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LETTER TO THE EDITOR

WILEY

Transitions between alternating childhood allergy sensitization and current asthma states: A retrospective cohort analysis

To The Editor:

Our recent findings show that childhood asthma risk may be modified by age and multiplicity of allergy sensitization[1]; this suggests current asthma risk may be transient as a child grows older. However, allergy sensitization is neither a necessary nor sufficient precursor of childhood asthma even in the context of a parental history of allergies or asthma.[2–6] Indeed, allergy sensitization and current asthma may evolve contemporaneously[7,8] and yet are often examined based on unrealistic simplifying assumptions in univariate and unidirectional risk-outcome analyses.[6,8] A better characterization of allergy sensitization and current asthma transitions is critical to a better understanding of the 'atopic march' needed to inform management of childhood asthma.

In clinical practice, allergy sensitization is used to inform the start or end of allergy management or prophylaxis, risk stratification as well as monitoring treatment response.[9] Allergy sensitization is also used for prediction of asthma disease onset[10] but this association may be modified by preventive intervention (e.g., tobacco smoking cessation, breastfeeding, allergen avoidance)[11] and eczema[12] during early childhood. However, there is a paucity of research on the utility of allergy sensitization as a marker of allergic asthma state transitions in populations at high genetic risk. For potentially sequential and correlated outcomes (i.e., allergy sensitization and current asthma), a multi-state Markov (MSM) modeling[13] approach can be used to describe and quantify the propensity of transitions between known states. The ability of the MSM approach to mimic contemporaneously evolving allergy sensitization and current asthma states allows for a more realistic and accurate representation of case profiles as seen in clinical practice. Quantifying the transition probabilities between detectable disease states (or stages) among high-risk children can add great value to understanding and informing preventive intervention and management of allergy-mediated asthma disease.

Our study objective was to use an MSM approach to determine the propensity of changes between allergy sensitization and current asthma states among children at high genetic risk of asthma including the extent to which primary preventive intervention and early-life eczema may impact these transitions.

1 | METHODS

This study utilized data from the Canadian Asthma Primary Prevention Study (CAPPS), a multifaceted prenatal intervention among children with an immediate family history of asthma or with two first-degree relatives with classical IgE-mediated allergy, followed from birth to 15 years.[11] Briefly, mothers were recruited during the third trimester of pregnancy and randomized to a multifaceted intervention or usual care recommended by their physician (control). CAPPS intervention measures implemented during the third trimester and first postpartum year included avoidance of house dust, pets, and environmental tobacco smoke and encouragement of exclusive breastfeeding with delayed introduction of solid foods.

Diagnoses of current asthma at 1, 2, 7, and 15 years and eczema (atopic dermatitis) during the 1st year were based on the research study pediatric allergist's clinical decision independent of primary-care providers. The presence of asthma-like symptoms during year 1 and 2 is referred to cautiously as "probable' or "possible" current asthma in full recognition of the likelihood of differential diagnoses, challenges associated with lung function assessment, and the lack of a gold standard protocol for a current asthma diagnosis during early childhood. Similar to previous studies[1,11,14] and for simplicity, we analyze asthma-like symptoms identified during early childhood (1–2 years) as "current asthma" because it is clinically different than disease states with or without allergy sensitization. Asthma treatment referrals were made for all cases identified based on existing guidelines during the CAPPS study. Allergy sensitization (i.e., a *positive* skin prick test) was examined for common aeroallergens and food allergens.[11] We define asthma remission as the absence of a current asthma diagnosis. Only children who had at least one skin prick test and current asthma assessment were included in our analysis.

Based on allergy sensitization and current asthma status at each assessment timepoint, children were classified into four mutually exclusive transition states: no positive skin prick tests for allergy sensitization and no current asthma diagnosis – state I, one positive skin-prick test result but no current asthma – state II, more than one positive skin-prick test result but no current asthma – state III, and

current asthma with or without allergy sensitization – state IV. We assume that some disease states may not be observable because state I to IV are based on pre-determined assessment time-points.

The probability (prevalence) of transition states was summarized by age within strata defined by sex, CAPPS intervention, and first-year eczema diagnosis. Repeated measures ordinal logistic regression using a generalized estimating equations approach with a first-order autoregressive correlation matrix (repolr R package) was used to examine between and within group changes in transition states with increasing age adjusted for differences in sex, CAPPS intervention and eczema. Statistical interaction terms were explored to examine whether state transitions differed by sex, CAPPS intervention, or eczema grouping.

A four-state (state I to IV) alternating MSM model (msm R package) was used to estimate transition probabilities and ratios between allergy sensitization and current asthma states adjusted for asthma treatment exposures. We also examined potential effect modification and confounding by sex, CAPPS intervention, and early-life eczema, established asthma risk factors, on transition probabilities/ratios. A time-inhomogeneous model (turning point defined at ±2 years) was used to calculate transition probabilities and duration of each state because immaturity of the immune system in early childhood (0–2 years) can contribute to failure of tolerance induction and higher risk of allergic disease.

Mean values generated from a multivariate imputed chained equations (MICE) approach[15] with 10 replications using all study data were used as replacement values for missing data on allergy sensitization and current asthma status.

2 | RESULTS

Study participants' demographic and clinical profiles are summarized elsewhere.[11] Our analytic sample included 493 children (94% of the full CAPPS study sample) who had at least one skin-prick test and current asthma assessment. In this sample, 52% of the children were male, 51% were assigned to the CAPPS intervention, and the prevalence of eczema in the 1st year of life was 9.5%. Less than 10% of these 493 children had missing allergy sensitization/asthma assessments at the 1-, 2-, 7-, and 15 years assessments; missing data were replaced by mean values using the MICE approach.

Our transition model had four bidirectional states (Figure 1A): I) no allergy sensitization/no current asthma, II) one allergy sensitization/no current asthma, III) multiple allergy sensitization /no current asthma, and IV) a current asthma diagnosis (with or without allergy sensitization) that showed good fit to our data (Figure 1B). The duration of each state was not different ($p > .05$) between sex, CAPPS intervention (versus control) and eczema strata (yes/no) but there was larger variance in the CAPPS control group. Table 1 summarizes the age-specific prevalence of each transition state during the 15 years follow-up period.

Our repeated measures ordinal logistic regression model results (Table 1) showed that the prevalence of transition states changed with older age ($p < .01$); the prevalence of state I decreased with older age while that of state III increased with older age (linear trend: $p < .01$). Overall, within-group changes in transition states were statistically significant for strata groups defined by sex, CAPPS intervention, and early-life eczema ($p < .01$). The age-specific prevalence of transition states differed between groups defined by sex ($p < .01$) and early eczema ($p < .01$) but not by the CAPPS intervention group ($p = .58$).

Figure 2A shows that 11%, 18% and 17% of the children transitioned from state I to IV (i.e., disease progression) after the 1st, 2nd, and 7th year of follow-up, respectively. Adjusted for sex, age, CAPPS intervention and early-life eczema, transition to state IV was more likely from state II (adjusted transition ratio [aTR]: 3.14; 95%CI: 1.33, 7.41) and III (aTR: 2.89; 95%CI: 1.50, 5.59) than state I.

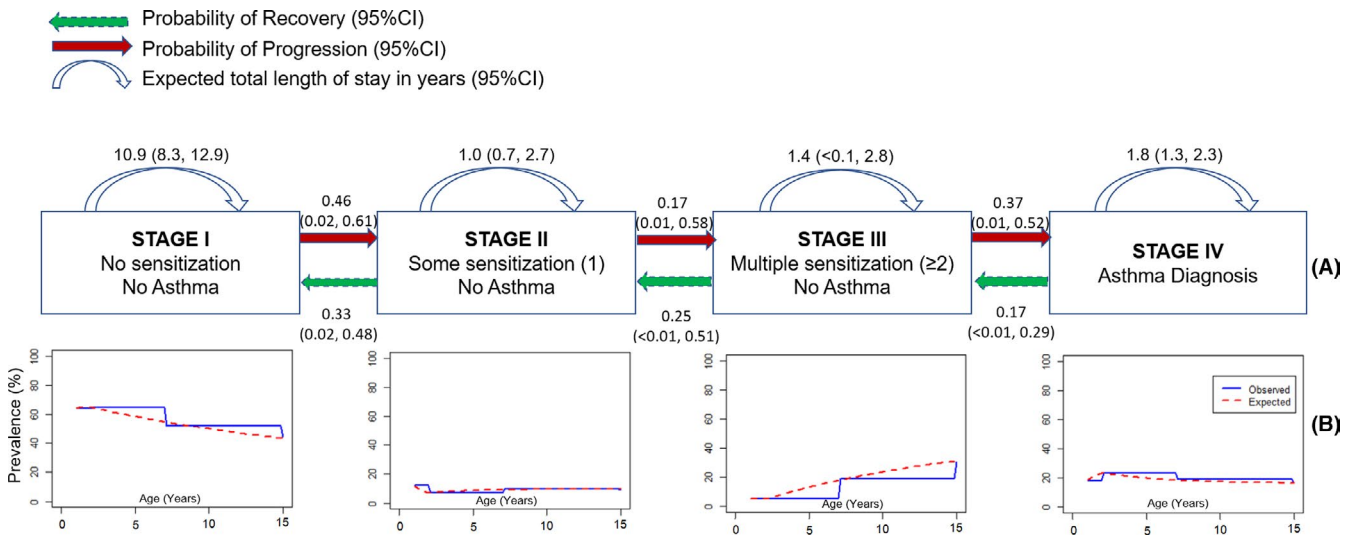

FIGURE 1 Summary of an Alternating Four-State Transition Model of Childhood Allergy Sensitization and Current Asthma Status. Progression (solid red arrows), Recovery (green dashed arrows), and expected total length of stay in each transition state (blue arrows). A. Multistate transition model. B. Goodness of fit model (observed versus model predicted prevalence of each transition state over time)

TABLE 1 Prevalence of allergy sensitization and current asthma transition states by age, sex, CAPPS intervention, and 1st year eczema diagnosis ($N = 493$)

	N (prevalence, %)				
Age in years	**1**	**2**	**7**	**15**	***p* value[a]**
Overall					<.0001
No sensitization/ no asthma (State I)	316 (64%)	319 (65%)	254 (52%)	215 (44%)	
Some sensitizations/ no asthma (State II)	61 (12%)	34 (6.9%)	48 (9.7%)	44 (8.9%)	
Multiple sensitization/ no asthma (State III)	27 (5.5%)	24 (4.9%)	93 (19%)	149 (30%)	
Asthma (State IV)	89 (18%)	116 (24%)	98 (20%)	85 (17%)	
Sex					.0019[b]
Male ($n = 238$)					<.0001[c]
State I	157(66%)	167 (70%)	143 (60%)	115 (48%)	
State II	31 (13%)	13 (5.5%)	27 (11%)	20 (8.4%)	
State III	11 (4.6%)	12 (5.0%)	35 (15%)	65 (27%)	
State IV	39 (16%)	46 (19%)	33 (14%)	38 (16%)	
Female ($n = 255$)					<.0001[c]
State I	159 (62%)	152 (60%)	111 (44%)	100 (39%)	
State II	30 (12%)	21 (8.2%)	21 (8.2%)	24 (9.4%)	
State III	16 (6.3%)	12 (4.7%)	58 (23%)	84 (33%)	
State IV	50 (20%)	70 (27%)	65 (25%)	47 (18%)	
CAPPS intervention					.5779[b]
Intervention ($n = 253$)					<.0001[c]
State I	166 (66%)	168 (66%)	122 (48%)	102 (40%)	
State II	30 (12%)	20 (7.9%)	33 (13%)	27 (11%)	
State III	18 (7.1%)	16 (6.3%)	55 (22%)	86 (34%)	
State IV	39 (15%)	49 (19%)	43 (17%)	38 (15%)	
Control ($n = 240$)					.0004[c]
State I	150 (62%)	151 (63%)	132 (55%)	113 (47%)	
State II	31 (13%)	14 (5.8%)	15 (6.2%)	17 (7.1%)	
State III	9 (3.8%)	8 (3.3%)	38 (16%)	63 (26%)	
State IV	50 (21%)	67 (28%)	55 (23%)	47 (20%)	
1st year eczema					<.0001[b]
Yes ($n = 47$)					.0011[c]
State I	18 (38%)	14 (30%)	12 (26%)	7 (15%)	
State II	13 (28%)	10 (21%)	9 (19%)	5 (11%)	
State III	6 (13%)	7 (15%)	8 (17%)	17 (36%)	
State IV	10 (21%)	16 (34%)	18 (38%)	18 (38%)	
No ($n = 446$)					<.0001[c]
State I	298 (67%)	305 (68%)	242 (54%)	208 (47%)	
State II	48 (11%)	24 (5.4%)	39 (8.7%)	39 (8.7%)	
State III	21 (4.7%)	17 (3.8%)	85 (19%)	132 (30%)	
State IV	79 (18%)	100 (22%)	80 (18%)	67 (15%)	

[a]Repeated measures ordinal logistic regression using a generalized estimating equations approach with a first-order autoregressive correlation matrix adjusted for all covariates examined.

[b]Between-group changes in transition states (group x year – interaction term).

[c]Within-group changes in transition states.

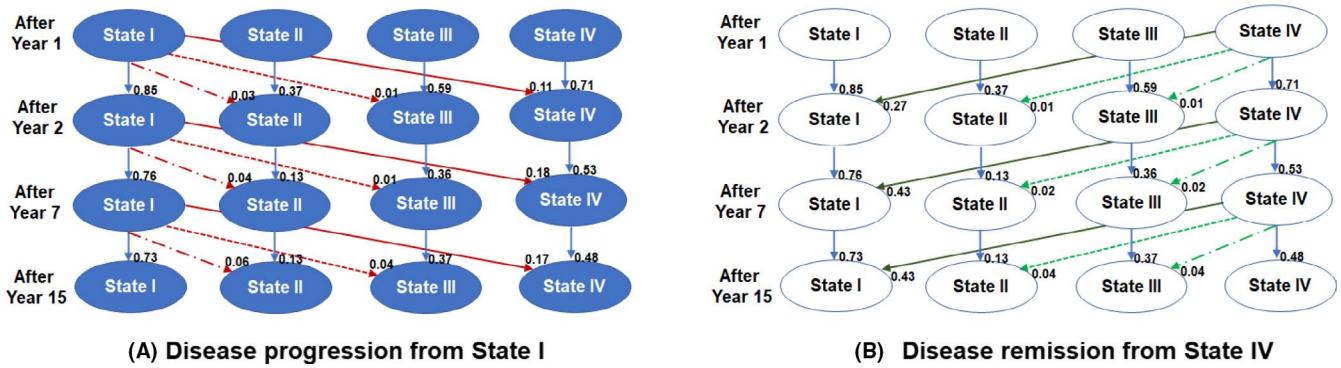

FIGURE 2 Transition probabilities between allergy sensitization and current asthma states among children at high–genetic risk of asthma ($N = 493$). The study cohort is redistributed across allergy sensitization and current asthma transition states after each assessment cycle (year of assessment). Children start at different states, and they can progress (A) or regress (B) to other transition states

Conversely, regression to a previous state was more likely than progression from state II (aTR 3.47; 95%CI: 2.01, 5.99) but less likely from state III (aTR: 0.19; 95%CI: 0.07, 0.50) or IV (aTR: 0.33; 95%CI: 0.13, 0.81) adjusted for sex, age, CAPPS intervention and early eczema. Figure 2B shows that 27%, 43% and 43% of the children transitioned from state IV to I (i.e., remission) after the 1st, 2nd, and 7th year of follow-up, respectively. Transition from state IV to state I was modified by CAPPS intervention and early-life eczema (interaction terms: $p < .01$). The transition ratio was higher among children in the CAPPS intervention (aTR: 3.89; 95%CI: 2.05, 7.39) than control (aTR: 2.11; 95%CI: 1.19, 3.73) group adjusted for sex, age, and early-life eczema. Remission was also two-fold higher among children without eczema (aTR: 2.11; 95%CI: 1.19, 3.73) but not children diagnosed with eczema (aTR: 0.45; 95%CI: 0.10, 2.09) adjusted for sex, age, and CAPP intervention.

3 | DISCUSSION

Our findings show that among children at genetically high-risk, allergy sensitization to current asthma states are reversible, but remission is less likely among children with multiple allergy sensitization and a history of eczema (atopic dermatitis). Early-life primary prevention efforts (i.e., CAPPS intervention) are associated with a higher propensity of current asthma remission.

Independently, the risk of asthma disease progression[4–8] or remission[9] has been examined in previous unidirectional analyses. Consistent with our findings, the risk of childhood asthma differs by sex,[16,17] atopy,[1,3,6,12] and early-life allergy sensitization.[1,8,12] Conversely, remission due to treatment has been shown to have substantial variability for children with allergic versus non-allergic asthma.[9] This is underscored in our results by both the persistence and the regression from state IV (i.e., current asthma) as a child grows older. Our MSM results are consistent with previous generalized linear mixed model (GLMM) analyses that showed that CAPPS intervention was associated with lower risk of current asthma at 7 years.[11] However, it is important to note, that the GLMM approach is a unidirectional approach (i.e., asthma risk but not remission was examined). Our current MSM analysis explores both asthma risk and remission in the same study sample – a clinically important distinction that has not been previously examined among children at genetically high risk of asthma.

To our knowledge, this is the first study that examines the bidirectional relationship between allergy sensitization and current asthma states including an estimate of the duration of each transient state. The probability of asthma disease progression and remission is critical to inference about risk prediction and treatment response. For clinicians, this knowledge can aid patient communication regarding the need for preventive intervention and the promotion of treatment compliance. Existing literature based on unidirectional statistical assumptions that examine childhood allergy-asthma risk separately often as uncorrelated endpoints[4,5,8,16,17] cannot be used for joint inference regarding these dual and complimentary objectives of asthma disease management.

Our findings provide evidence of a higher propensity for asthma remission among 'at-risk' children targeted by primary prevention efforts (i.e., allergen avoidance); this lends credence to existing prevention recommendations[2] despite null findings for curtailing disease progression. These findings are consistent with previous research[4,5,8,12,16,17] that suggest during early life immature mucosal defenses permit the increased absorption of allergens, which then act on an immature immune system. Consequently, allergy-prone children may first present with IgE-mediated disease. However, when such early-life perturbations are avoided, as children grow older, they build resilience demonstrated in our results by the increased propensity for asthma remission among children without a diagnosis of early-life eczema.

Study limitations include incomplete observation of all allergy sensitization and current asthma states because our analysis is based on pre-determined assessment time-points. The likelihood of treatment heterogeneity (due to differences in prescribed asthma/allergy medications and adherence) was not assessed; this may have contributed to residual confounding of transition ratios. Exclusion of children without any skin-prick tests or current asthma assessments

may have inadvertently led to an overestimation of transition probabilities to allergy-asthma states (selection bias) if such children had low risk of allergies or asthma. Additionally, the potential for allergy sensitization/current asthma-related misclassification bias especially during early childhood cannot be ruled out because associated diagnostic testing is not 100% accurate.[14,18]

In conclusion, our findings support the notion that preventive interventions that emphasize allergen avoidance as the cornerstone in the prevention and management of respiratory allergies, if instituted early among high-risk children, may decrease the risk of allergic sensitization, asthma disease progression, and, more importantly, increase the likelihood of asthma disease remission as a child grows older.

KEYWORDS

allergies, childhood asthma, multi-state transitions, remission, risk

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AUTHOR CONTRIBUTION

Arthur Hamie Owora: Conceptualization (lead); Formal analysis (lead); Funding acquisition (lead); Investigation (lead); Methodology (lead); Writing – original draft (lead); Writing – review & editing (lead). **Robert S Tepper:** Writing – review & editing (supporting). **Clare Ramsey:** Writing – review & editing (supporting). **Wade WATSON:** Writing – review & editing (supporting). **Moira CHAN-YEUNG:** Writing – review & editing (supporting). **Allan Becker:** Conceptualization (supporting); Writing – review & editing (supporting).

PEER REVIEW

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