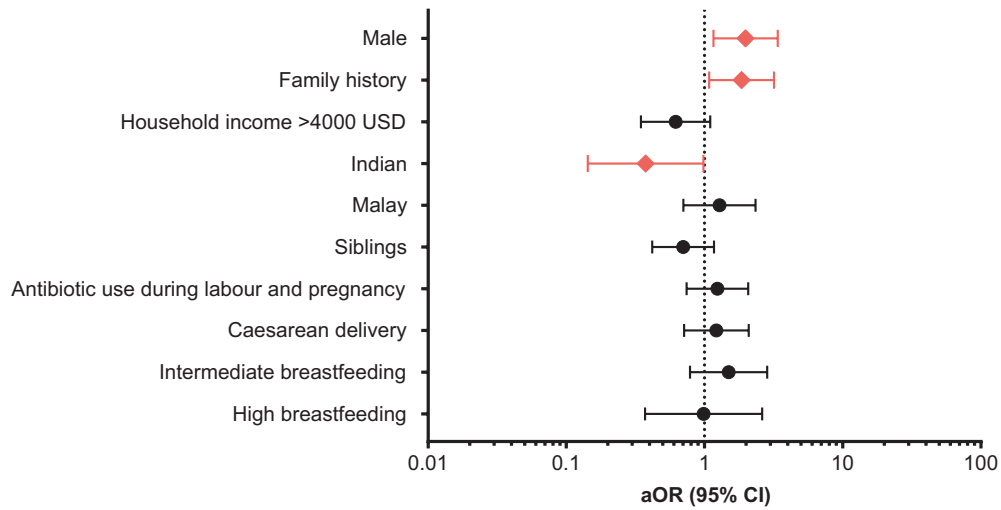
participants, by a trained physician who diagnosed AD on physical examination. The "doctor's diagnosis" definition had a higher sensitivity (sensitivity 93.3% and specificity 90.5%), while "itchy rash with the use of topical steroids" definition had a high specificity but low sensitivity (sensitivity 50% and specificity 96.7%). The higher sensitivity of the "doctor diagnosis of AD" definition indicated that it performed better than AD symptoms in accurately identifying participants with the disease, and thus, this definition was retained in the main analyses.

4 | DISCUSSION

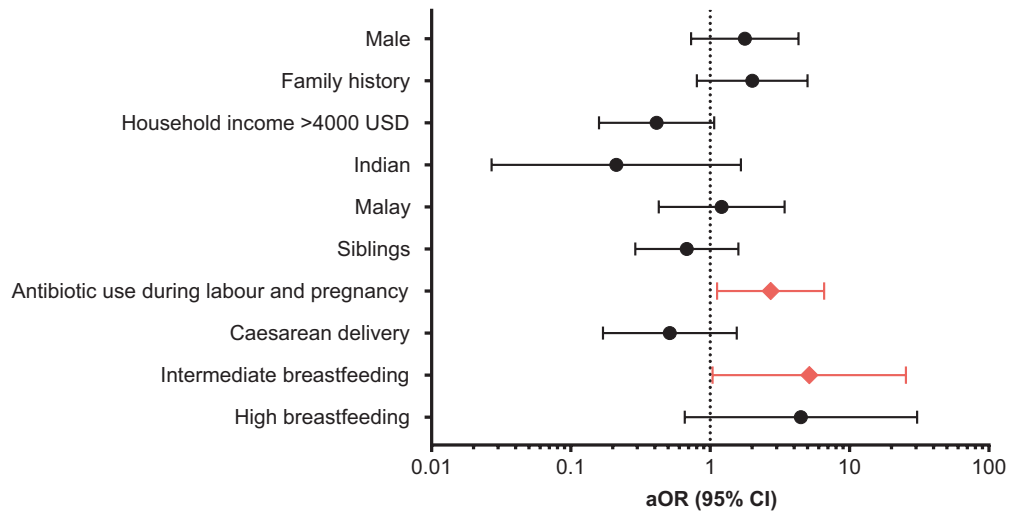
The unsupervised machine learning approach carried out in this study identified three AD trajectories during the first 8 years of life—early-onset transient (EOT), early-onset persistent (EOP) and late-onset persistent (LOP) AD. The EOT trajectory was linked to non-modifiable risk factors, notably male gender, ethnicity and family history of atopy, and these children tended to develop wheezing later in childhood. The EOP AD trajectory was associated with maternal antibiotic use and breastfeeding. Children in this trajectory also had increased odds of developing food sensitization and

FIGURE 3 Forest plot representing multinomial regression analyses for prenatal and environmental factors. Figure legend: Multinomial logistic regressions were used to examine associations between prenatal and environmental risk factors with each trajectory. ♦ indicate significant factors, $p < .05$. x-axes are on a logarithmic scale. All comparisons were made with the non-AD group as the reference group. Reference groups for the categorical variables are as follows in the order presented in the figure: female, no family history of atopy, household income <4000 USD, Chinese race, no siblings, no antibiotic use during labour and pregnancy, vaginal delivery and low breastfeeding level

Early Onset Transient



Early Onset Persistent



Late Onset Persistent

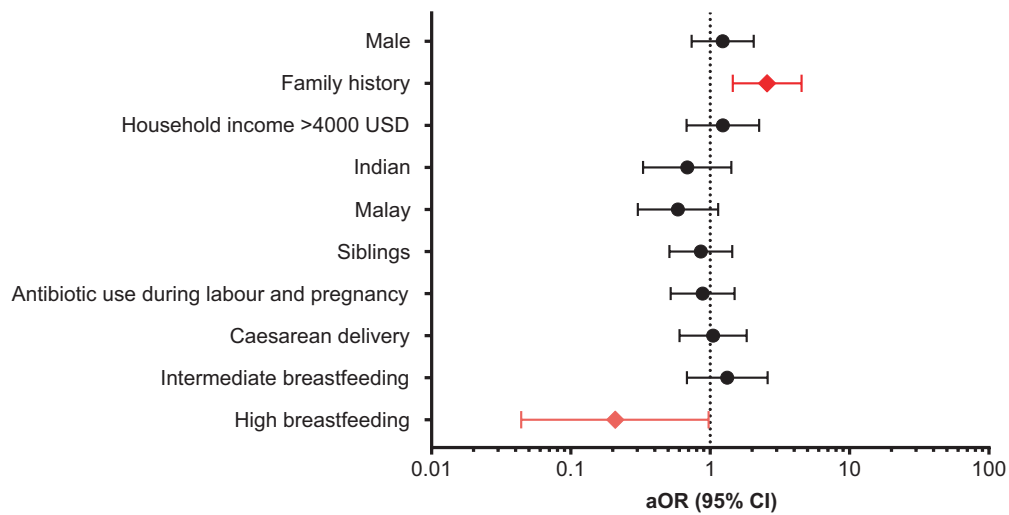


TABLE 3 Multinomial logistic regression of comorbidities at 18 months, 3 years, 5 years and 8 years with AD trajectories^a

	Early-onset transient		Early-onset persistent		Late-onset persistent	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
18 months (n = 548)						
HDM sensitization	3.15 (1.4–7.06)	.005	3.13 (0.76–12.97)	.115	1.6 (0.6–4.23)	.346
Food sensitization	2.94 (0.83–10.45)	.096	16.94 (3.14–91.35)	.001	1.67 (0.32–8.79)	.546
AR	1.1 (0.4–3.05)	.853	1.41 (0.23–8.57)	.709	1.57 (0.62–4.01)	.343
Wheezing	1.04 (0.25–4.3)	.961	0 (0–c)	.995	2.02 (0.56–7.33)	.285
36 months (n = 524)						
HDM sensitization	4.34 (2.25–8.4)	<.001	1.55 (0.43–5.59)	.506	1.95 (0.96–3.96)	.066
Food sensitization	NA	NA	NA	NA	NA	NA
AR	2.11 (0.98–4.57)	.057	0.58 (0.1–3.36)	.54	2.55 (1.2–5.42)	.015
Wheezing	2.65 (1.09–6.47)	.032	2.41 (0.49–11.77)	.276	3.84 (1.64–8.99)	.002
60 months (n = 482)						
HDM sensitization	2.28 (1.1–4.73)	.027	1.61 (0.39–6.67)	.514	4.77 (2.2–10.35)	<.001
Food sensitization	1.36 (0.32–5.88)	.679	24.6 (3.97–152.43)	.001	1.37 (0.35–5.41)	.655
AR	1.48 (0.46–4.76)	.511	0.25 (0.02–3.47)	.301	1.27 (0.38–4.28)	.697
Wheezing	2.82 (1.09–7.29)	.033	1.69 (0.29–9.94)	.562	0.33 (0.07–1.57)	.165
8 years ^b						
Current AR (n = 462)	1.19 (0.56–2.52)	.656	0.75 (0.17–3.34)	.71	2.52 (1.14–5.57)	.022
Current wheezing (n = 462)	3.9 (1.44–10.61)	.008	27.27 (4.61–161.42)	<.001	1.39 (0.34–5.71)	.645
Any sensitization (n = 462)	2.06 (0.99–4.28)	.053	2.35 (0.55–9.97)	.248	2.27 (1–5.16)	.051
Any HDM sensitization (n = 462)	2.09 (1–4.35)	.05	2.38 (0.56–10.14)	.241	2.28 (1–5.19)	.05
Any food sensitization (n = 463)	2.44 (0.92–6.46)	.072	4.66 (0.84–25.72)	.077	2.09 (0.67–6.51)	.205
Current AR + sensitization (n = 478)	0.91 (0.38–2.18)	.831	0.8 (0.19–3.46)	.768	3.53 (1.58–7.88)	.002
Current wheezing + sensitization (n = 223)	9.35 (1.87–46.91)	.007	696.56 (1.99–243432.57)	.028	9.1 (1.24–66.84)	.03
Persistent AR (n = 365)	1.54 (0.58–4.14)	.389	0.63 (0.03–12.66)	.761	5.35 (1.87–15.35)	.002
Persistent AR + sensitization (n = 376)	1.63 (0.51–5.2)	.408	1.11 (0.06–20.23)	.946	4.94 (1.53–15.91)	.007

Note: Any sensitization: positive skin prick test result to any of the house dust mite allergens (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae* and *Blomia tropicalis*), food allergens (egg, peanut, cow's milk, shrimp and crab) or aeroallergens (*Blatella germanica* and *Periplaneta americana*). Abbreviations: AR, allergic rhinitis; HDM, house dust mite; NA, not applicable.

^aAll analyses were adjusted for prenatal and environmental factors shown in Figure 3, including pet ownership, household smoking, childcare attendance and infant's use of antibiotics during the first year. All comparisons were made with the non-AD group as the reference group.

^bFor this model, multinomial logistic regressions were carried out stepwise adding each non-overlapping variable to the model separately. This was repeated until all the variables were included in a model. As a result, the numbers included in each analysis vary as shown in the table.

wheezing disorders. Of all the trajectories, the LOP AD trajectory showed the strongest links to other atopic risk and allergic outcomes at age 8 years.

Of the more recent studies on AD trajectories, one carried out in an Asian population described four phenotypes: early-onset AD with high eosinophils and food sensitization; early-onset, non-allergic AD; early-onset AD with high C-reactive protein (CRP); and middle-onset AD with inhalant sensitization.¹¹ This study provided further evidence to the heterogeneity of AD in early childhood, whereby six variables such as age of onset, age of diagnosis, white

blood cell count and eosinophil count, were sufficient to accurately classify 95.5% of Korean children under 3 years of age. However, despite having high accuracy, its utility in the clinical setting is impractical as CRP and eosinophil counts are not routinely performed as part of allergy evaluation.

Our study builds on the current literature by exploring an extended number of demographic and risk factors. In addition, Roduit et al. identified four clusters—early-onset, transient; early-onset, persistent; late-onset (after age 2); and never/infrequent in a European cohort.²² The highest risk of asthma was again observed

in the early persistent AD phenotype; however, the study was restricted to a white European population and was unable to reflect observations in a non-white population. Our present study, therefore, bridges the gap of existing studies by using a machine learning method to identify latent AD trajectories and assess associations between a wide range of potential risk factors in an Asian population group. Nonetheless, direct comparisons between the various studies should be interpreted cautiously given the different methodologies used.

4.1 | Early-onset transient AD

In this study, we have found that EOT AD was associated with wheezing at multiple time-points, including allergic wheeze at age 8 years. The association of early transient AD with persistent wheeze throughout childhood to 8 years with HDM sensitization is unique to our study. Other cohorts, such as the ALSPAC,^{23,24} Tucson,²⁵ ORCA²⁶ and PASTURE²² cohorts, which have described early AD phenotypes in relation to allergic outcomes, have linked persistent wheezing/asthma with EOP AD and multiple sensitization. Animal studies suggest that although mild and transient AD may not induce persistent or severe skin inflammation, it is still associated with systemic immune priming and triggering distal airway inflammation.^{27,28}

4.2 | Early-onset persistent AD

Antenatal and intrapartum antibiotic use was associated with increased odds of EOP AD in this study. A possible mechanism for this is through alterations of maternal and fetal microbiota,²⁹ which in turn modulate fetal immune programming.^{30,31} Current literature on the links between antibiotic use and AD is contradictory. A recent systematic review evaluating antibiotic use and allergic outcomes found only three publications meeting inclusion criteria.³² One reported a significant relationship with AD³³; another reported a significant relationship only when the intrapartum antibiotic exposure lasted more than 24 h,³⁴ while the other reported a significant relationship only when the mother was atopic and had taken antibiotics throughout pregnancy.³⁵ Intrapartum antibiotics have been associated with dysbiosis, particularly richness and diversity, of intestinal microbiota in full-term newborns³⁶; however, breastfeeding appears to be able to minimize these deleterious effects.³⁷

Findings on breastfeeding, however, are more conflicting. We found that breastfeeding was associated with increased odds of EOP AD, and postulate that reverse causation may be a key reason for this observation, whereby pre-existing AD causes a change in breastfeeding behaviour. This is consistent with findings by Paternoster et al²⁴ comparing two cohorts—the ALSPAC and PIAMA cohort. In the ALSPAC cohort, breastfeeding was associated with early-onset persistent and late resolving AD trajectories, while there was a lack of evidence for an association in the PIAMA

cohort. Some studies, however, have shown support for breastfeeding as a protective factor for AD³⁸ as is observed in the LOP AD group in our study. These findings suggest that the presence of early infantile AD could have potentially modified breastfeeding practices (ie mothers breastfeeding for a longer duration) in the hope that this might reduce AD severity or the risk of other allergic diseases.

Food sensitization was strongly associated with EOP AD. This is consistent with the dual-allergen hypothesis where epicutaneous sensitization occurs due to a disrupted skin barrier in early life, and predisposes a child to food sensitization and food allergy.^{39,40} Although AD severity assessments were not available for the majority of participants in our cohort, the persistent nature of this AD phenotype suggests more chronic skin inflammation, which would increase the risks of epicutaneous food sensitization. Topical steroid usage, a proxy of AD severity, was more prevalent in the EOP than the EOT trajectory, which may account for the association observed with food sensitization in the former but not the latter trajectory. However, detailed analyses for associations were not performed due to the small sample size.

Furthermore, in this study, EOP AD does not appear to be a risk factor for other allergic sequelae, contrary to the classical atopic march hypothesis. This runs contrary to other studies where EOP AD has been shown to be associated with the greatest risk of allergic morbidity in later childhood.^{9,22,41,42} Longitudinal cohort studies also now suggest that only a small proportion of children actually follow the typical atopic march trajectory,^{24,43} lending support to the notion that multiple allergic phenotypes exist.

4.3 | Late-onset persistent AD

We found that the LOP AD trajectory was the phenotype most closely associated with allergic airway disorders from 3 years onwards, particularly in children with a family history of atopy. Children in this trajectory were more likely to be HDM sensitized, and this was associated with current/persistent allergic rhinitis and atopic wheezing up to age 8 years. It might be postulated that environmental exposure to HDM from infancy, together with a defective epithelial barrier in the presence of AD, predisposes to the acquisition of HDM sensitization that occurs a little later in life, alongside the later onset of AD. This is supported by our prior findings that overall HDM sensitization in this cohort doubled from 11% at 18 months to 22% at 3 years⁴⁴; increasing to 34.4% by age 5 years and 53.1% by age 8 years.

HDM aeroallergen sensitization plays a major role in the pathogenesis of allergic airway disorders in tropical Singapore, primarily due to the high environmental HDM exposures in early life compared with other countries where HDM exposures are lower.^{45,46} Furthermore, an assessment of TEWL in children up to 12 months showed increased risk of aeroallergen sensitization among those with AD.⁴⁷ 89% of AD children had a positive atopy patch test (APT) result, with a higher mean TEWL observed among those with two

or more positive APT. Murine studies similarly suggest that HDM sensitization through the impaired skin barrier can induce systemic and airway inflammation leading to the preferential development of allergic airway disorders.^{48–52}

4.4 | Strengths and limitations

A key strength of this study is our large cohort, which allows subgroups to be defined on the basis of their longitudinal disease trajectories. The unsupervised machine learning approach in our study design maintained prediction accuracy without the need for separate training and validation datasets, while allowing data-driven discovery of latent AD trajectories unbiased by pre-selected investigator-determined definitions. Limitations of this study were mainly the parental-reported outcomes, which may be subject to recall bias. However, this was mitigated by the very close intervals between each follow-up time-point, use of ISAAC questionnaires, which have been extensively validated as reliable tools for assessing allergic disease outcomes, and the comprehensive clinical and sensitization profiling in this cohort.

5 | CONCLUSION

Collectively, disparities in the longitudinal progression of early, late, transient and persistent AD support the notion that there are distinct subtypes of AD.⁵³ We have shown unique characteristics of each AD trajectory, which differ from that shown in cohorts in other parts of the world. Unlike the typical atopic march, in which EOP AD precedes allergic morbidity, LOP AD appears to be the strongest phenotype linked to allergic disorders in our cohort, with HDM sensitization appearing to play a major role. Nonetheless, it is yet to be seen whether the trajectories differ at the molecular and immunological level and whether these differences translate to differential treatment outcomes.⁵³

This emphasizes the importance of a personalized treatment approach in AD. The routine use of prophylactic emollients from the neonatal period as a proactive AD prevention strategy has been suggested to reduce the risk of AD,⁵⁴ and this can be made possible through early identification of at-risk infants. This has important clinical implications as evidence suggests that early diagnosis and intervention improves the quality of life for AD patients at high risk of developing comorbidities.^{55,56} Understanding the various AD phenotypes and endotypes can also guide diagnosis, risk stratification, treatment and the development of preventive strategies, leading the way towards a phenotype-driven, precision medicine approach to the management of childhood AD. More refined and holistic endotyping predictive models can also be employed with the addition of biomarkers from microbiome, blood and saliva/buccal samples.⁵⁷ In doing so, earlier identification of at-risk endophenotypes can occur earlier in life during the critical window for intervention.

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CONFLICT OF INTEREST

Chong YS has received reimbursement for speaking at conferences sponsored by Abbott Nutrition, Nestle and Danone. Godfrey KM has received reimbursement for speaking at conferences sponsored by Nestle, and Shek LP has received reimbursement for speaking at conferences sponsored by Danone and Nestle and consulting for Mead Johnson and Nestle. Godfrey KM and Chong YS are part of an academic consortium that has received research funding from Abbott Nutrition, Nestle and Danone. Shek LP has received research funding from Danone.

AUTHOR CONTRIBUTION

Noor H. A. Suaini contributed to the design of the study, carried out data cleaning and data analysis, was involved in interpretation of the data, provided intellectual input, drafted and revised the manuscript. Gaik Chin Yap and Do Phuong Tung Bui contributed to the design of the study, carried out data cleaning and data analysis, were involved in interpretation of the data and provided intellectual input in the draft and revised manuscripts. Evelyn Xiu Ling Loo, Anne Eng Neo Goh, Oon Hoe Teoh, Kok Hian Tan, Keith M. Godfrey, Bee Wah Lee, Lynette Pei-chi Shek, Hugo Van Bever and Yap Seng Chong provided intellectual input, contributed to the interpretation of data and critically revised the manuscript. Elizabeth Huiwen Tham led the design and conception of the study and data analysis, provided intellectual input, contributed to the interpretation of data and contributed to the draft and revised manuscripts.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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