

Trajectories of early-onset rhinitis in the Singapore GUSTO mother-offspring cohort

Evelyn Xiu Ling Loo^{1,2*} | Tau Ming Liew^{3,4*} | Gaik Chin Yap² | Lydia Su Yin Wong⁵ | Lynette Pei-Chi Shek^{2,5} | Anne Goh⁶ | Hugo P.S. Van Bever^{2,5} | Oon Hoe Teoh⁶ | Fabian Yap⁷ | Kok Hian Tan⁸ | Biju Thomas⁶ | Mahesh Babu Ramamurthy^{2,5} | Daniel Yam Thiam Goh^{2,5} | Johan G Eriksson^{1,9,10,11} | Yap-Seng Chong^{1,9} | Keith M. Godfrey¹² | Bee Wah Lee^{2,5} | Elizabeth Huiwen Tham^{2,5} 

¹Singapore Institute for Clinical Sciences, Agency for Science, Technology and Research Singapore, Singapore, Singapore

²Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore

³Department of Psychiatry, Singapore General Hospital, Singapore, Singapore

⁴Saw Swee Hock School of Public Health, National University of Singapore, Singapore, Singapore

⁵Khoo Teck Puat-National University Children's Medical Institute, National University Health System, Singapore, Singapore

⁶Department of Paediatric Allergy and Respiratory Medicine, KK Women's and Children's Hospital, Singapore, Singapore

⁷Department of Endocrinology, KK Women's and Children's Hospital, Singapore, Singapore

⁸Department of Maternal and Fetal Medicine, KK Women's and Children's Hospital, Singapore, Singapore

⁹Department of Obstetrics & Gynaecology, National University of Singapore, Singapore, Singapore

¹⁰University of Helsinki and Helsinki University Hospital, Helsinki, Finland

¹¹Folkhälsan Research Center, Helsinki, Finland

¹²MRC Lifecourse Epidemiology Unit and NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK

Abstract

Background: The natural history of childhood rhinitis is not well described.

Objective: This study aimed to identify different rhinitis trajectories in early childhood and their predictors and allergic associations.

Methods: Rhinitis symptoms were ascertained prospectively from birth until 6 years using standardized questionnaires in 772 participants. Rhinitis was defined as one or more episodes of sneezing, runny and/or blocked nose >2 weeks duration. Latent trajectories were identified using group-based modelling, and their predictive risk factors and allergic associations were examined.

Results: Three rhinitis trajectory groups were identified: 7.6% (n = 59) were termed *early transient rhinitis*, 8.6% (n = 66) *late transient rhinitis*, and 6.6% (n = 51) *persistent rhinitis*. The remaining 77.2% (n = 596) were classified as *non-rhinitis/reference group*. Early transient rhinitis subjects were more likely of Indian ethnicity, had siblings, reported childcare attendance, early wheezing and eczema in the first 3 years of life. Late transient rhinitis was associated with antenatal exposure to smoking, higher maternal education levels, and wheezing at age 36-72 months. Persistent rhinitis was associated with male gender, paternal and maternal history of atopy, eczema, and house dust mite sensitization.

Conclusions & Clinical Relevance: Risk factors for early transient rhinitis involve a combination of genetic and early environmental exposures, whereas late transient rhinitis may relate to maternal factors and early respiratory infections independent of atopy. In contrast, persistent rhinitis is strongly associated with atopic risk and likely represents the typical trajectory associated with allergic disorders. Allergic rhinitis symptoms may commence as early as the first year of life and may inform development of early interventional strategies.

Abbreviations: ETR, early transient rhinitis; GUSTO, Growing Up in Singapore Towards Healthy Outcomes study; ISAAC, International Study of Asthma and Allergies in Childhood; LTR, late transient rhinitis; PR, persistent rhinitis; SPT, skin prick test.

*co-first authors. Evelyn Xiu Ling Loo and Tau Ming Liew are co-first authors.

Correspondence

Elizabeth Huiwen Tham, Division of Allergy & Immunology, Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore.
Email: elizabeth_tham@nuhs.edu.sg

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KEYWORDS

asthma, environment and hygiene hypothesis, paediatrics, rhinitis

1 | INTRODUCTION

The term “atopic march” was originally coined to describe the progression from eczema in early infancy to other allergic diseases such as food allergy, asthma, and allergic rhinitis in later childhood.^{1,2} A recent study, however, suggested that the complete manifestations of the atopic march occur in less than 10% of children.³ The pathogenesis of allergic airway disorders are likely multifactorial, with childhood rhinitis and wheezing being heterogeneous clinical entities. Many studies have attempted to classify rhinitis and wheeze phenotypes according to atopic status, symptoms, allergic comorbidities, and long-term objective markers such as lung function.⁴ Earlier studies classified phenotypes according to expert or investigator-determined definitions based on symptoms reported at various time-points during follow-up.

However, classifications by investigator pre-determined parameters are often arbitrary and incomplete and may not characterize true endophenotypes. In recent years, the field has moved towards unsupervised data-driven statistical algorithms which utilize observable surrogate data variables collected to generate latent (unobservable) clusters of disease phenotypes determined by the calculated probability of individuals belonging to a specific cluster.⁵ Many studies have now adopted such methods to classify latent classes of childhood wheezing disorders, but most are cross-sectional, assessing outcomes at a single time-point.^{6,7}

There are, however, few longitudinal studies reporting childhood rhinitis trajectories over time. Only 3 other cohorts in Europe and the United Kingdom have reported latent disease trajectories of wheeze and rhinitis in children. The Pollution and Asthma Risk: an Infant Study (PARIS) birth cohort reported seven latent classes of childhood wheezing and rhinitis disorders: 3 wheeze, 3 rhinitis, and 1 reference group.⁸ The Avon Longitudinal Study of Parents and Children (ALSPAC) and Manchester Asthma and Allergy Study (MAAS) cohorts found eight latent classes of eczema, wheeze, and rhinitis: no disease, atopic march, persistent eczema and wheeze, persistent eczema with later-onset rhinitis, persistent wheeze with later-onset rhinitis, transient wheeze, eczema only, and rhinitis only.³

Cross-sectional studies typically evaluate prevalence, risk factors, and allergic outcomes to determine classes of allergic conditions at a single time-point; however, longitudinal studies are able to incorporate timing of onset, natural history, and changes in the prevalence of allergic conditions over time to derive differential trajectories of disease.

In this study, we utilized an unsupervised data-driven approach to identify rhinitis trajectories in the Growing Up in Singapore Towards Healthy Outcomes (GUSTO) cohort across the first 6 years of life. We also explored their associations with allergic comorbidities such as wheezing and allergic sensitization and examined risk factors predictive of each rhinitis trajectory.

2 | METHODS

2.1 | Study design

The methodology of the GUSTO study has previously been described in detail.⁹ Briefly, we recruited healthy pregnant mothers who agreed to enrol their offspring for future follow-up. Interviewers gathered information on demographic characteristics, family history of allergy, social data, and lifestyle factors. Definitions of allergic outcomes were standardized in the questionnaires administered at 3 weeks, 3, 6, 9, 12, 15, 18, 24, 36, 48, 60, and 72 months to ensure consistency during interviews and home visits. We used standardized questionnaires for evaluation of allergic symptoms and classified rhinitis symptoms according to the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines.¹⁰⁻¹³ “Rhinitis” was defined by a positive response to the question “Has your child ever had sneezing, running nose, blocked or congested nose, snoring or noisy breathing during sleep or when awake that has lasted for 2 or more weeks duration?” This was also based on the World Health Organization and Global Allergy and Asthma European Network (GA(2)LEN) consensus statement on the ARIA guidelines which recommended that symptoms that persist longer than 2 weeks should prompt a search for a cause other than infection,¹² as upper respiratory infections

in children rarely last beyond 14 days.¹⁴ These questions have also been previously validated in children from 1 year of age in GUSTO as well as several other birth cohorts.^{11,15,16}

Physician-diagnosed eczema was defined by a positive answer to the question: "Has your child ever been diagnosed with eczema?"; "Wheezing" was defined by affirmative responses to both questions: "Has your child ever wheezed?" and "Has your child ever been prescribed with a nebulizer/inhaler?"

Rhinitis severity was assessed through (a) the total number of positive rhinitis responses in the questionnaires administered at 3 weeks, 3, 6, 9, 12, 15, 18, 24, 36, 48, 60, and 72 months and (b) usage of nasal steroid sprays, defined by a positive response to the question "Was your child treated with topical nasal steroids?" verified with the name of the medication.

Allergen sensitization was determined by skin prick testing (SPT) to house dust mite allergens (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, and *Blomia tropicalis*) and food allergens (egg, peanut and cow's milk) at 18, 36, and 60 months. At 60 months, skin prick testing for shrimp and crab allergens was also performed. The allergens for skin prick testing were obtained from Greer Laboratories (Lenoir, NC, USA), except for *B tropicalis*, which was obtained from our laboratory (Singapore). Tests were interpreted as positive if the wheal was at least 3 mm, and a child was considered as SPT positive if any one or more of the individual tests was positive with a positive reaction to the positive control (histamine) and a negative reaction to the negative control (saline).

Maternal blood cotinine levels were measured at 26–28 weeks of gestation and were used as a surrogate measure of antenatal smoking exposure. Maternal blood cotinine levels below 0.17 ng/ml were considered negative. Cotinine levels between 0.17 and 13.99 ng/ml were considered as low, and levels exceeding 14 ng/ml were considered as high.¹⁷ 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). The conduct of this study was based on the guidelines in the Declaration of Helsinki. Informed consent was obtained from all mothers.

2.2 | Statistical methods

Group-based trajectory modelling (GBTM) was used to identify the latent trajectories of rhinitis symptoms, based on reported presence of rhinitis symptoms at 3 weeks, 3, 6, 9, 12, 15, 18, 24, 36, 48, 60, and 72 months (12 time-points in total). GBTM is a semiparametric analysis that classifies participants into mutually exclusive groups with distinct trajectories of rhinitis symptoms.¹⁸ For each participant, it computes the probability of belonging to the various trajectories and assigns the participant to a trajectory with the highest probability. As some of the participants did not provide data over all 12 time-points, GBTM only included participants who had at least 6 out of the 12 time-points to ensure the accuracy in identifying latent trajectories. Models with 1–7 trajectories were evaluated in the GBTM, with the

binary responses of rhinitis symptoms (1 = Yes; 0 = No) modelled using logistic models. To determine the appropriate number of trajectories, the Bayesian information criterion (BIC) was used—BIC values which are lesser by at least 10 points indicate better model fit and parsimony.¹⁹ To determine the appropriate trajectory shape, for each model specifying a given number of trajectories, linear, quadratic, and cubic terms were included in the model and removed sequentially (starting from the higher-order cubic terms) if they were not significant ($P > .05$). Upon finalizing the appropriate number and shape of trajectories, average posterior probabilities (APP)¹⁹ were also examined and only individuals with APP of at least 0.50 (indicating that the individuals had higher-than-chance probabilities of belonging to specific trajectories) were included in the current study to avoid biased findings in subsequent analyses.

Statistical comparisons of categorical (demographic and allergic comorbidities) variables between the trajectory groups, as well as between the participants included and excluded from analysis, were performed using Pearson's chi-square tests. The strength of associations between trajectories groups and variables of interest (ie allergic outcomes, prenatal risk factors, and postnatal environmental factors) were assessed using multinomial logistic regression using a P value of $<.05$ as significant; we reported adjusted odds ratios with 95% confidence intervals (CI). The non-rhinitis group was used as the reference category in all multinomial logistic regression analyses. Potential confounding variables (reference groups stated in parentheses): gender (female), ancestry (Chinese), maternal education levels (non-tertiary education), maternal history of allergy (no history), paternal history of allergy (no history), presence of siblings (no sibling), maternal cotinine levels during pregnancy (low cotinine levels), childcare attendance (never attended childcare), pet ownership (no pet ownership), and smoking exposure (no smoking exposure) during the first year of life were adjusted for in multivariable analyses. Frequency of reported rhinitis symptoms and usage of nasal steroids were analysed with Mann–Whitney U and Pearson's chi-square tests, respectively. Bonferroni correction was used for multiple comparisons. To confirm the stability and robustness of the model, sensitivity analysis was conducted by restricting the multinomial logistic regression only to subjects who provided complete data at all 12 time-points. All statistical significance tests and CIs were 2-sided and set at a p value of less than 0.05. GBTM was conducted in Stata version 14, while other analyses were carried out using IBM SPSS version 25.0 (IBM, SPSS statistics, Armonk, NK).

3 | RESULTS

Among the GUSTO children conceived in singleton pregnancies, 772 provided longitudinal data on rhinitis trajectories and were included in this study. The flow chart of participant selection is shown in Supplementary Figure S1. There were no differences in baseline characteristics (gender, ancestry, maternal education levels, sibling status, maternal cotinine levels, mode of delivery, childcare attendance, maternal and paternal history of allergy, and pet ownership)

between participants included in the analysis and those who were excluded (Supplementary Table S1).

3.1 | Identification of rhinitis trajectories

Three rhinitis trajectory groups were identified (Supplementary Table S2) and are presented in Figure 1. Based on their patterns, we termed them: (a) early transient rhinitis (ETR) (7.6%), with a high probability of reported rhinitis during infancy (first year of life), after which the majority recovered; (b) late transient rhinitis (LTR) (8.6%), with a high probability of rhinitis beginning at 2-3 years of age and which gradually decreased after age 3; and (c) persistent rhinitis (PR) (6.6%), with an increasing probability of rhinitis from early infancy and which remained high at 6 years. A group (77.2%) which had a low probability of reported rhinitis symptoms throughout the first 6 years of life was termed the non-rhinitis group and was used as the reference group for analysis. The characteristics of children in each trajectory group are shown in Table 1.

3.2 | Early transient rhinitis (ETR)

Children in the ETR group were more likely to be of Malay [13 (22.2%)] and Indian [25 (42.4%)] ancestry compared to Chinese, to have siblings [44 (74.6%)], have attended childcare in first year of life [8 (30.8%)] and have mothers with lower education levels [25 (42.4%)] as compared to the reference group (Table 1). Multivariable analysis showed that being of Indian ancestry [Adj OR 2.2, 95% CI (1-4.9), $P = .04$], presence of a sibling [Adj OR 2.2, 95% CI (1-4.6), $P = .04$] and childcare attendance [Adj OR 17.7, 95% CI (3.6-87.6), $P < .001$] remained significantly associated with increased odds of developing ETR (Figure 2) after adjustment for confounders.

The ETR group also had the highest proportion of children with wheezing at all time-points in the first 6 years of life but had low prevalence of allergen sensitization, which was similar to the reference group (Table 2) indicating the absence of atopy. The ETR phenotype was thus likely of the non-allergic type. In multivariable analysis, ETR was also associated with early wheezing and eczema in the first 3 years of life (Figure 2, Supplementary Table S3).

3.3 | Late transient rhinitis (LTR)

The LTR group was comparable to the reference group in terms of baseline demographic characteristics including ancestry, maternal education level, paternal and maternal history of allergy, suggesting that LTR is not associated with ancestry, familial and socio-economic factors. The proportion of allergen-sensitized children was comparable to the reference group and lower than the PR group (Table 2). Multivariable analysis showed that LTR was associated with wheezing at ages 36 and 72 months, but not before 18 months of age, and was also not associated with eczema or allergen sensitization (Figure 2, Table S3). A high maternal antenatal cotinine concentration (≥ 14 ng/ml) and maternal tertiary education were also associated with increased odds of development of LTR [Adj OR 5.3, 95%CI (1.5-19.4), $P = .01$ and Adj OR 2, 95%CI (1-4.1), $P = .03$, respectively].

3.4 | Persistent rhinitis (PR)

The PR group had the highest proportion of males [36 (70.6%)], childcare attendance in first year of life [7 (35.0%)], more highly educated mothers [38 (74.5%)], and paternal [18 (37.5%)] and maternal [22 (45.8%)] history of atopic disorders (Table 1). On multivariable analysis, these factors were also associated with increased odds of

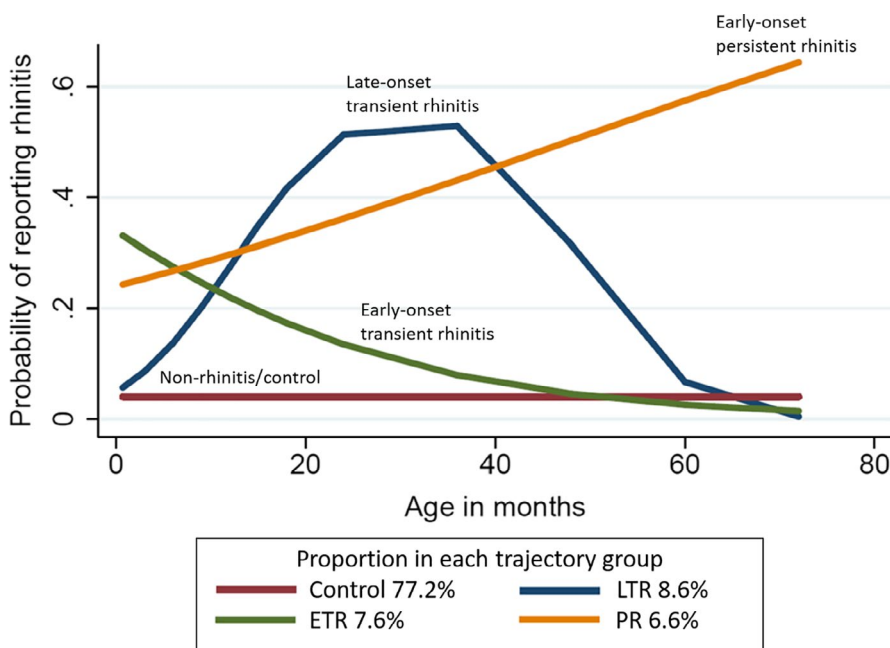


FIGURE 1 Identification of three rhinitis trajectories profiles using group-based trajectory modelling

TABLE 1 Demographic characteristics of the rhinitis trajectories

	Total (N=772)	Trajectory groups						
		Non-rhinitis / Control group (n=596)	ETR (n=59)	p value	LTR (n=66)	p value	PR (n=51)	p value
Male	403 (52.2%)	296 (49.7%)	34 (57.6%)	0.729	37 (56.1%)	0.972	36 (70.6%)*	0.012
Ancestry								
Chinese	442 (57.3%)	352 (59.1%)	21 (35.6%)*	0.003	39 (59.1%)	1	30 (58.8%)	1
Malay	136 (17.6%)	101 (16.9%)	13 (22%)*		12 (18.2%)		10 (19.6%)	
Indian	194 (25.1%)	143 (24%)	25 (42.4%)*		15 (22.7%)		11 (21.6%)	
Maternal tertiary education	463 (60.4%)	354 (60%)	25 (42.4%)*	0.027	46 (69.7%)	0.378	38 (74.5%)	0.123
Vaginal delivery	478 (64.3%)	365 (63.6%)	38 (65.5%)	1	41 (66.1%)	1	34 (69.4%)	1
Paternal history of atopy	149 (21.4%)	104 (19.5%)	13 (26%)	0.81	14 (21.9%)	1	18 (37.5%)*	0.009
Maternal history of atopy	164 (23.6%)	113 (21.2%)	13 (26%)	1	16 (25%)	1	22 (45.8%)*	<0.001
Presence of sibling	429 (55.6%)	322 (54%)	44 (74.6%)*	0.006	41 (62.1%)	0.63	22 (43.1%)	0.405
Childcare attendance in first year	55 (14.4%)	33 (11.1%)	8 (30.8%)*	0.012	7 (18.4%)	0.573	7 (35%)*	0.006
Pet ownership at 12 months	38 (8.9%)	28 (8.4%)	3 (11.5%)	1	4 (9.5%)	1	3 (13%)	1
Smoking exposure in first year	44 (4.7%)	21 (3.8%)	6 (10.5%)	0.057	4 (6.2%)	0.969	3 (6.1%)	1
Maternal antenatal cotinine level								
Low	95 (13.9%)	70 (13.4%)	9 (17.3%)	0.345	10 (16.4%)	0.681	6 (12.5%)	1
High	23 (3.4%)	15 (2.9%)	4 (7.7%)		4 (6.6%)		0	

Note: Abbreviations: ETR: early transient rhinitis; LTR: late transient rhinitis; PR: persistent rhinitis

*p value ≤0.05 compared to non-rhinitis/control group in univariate analysis (Bonferroni adjustment for multiple comparison)

developing PR [male gender: Adj OR 2.3, 95% CI (1.1-4.5), $P = .02$; paternal history of atopy: Adj OR 2.3, 95% CI (1.1-4.4), $P = .02$; maternal history of atopy: Adj OR 2.5, 95% CI (1.3-5.0), $P = .01$, respectively] (Figure 2). Maternal cotinine levels during pregnancy and education levels were not associated with development of PR.

The PR group had the highest proportions of children with eczema and house dust mite sensitization across all time-points, higher than the ETR, LTR, and reference groups (Table 2). Multivariable analysis further confirmed that eczema and house dust mite sensitization, but not wheezing, were associated with this trajectory at almost all time-points (Figure 2, Table S3), suggesting that children in this group were more atopic and likely predisposed to development of allergic disorders.

3.5 | Sensitivity analysis

The multivariable analysis was repeated in 470 subjects who had complete data across all the 12 time-points. (Table S4) In the ETR group, childcare attendance and wheezing at 12 and 18 months remained significantly associated with this trajectory. Maternal

antenatal cotinine levels and wheezing at 72 months remained significantly associated with the LTR trajectory. Male gender, eczema across all the time-points from 6 to 72 months, allergen sensitization at 60 months, and house dust mite sensitization at 36 and 60 months remained significantly associated with the PR trajectory.

3.6 | Rhinitis persistence and severity

The overall frequency of reported rhinitis symptoms across time-points was highest in the PR group (median 4.0, IQR 3.0), followed by the LTR (median 3.0, IQR 1.0) and ETR groups (median 2.0, IQR 1.0), compared to the reference group (median 0, IQR 1.0) (all $P < .001$) (Figure 3).

The onset of nasal steroid use was earlier in the ETR group compared to the LTR and PR groups. Children in the latter two groups only reported nasal steroid use from 48 months onwards, consistent with the later onset of symptoms in these children (Figure 1). At age 48 months, use of nasal steroids was highest in the LTR group (6/66, 9.2%) compared to the reference group ($P < .001$), followed by the PR group (2/51, 4.0%). The PR group reported the highest use of

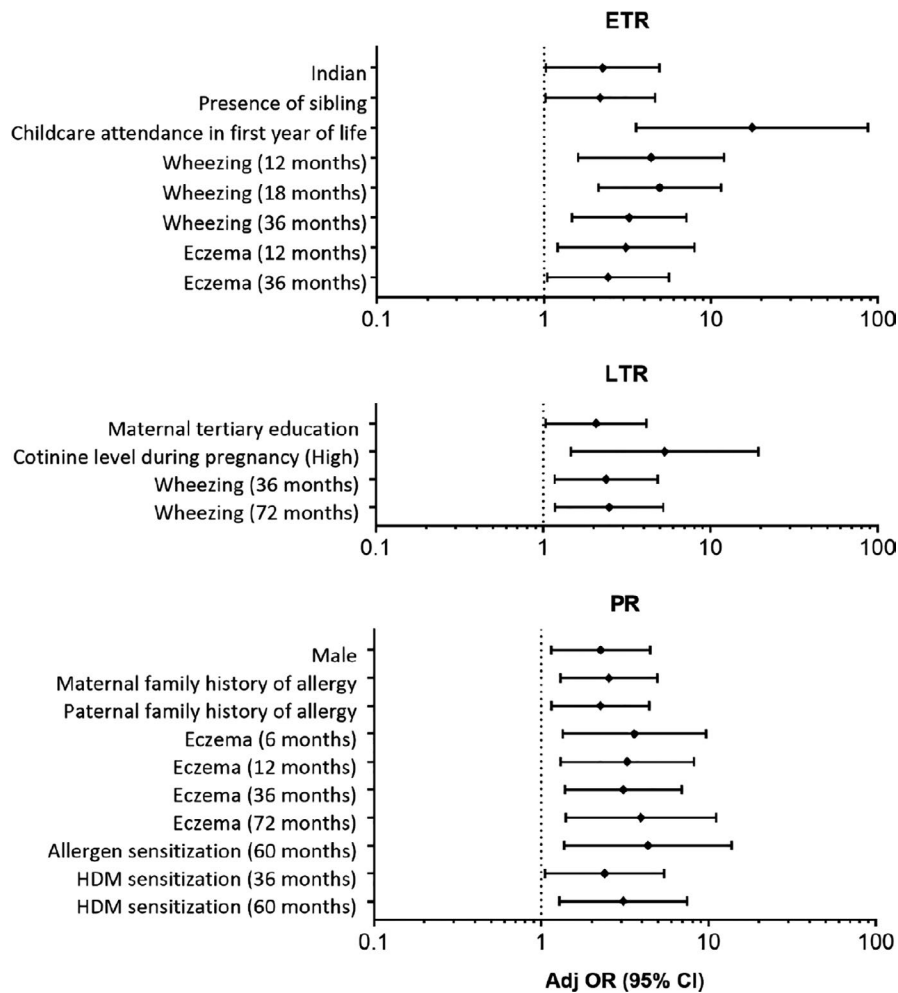


FIGURE 2 Multivariate analyses for risk factors, postnatal environmental factors, and comorbidities associated with rhinitis trajectories profiles

nasal steroids at ages 60 (5/51, 10.2%) and 72 months (11/51, 22%) compared to all the other trajectory groups. Subjects in the PR trajectory also reported more prolonged usage of nasal steroids, over a greater number of time-points, compared to those in the LTR and ETR trajectories, suggesting that rhinitis symptoms were more persistent and/or severe in this group.

4 | DISCUSSION

In this study, we utilized a data-driven approach analysing data from twelve longitudinal time-points in a large prospective birth cohort to identify three latent classes of rhinitis trajectories, each with different sets of clinical characteristics and predictive risk factors. The ETR trajectory was associated with Indian ethnicity, siblings, childcare attendance, and early wheezing and eczema. The LTR trajectory was associated with antenatal smoking, higher maternal education levels, and wheezing. Persistent rhinitis was associated with male gender and atopic features.

Our study also supports emerging evidence that not all allergic pathways follow the temporal sequence suggested by the conventional atopic march. Allergic rhinitis symptoms began as early as in the first year of life, alongside eczema, contrary to the traditional

notion whereby eczema and food allergy are expected to begin in infancy, with allergic rhinitis developing in later childhood.²⁰ Our study also suggests that the allergic rhinitis phenotype may be differentiated from other types of rhinitis phenotypes through predictive risk factors present in early life.

The ETR and LTR trajectories were distinguished from the PR trajectory by an absence of atopic features and thus are likely modulated by environmental factors. The pathogenesis of the ETR trajectory is likely attributable to a combination of genetic and environmental influences in early life—a tenet of the Developmental Origins of Health and Disease (DOHaD) paradigm, which postulates that early environmental stimuli may contribute to the early onset of non-communicable diseases via epigenetic effects on fetal and neonatal immune regulation.²¹ Environmental factors such as childcare attendance and siblings are also associated with increased respiratory morbidity.^{22,23} Childcare attendance has been linked to the transmission of pathogens due to close contact with other children.²⁴ A study involving 3766 children in Northeast Texas also reported early childcare attendance to be associated with increased respiratory infections, rhinitis and wheezing.²⁵ These factors may explain the link between increased environmental microbial exposures and early-onset rhinitis which does not persist beyond early childhood. Besides environmental factors, we found that Indian ancestry was

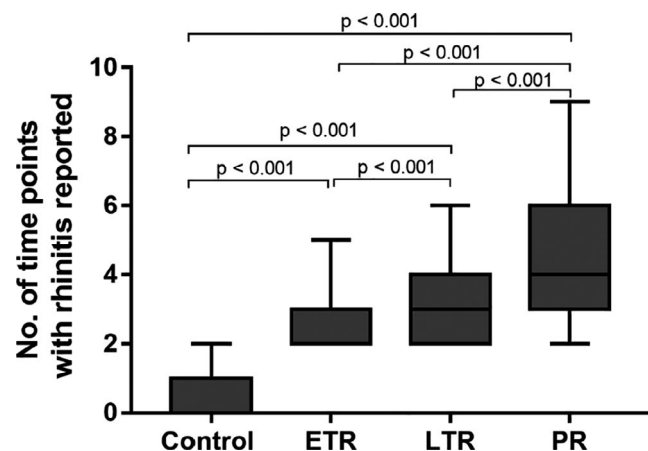
TABLE 2 Participants with allergic comorbidities in each trajectory group

	Trajectory group						
	Non-Rhinitis / Control	ETR	p value	LTR	p value	PR	p value
	(n=596)	(n=59)		(n= 66)		(n=51)	
Wheezing by 6 months	13 (2.5%)	6 (10.9%)*	0.003	3 (5%)	0.678	2 (5%)	0.882
Wheezing by 12 months	28 (6.1%)	15 (28.3%)*	<0.001	7 (12.3%)	0.249	5 (13.2%)	0.288
Wheezing by 18 months	43 (10%)	18 (36%)*	<0.001	10 (17.9%)	0.231	6 (17.6%)	0.492
Wheezing by 36 months	81 (15%)	19 (33.9%)*	<0.001	18 (28.1%)*	0.021	13 (28.3%)	0.057
Wheezing by 72 months	109 (27.3%)	21 (45.7%)*	0.027	24 (44.4%)*	0.027	20 (58.8%)*	<0.001
Eczema by 6 months	32 (6.1%)	5 (9.4%)	1	9 (15.3%)*	0.027	9 (22.5%)*	<0.001
Eczema by 12 months	53 (10.8%)	11 (21.6%)	0.069	11 (19.3%)	0.174	12 (30.8%)*	<0.001
Eczema by 18 months	86 (14.4%)	12 (20.3%)	0.675	13 (19.7%)	0.765	17 (33.3%)*	<0.001
Eczema by 36 months	103 (19.1%)	16 (28.1%)	0.324	17 (27%)	0.417	21 (46.7%)*	<0.001
Eczema by 72 months	120 (25.5%)	20 (41.7%)*	0.048	20 (35.7%)	0.303	25 (62.5%)*	<0.001
Allergen sensitization at 18 months	61 (12%)	7 (14.3%)	1	10 (16.4%)	0.99	11 (23.9%)	0.066
Allergen sensitization at 36 months	115 (22.3%)	9 (17%)	1	14 (23.3%)	1	17 (40.5%)*	0.024
Allergen sensitization at 60 months	169 (33.5%)	14 (26.4%)	0.882	18 (34%)	1	24 (58.5%)*	0.003
HDM sensitization at 18 months	50 (9.9%)	3 (6.1%)	1	9 (14.8%)	0.711	10 (21.7%)*	0.039
HDM sensitization at 36 months	111 (21.4%)	8 (15.1%)	0.846	14 (23%)	1	17 (40.5%)*	0.015
HDM sensitization at 60 months	169 (33.5%)	14 (25.9%)	0.786	17 (32.1%)	1	23 (56.1%)*	0.012

Note: Abbreviations: ETR: early transient rhinitis; LTR: late transient rhinitis; PR: persistent rhinitis; HDM: house dust mite

*p value <0.05 compared to non-rhinitis/control group in univariate analysis (Bonferroni adjustment for multiple comparison)

associated with ETR. Studies have shown that differences in genetic allele distribution between ethnic groups, modulated by environmental risk factors, may be associated with earlier-onset transient rhinitis.²⁶

**FIGURE 3** Frequency of reported rhinitis symptoms in each trajectory

In contrast, the LTR trajectory was characterized by antenatal and socio-economic factors and was not associated with ancestry, childcare attendance, or atopy. Concomitant onset of rhinitis and wheeze was observed in the LTR trajectory, suggesting that these were likely due to respiratory viral infections in early childhood rather than familial factors. The Canadian Asthma Primary Prevention study likewise reported that exposure to common viruses such as parainfluenza and respiratory syncytial viruses were associated with rhinitis and wheezing, respectively.²⁷

Antenatal tobacco smoke exposure was also a risk factor for the LTR trajectory in this study. The pathogenesis of this phenotype may be mediated through respiratory tract impairments that increased susceptibility to respiratory viral infections.²⁸ Exposure to maternal tobacco smoke in utero has been found to induce long-term deficits in respiratory function,²⁹ which might explain the strong wheezing comorbidity seen in these subjects. Compelling evidence suggests that the early environment of a child, which includes maternal immune signalling transferred in utero, can affect development of the immune system, affecting subsequent disease risk.^{21,30} Support for our observations is also provided by a pooled analysis of 27,993 mother-child dyads from 15 European birth cohorts, which showed

increased risk of wheeze in children with antenatal tobacco smoke exposure.³¹ Another study of 3357 schoolchildren aged 10–16 years from South California also demonstrated an association of antenatal smoke exposure with reduction in peak expiratory flow rate, mean mid expiratory flow and forced expiratory flow in the children.³²

We also found that higher maternal education was a risk factor for LTR, in agreement with a systematic review of 183 studies showing a higher prevalence of rhinitis in higher socioeconomic status groups.³³ In another study in Tehran, a relationship was also reported between higher maternal education levels and prevalence of rhinitis.³⁴ The association between higher socioeconomic status and allergic disorders is well known, and has been postulated to be related to increased disease reporting and health-seeking behaviour by better educated families; or to disturbances in early life microbiota exposures, as proposed by the hygiene hypothesis.^{35,36} This hypothesis suggests that diminished early life exposure to environmental microbiota primes the naïve immune system towards a Th2-predominant state, increasing the risk of developing allergic disorders.³⁷ Exposure to high microbial loads and increased biodiversity in early life such as a farming lifestyle, the presence of older siblings and pet ownership, may conversely be protective against atopy by shifting the immune milieu back towards a healthy Th1/Th2 balance.^{35,38–40}

In contrast, we observed that the PR trajectory involved mainly non-modifiable risk factors and strong associations with atopy, such as eczema and allergen sensitization. Male gender and a family history of atopy are well-known risk factors for allergic disease, suggesting a role for genetic atopic predisposition in children belonging to this trajectory. The Isle of Wight birth cohort likewise found that male gender was strongly associated with allergic rhinitis at 4 and 18 years of age.⁴¹

It has been proposed that the presence of an impaired skin barrier such as eczema predisposes to allergic sensitization and the ensuing systemic Th2 inflammation is responsible for the subsequent development of allergic comorbidities such as allergic rhinitis and asthma.⁴² This has been the conventional concept underpinning the notion of the atopic march,^{2,43} which has also been supported by many longitudinal birth cohorts as well as mechanistic work.²³ The Multi-center Allergy Study in Germany showed that early allergen sensitization, early onset of eczema, and paternal history of allergic rhinitis were predictive of allergic rhinitis up to 20 years of age.⁴⁴ In the Isle of Wight cohort, filaggrin loss-of-function skin barrier mutations were strongly associated with eczema as well as rhinitis at 10 years of age.⁴⁵

In contrast, we have shown here that the onset of persistent rhinitis symptoms may occur alongside eczema in early life in individuals at high risk of atopy who then go on to manifest with other atopic phenotypes later in childhood, lending support to the notion that there are alternative atopic pathways apart from the conventional atopic march. The Avon Longitudinal Study of Parents and Children and Manchester Asthma and Allergy Study (ALPSAC) involving 9801 children also reported that fewer than 7% were found to follow the classic atopic march trajectory.³ The PARIS cohort also reported that there was more than one temporal pattern of allergic diseases and reported the cough/rhinitis phenotype to have common risk

factors, including genetics and allergen exposures known to influence allergy development.⁴⁶ These cohorts, however, reported very heterogeneous clusters of allergic disorders with overlaps between phenotypes of rhinitis, wheeze, eczema/dermatitis, and coughing symptoms which rendered comparisons between studies difficult. These clusters are evident only on hindsight when all allergic disorders have already manifested, but are not easily translatable to clinical practice for risk stratification of individuals who present at a single time-point with isolated symptoms.

Current rhinitis classifications according to the ARIA and ISAAC questionnaire-based definitions typically phenotype rhinitis by symptom duration and severity according to the effect on the patient's quality of life.¹² However, the diagnosis of allergic rhinitis is difficult in children below age 3 years. There are very few studies using questionnaire-based definitions for the diagnosis of rhinitis in pre-schoolers^{15,16} and none that have evaluated its sensitivity or specificity compared to a physician's diagnosis. Most epidemiological studies have been performed in school-age children using the ISAAC questionnaire which has not been validated for use in children below age 5 years.

Evidence from a few studies suggests that the ARIA questionnaire has good agreement with allergen sensitization. A cohort study of 237 asthmatic children aged 3 to 18 years old found that 82% of those diagnosed with allergic rhinitis by the ARIA classification were also sensitized.⁴⁷ Besides this, 91% of children from the Multi-center Allergy Study with severe persistent AR and 70% with mild persistent AR were sensitized to at least one aeroallergen.¹⁶

However, in practice, these questionnaires have been used to diagnose disease and evaluate its severity at single time-points,⁴⁸ and do not capture the longitudinal pattern of symptom evolution from early life to adulthood. The unsupervised data-driven approach used in this study revealed heterogeneity in the longitudinal patterns of symptoms in each individual child and allowed us to gain deeper insights into how patterns of symptom transition can be used to identify longitudinal disease phenotypes.³ Although a similar method was also used in the PARIS, ALPSAC, and MAAS studies, data were derived from just two and five time-points, respectively. The greater number of data points (12 in total) in our study significantly increases the reliability and robustness of the models. In addition, by focusing on rhinitis phenotypes alone and deciphering risk factors in early life which may predict their trajectories through childhood, we also provide insights that help inform risk stratification and intervention strategies for children presenting with rhinitis symptoms in early life.

The GUSTO cohort has its strengths in close longitudinal follow-up of all subjects with comprehensive clinical and sensitization profiling. Each standardized question on rhinitis, wheeze, and eczema was asked at each of the very closely spaced follow-up visits, which minimized the risk of recall bias. In addition, we used maternal cotinine levels as an objective assessment of antenatal smoke exposure, which increases the reliability of our findings. We also used unsupervised data-driven statistical techniques to elucidate latent classes of rhinitis phenotypes, unrestricted by investigator-determined assumptions which might introduce unwanted bias or

misclassify disease phenotypes. Limitations of our study included the reliance on parental reporting for assessment of rhinitis and other allergic outcomes, which are mitigated by the close follow-up intervals and validation of these questionnaires in the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines and in other birth cohorts.^{11,12,49} Due to the modest numbers of subjects in each trajectory, statistical powering for analysis of some risk factors were limited, thus replication studies in larger cohorts are needed. To address this limitation, GBTM analysis was performed in a subset of the GUSTO cohort who provided longitudinal data on rhinitis and we showed that despite this, there were no differences in demographics between those included and excluded from the analysis. The findings also remained consistent in the sensitivity analysis, suggesting the robustness of the findings. In conclusion, we have found that risk factors for transient rhinitis phenotypes comprise a combination of genetic and early environmental exposures which are independent of atopy. In contrast, persistent rhinitis is strongly associated with atopic risk and likely represents the typical trajectory associated with allergic disorders. Allergic rhinitis symptoms may commence as early as the first year of life, dispelling the myth of a classical atopic march.

The heterogeneity of allergic disease trajectories underscores the importance of understanding disease endophenotypes which in turn influence prognosis and management. The determination of distinctive risk factors for latent rhinitis trajectories in childhood allows for identification of at-risk phenotypes in early life which could be targeted for intervention. Modifiable risk factors such as antenatal smoking and respiratory infections may be addressed through education, vaccinations, and environmental interventions to achieve attenuation of disease morbidity incurred by transient rhinitis phenotypes. For an individual identified to be high risk with known non-modifiable risk factors for persistent (allergic) rhinitis, such as one with a strong family history of atopy and early-onset eczema, prognostication of disease trajectory can be made. In such patients, long-term follow-up of rhinitis symptoms even from early life would be recommended to monitor for the development of allergen sensitization, allergic rhinitis and asthma in later childhood. Proactive management in early life, such as aggressive eczema treatment and control of rhinitis may also mitigate the complications of multiple allergic comorbidities in later life.⁵⁰

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CONFLICT OF INTEREST

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.

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AUTHOR CONTRIBUTION

The named authors meet the Clinical & Experimental Allergy criteria for authorship of this paper. Loo EXL, Liew TM, Yap GC, and Tham EH performed the data analysis and prepared the manuscript. Wong LSY, Shek LP, Goh A, Van Bever HPS, Teoh OH, Yap F, Tan KH, Thomas B, Ramamurthy MB, Goh DYT, Eriksson JG, Chong YS Godfrey KM, and Lee BW reviewed this paper. All authors reviewed and approved the final draft for publication.

ORCID

Elizabeth Huiwen Tham  <https://orcid.org/0000-0003-1037-6143>

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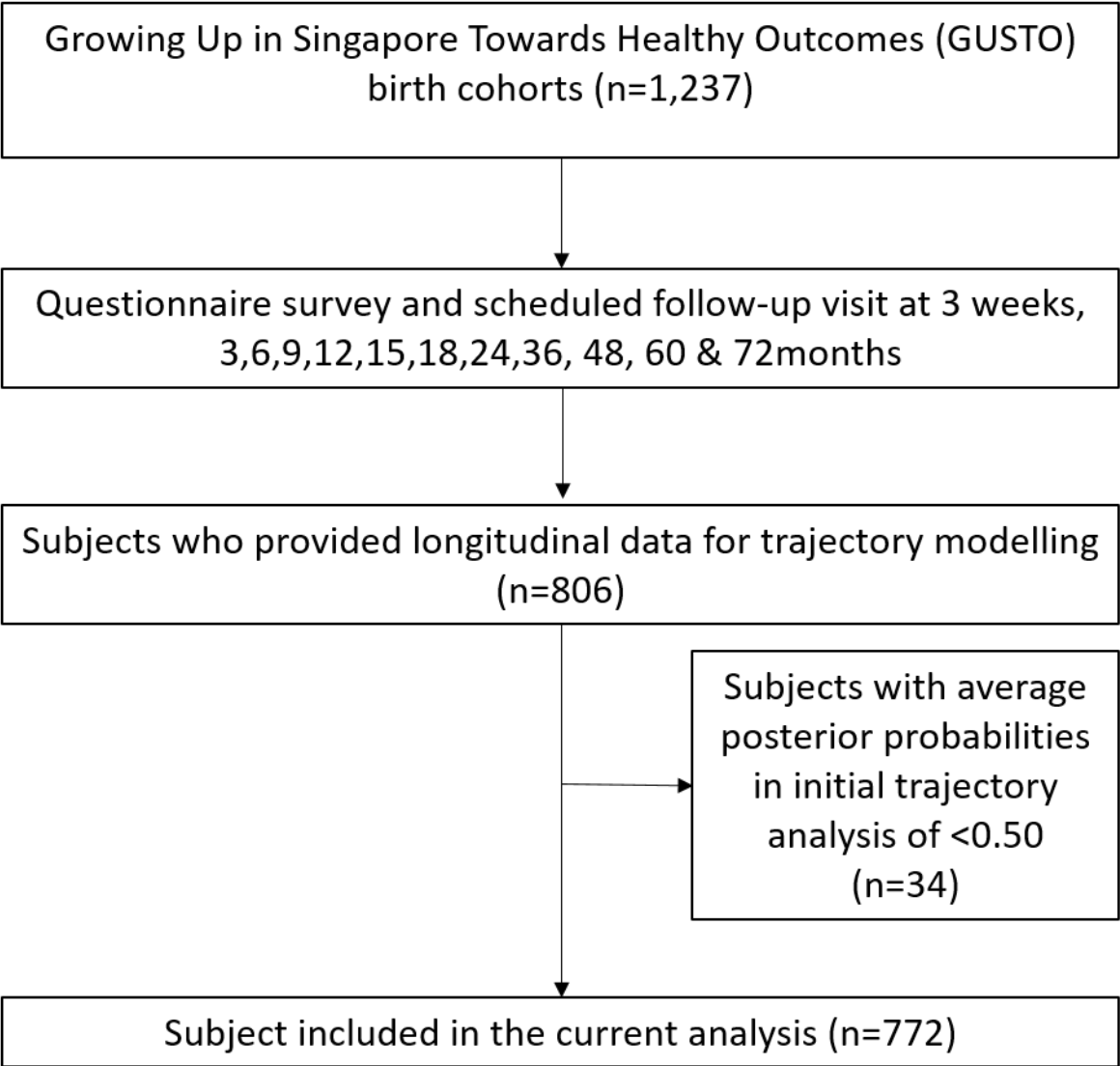
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SUPPORTING INFORMATION

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

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Supplementary Figure 1:



Supplementary Table 1. Comparison of demographic characteristics between participants excluded and included in the study

		Excluded (N=465) n (%)	Included (N=772) n (%)	p value
Male		216 (46.5)	403(52.2)	0.53
Ancestry	Chinese	249 (53.5)	442 (57.3)	0.44
	Malay	88 (18.9)	136 (17.6)	
	Indian	128 (27.5)	194 (25.1)	
Maternal tertiary education		251(54.0)	463 (60.0)	0.09
Vaginal delivery		246 (52.9)	478 (61.9)	0.94
Paternal history of atopy		51 (11.0)	149 (19.3)	0.25
Maternal history of atopy		45 (9.7)	164 (21.2)	0.70
Presence of sibling		206 (44.3)	429 (55.6)	0.23
Childcare attendance in first year		21 (4.5)	55 (7.1)	0.3
Pet ownership at 12 months		16 (3.4)	38 (4.9)	0.19
Smoking exposure in first year		10 (2.2)	34 (4.4)	0.99
Maternal antenatal cotinine level	Low	47 (16)	95 (13.9)	0.45
	High	13 (4.4)	23 (3.4)	

Supplementary Table 2. Model fit indices in Group-based Trajectory Modelling. The model that fulfilled the criteria of adequate fit is highlighted in bold.

Number of trajectories	Trajectory shapes	BIC ^a
1	1 cubic term	6046.403
2	2 cubic terms	5727.787
3	1 linear term, 2 constant terms	5723.059
4	1 quadratic term, 2 linear terms, 1 constant term	5678.253
5	1 cubic term, 2 quadratic terms, 1 linear term, 1 constant term	5696.742
6	2 quadratic terms, 3 linear terms, 1 constant term	5694.287
7	1 cubic term, 2 linear terms, 4 constant terms	5712.490

BIC, Bayesian Information Criteria.

^a A model is considered to have adequate fit if it has BIC which is lesser by at least 10 points compared to the other available models.

Supplementary Table 3. Multivariate analysis of prenatal risk factors, postnatal environmental factors and comorbidities associated with rhinitis trajectories profiles

	ETR		LTR		PR	
	adj OR (95% CI)	adj P value	adj OR (95% CI)	adj P value	adj OR (95% CI)	adj P value
<u>Risk factors</u>						
Male	1.4 (0.7-2.6)	0.35	1.3 (0.8-2.4)	0.32	2.3 (1.1-4.5)	0.02*
Female (ref)						
Malay	2.3 (1-5.6)	0.054	1.2 (0.6-2.6)	0.58	1.3 (0.6-3)	0.54
Indian	2.2 (1-4.9)*	0.04*	1 (0.5-2.1)	0.97	0.9 (0.4-2.1)	0.82
Chinese (ref)						
Caesarean Section						
Vaginal delivery (ref)	1 (0.5-2.1)	0.9	0.9 (0.5-1.7)	0.83	0.7 (0.3-1.4)	0.28
Presence of sibling	2.2 (1-4.6)*	0.04*	1.2 (0.7-2.3)	0.48	0.7 (0.4-1.3)	0.24
No (ref)						
Maternal tertiary education	0.8 (0.4-1.6)	0.5	2 (1-4.1)*	0.03*	1.9 (0.9-4.2)	0.1
No (ref)						
Paternal family history of allergy	1.2 (0.5-2.5)	0.71	1.1 (0.6-2.2)	0.76	2.3 (1.1-4.4)*	0.02*
No (ref)						
Maternal family history of allergy	1.7 (0.8-3.4)	0.16	1.1 (0.6-2.3)	0.72	2.5 (1.3-5)*	0.01*
No (ref)						
Maternal cotinine level during pregnancy						
High (14 ng/ml or more)	3 (0.8-10.9)	0.1	5.3 (1.5-19.4)*	0.01*	Nil	Nil
Low (0.17 to 13.99 ng/ml)	1.2 (0.5-3)	0.71	2 (0.9-4.7)	0.07	1.1 (0.4-3)	0.91
Negative(less than 0.17 ng/ml)						
<u>Postnatal environmental factors</u>						
Pet ownership in first year of life	2.1 (0.2-23)	0.55	2.1 (0.6-7.6)	0.24	0.7 (0.1-6.6)	0.73
No (ref)						

Childcare attendance in first year of life	17.7 (3.6-87.6)*	<0.001*	1.8 (0.6-5.5)	0.31	3.3 (0.9-11.9)	0.07
No (ref)						
Smoking exposure in first year of life	1.6 (0.2-13.3)	0.68	2.3 (0.5-11.2)	0.32	2 (0.1-28.9)	0.61
No (ref)						
Associated atopic comorbidities						
Wheezing (6 mth)	2.4 (0.4-13.5)	0.33	2.5 (0.6-10.9)	0.22	1.1 (0.1-10.5)	0.96
Wheezing (12 mth)	4.4 (1.6-12)*	<0.001*	2.5 (0.9-7)	0.09	1.5 (0.4-6)	0.56
Wheezing (18 mth)	4.9 (2.1-11.5)*	<0.001*	2.2 (0.9-5.3)	0.07	1.5 (0.4-5)	0.51
Wheezing (36 mth)	3.2 (1.5-7.1)*	<0.001*	2.4 (1.2-4.8)*	0.02*	1.4 (0.5-3.4)	0.5
Wheezing (72 mth)	1.8 (0.8-4.3)	0.17	2.5 (1.2-5.2)*	0.02*	1.1 (0.4-3.1)	0.8
-						
Eczema (6 mth)	2.2 (0.7-6.6)	0.16	2.1 (0.8-5.5)	0.15	3.6 (1.3-9.7)*	0.01*
Eczema (12 mth)	3.1 (1.2-8.0)*	0.02*	2.0 (0.8-4.6)	0.12	3.3 (1.3-8.2)*	0.01*
Eczema (18 mth)	1.9 (0.7-4.8)	0.18	1.3 (0.6-3.1)	0.49	2.3 (0.9-6)	0.08
Eczema (36 mth)	2.4 (1-5.6)*	0.04*	1.6 (0.8-3.3)	0.22	3.1 (1.4-6.9)*	0.01*
Eczema (72 mth)	2.2 (0.9-5.7)	0.1	1.9 (0.9-4.3)	0.11	3.9 (1.4-11.1)*	0.01*
Allergen sensitization (18 mth)	0.8 (0.3-2.5)	0.73	1.2 (0.5-3.2)	0.65	2.5 (0.9-6.8)	0.08
Allergen sensitization (36 mth)	0.4 (0.2-1.2)	0.11	0.8 (0.4-1.8)	0.59	2.2 (1-5)	0.06
Allergen sensitization (60 mth)	0.7 (0.3-1.9)	0.52	0.5 (0.2-1.2)	0.12	4.3 (1.4-13.7)*	0.01*
HDM sensitization (18 mth)	0.4 (0.1-1.7)	0.19	1.3(0.5-3.7)	0.56	2.8 (0.9-8)	0.06
HDM sensitization (36 mth)	0.4 (0.1-1.0)	0.06	0.8 (0.4-1.8)	0.59	2.4 (1.1-5.4)*	0.04*
HDM sensitization (60 mth)	0.7 90.3-1.6)	0.35	0.6 (0.3-1.3)	0.2	3.1 91.3-7.4)*	0.01*

* Significant at p value <0.05 compared to non-rhinitis/control group

ETR: Early Transient Rhinitis; LTR: Late Transient Rhinitis; PR: Persistent Rhinitis HDM: House dust mite

Supplementary Table 4. Sensitivity Analysis for multivariate analysis of risk factors and comorbidities associated with rhinitis trajectories profiles, among subjects with complete data on rhinitis over all 12 time-points (n=470)

	ETR		LTR		PR	
	adj OR (95% CI)	adj P value	adj OR (95% CI)	adj P value	adj OR (95% CI)	adj P value
<u>Risk factors</u>						
Male	0.7 (0.3-1.6)	0.4	0.6 (0.3-1.2)	0.16	0.3 (0.1-0.9)	0.02*[#]
Female (ref)						
Malay	2.0 (0.6-6.3)	0.25	1.2 (0.5-3)	0.73	1.0 (0.3-4.0)	0.98
Indian	1.5 (0.6-4.2)	0.41 [#]	1.1 (0.4-2.6)	0.90	2.3 (0.8-6.6)	0.13
Chinese (ref)						
Caesarean Section	0.7 (0.3-1.8)	0.48	1.0 (0.5-2.1)	0.99	0.5 (0.2-1.3)	0.147
Vaginal delivery (ref)						
Presence of sibling	1.9 (0.7-5.3)	0.19 [#]	1.4 (0.7-2.8)	0.41	0.9 (0.4-2.3)	0.86
No (ref)						
Maternal tertiary education	0.8 (0.3-2.0)	0.6	1.8 (0.8-4.3)	0.64 [#]	2.6 (0.9-8.0)	0.071
No (ref)						
Paternal family history of allergy	1.4 (0.5-3.8)	0.48	0.9 (0.4-2.2)	0.94	1.7 (0.6-4.5)	0.30 [#]
No (ref)						
Maternal	1.9 (0.8-4.6)	0.17	1.2 (0.5-2.8)	0.64	2.3 (0.9-5.7)	0.07 [#]

family history of allergy						
No (ref)						
Maternal cotinine level during pregnancy						
High (14 ng/ml or more)	5.1 (1.0-25.2)	0.046*	1.8 (0.2-17.0)	0.60 [#]	Nil	Nil
Low (0.17 to 13.99 ng/ml)	1.9 (0.6-6.0)	0.289	2.9 (1.2-7.2)	0.02*	1.1 (0.3-4.6)	0.85
Negative(less than 0.17 ng/ml) (ref)						
<u>Postnatal environmental factors</u>						
Pet ownership in first year of life	2.4 (0.2-28.0)	0.48	3.0 (0.7-12.0)	0.12	0.9 (0.1-10.9)	0.95
No (ref)						
Childcare attendance in first year of life	20.1 (3.3-123.9)	0.001*[#]	2.7 (0.8-9.2)	0.12	4.3 (0.8-23.2)	0.09
No (ref)						
Smoking exposure in first year of life	4.6 (0.4-50.0)	0.21	3.5 (0.6-8.6)	0.21	4.4 (0.3-77.0)	0.31
No (ref)						
<u>Associated atopic comorbidities</u>						
Wheezing (6 mth)	NA	NA	2.4 (0.4-14.0)	0.31	1.0 (0.1-11.6)	0.98
Wheezing (12 mth)	5.2 (1.5-18.2)	0.01*[#]	2.7 (0.8-9.4)	0.12	0.8 (0.1-7.1)	0.82
Wheezing (18 mth)	5.6 (1.7-18.1)	0.004*[#]	3.0 (1.0-8.7)	0.044*	1.1 (0.2-6.1)	0.88
Wheezing (36 mth)	2.6 (0.9-7.8)	0.08 [#]	2.4 (1.0-5.6)	0.054 [#]	1.2 (0.4-4.3)	0.73
Wheezing (72 mth)	1.8 (0.8-4.3)	0.17	2.5 (1.2-5.3)	0.02*[#]	1.1 (0.4-3.1)	0.81
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Eczema(6 mth)	0.8 (0.2-3.7)	0.74	0.6 (0.2 - 2.1)	0.45	0.2 (0.1-0.5)	0.001*[#]
Eczema(12 mth)	0.5 (0.1-1.6)	0.24 [#]	0.7 (0.3-2.0)	0.53	0.3 (0.1-0.7)	0.011*[#]
Eczema(18 mth)	1.0 (0.3-3.4)	0.999	0.9 (0.4-2.5)	0.90	2.9 (1.0-8.5)	0.049*

mth)						
Eczema(36 mth)	2.1 (0.7-5.9)	0.18 [#]	1.4 (0.6-3.5)	0.43	4.6 (1.6-13.0)	0.005*[#]
Eczema(72 mth)	2.2 (0.9-5.7)	0.10	1.9 (0.9-4.3)	0.11	3.9 (1.4-11.1)	0.009*[#]
Allergen sensitization(18 mth)	1.0 (0.3-4.0)	0.97	1.3 (0.5-3.6)	0.65	2.6 (0.9-8.4)	0.1
Allergen sensitization(36 mth)	0.4 (0.1-1.6)	0.21	1.0 (0.4-2.5)	0.98	2.4 (0.8-7.0)	0.11
Allergen sensitization(60 mth)	0.7 (0.2-1.8)	0.43	0.7 (0.3-1.5)	0.34	3.5 (1.1-11.3)	0.04*[#]
HDM sensitization(18 mth)	2.8 (0.6-13.0)	0.19	0.7 (0.3-2.0)	0.57	0.4 (0.1-1.1)	0.06
HDM sensitization(36 mth)	2.8 (1.0-8.2)	0.06	1.2 (0.6-2.7)	0.60	0.4 (0.2-1.0)	0.04*[#]
HDM sensitization(60 mth)	1.5 (0.6-3.6)	0.35	1.7 (0.8-3.7)	0.20	0.3 (0.1-0.8)	0.01*[#]

[#] Significant at p value <0.05 compared to non-rhinitis/control group in the original analysis

* and bolded text : Significant at p value <0.05 compared to r non-rhinitis/control group in the sensitivity analysis, for subjects with no missing data across all 12 time-points.

ETR: Early Transient Rhinitis; LTR: Late Transient Rhinitis; PR: Persistent Rhinitis HDM: House dust mite

