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Wheeze trajectories are modifiable through early-life intervention and predict asthma in adolescence

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Abstract

Background: The objectives of this study were to identify developmental trajectories of wheezing using data-driven methodology, and to examine whether trajectory membership differentially impacts the effectiveness of primary preventive efforts that target modifiable asthma risk factors.

Methods: Secondary analysis of the Canadian Asthma Primary Prevention Study, a multifaceted prenatal intervention among children at high risk of asthma, followed from birth to 15 years. Wheezing trajectories were identified by latent class growth analysis. Predictors, intervention effects, and asthma diagnoses were examined between and within trajectory groups.

Results: Among 525 children, 3 wheeze trajectory groups were identified: Low-Progressive (365, 69%), Early-Transient (52, 10%), and Early-Persistent (108, 21%). The study intervention was associated with lower odds of Early-Transient and Early-Persistent wheezing ($P < .01$). Other predictors of wheeze trajectories included, maternal asthma, maternal education, city of residence, breastfeeding, household pets, infant sex and atopy at 12 months. The odds of an asthma diagnosis were three-fold to six-fold higher in the Early-Persistent vs Low-Progressive group at all follow-up assessments ($P = .03$), whereas Early-Transient wheezing (limited to the first year) was not associated with asthma. In the Early-Persistent group, the odds of wheezing were lower among intervention than control children (adjusted odds ratio: 0.67; 95% CI: 0.48; 0.93) at 7 years.

Conclusions: Using data-driven methodology, children can be classified into clinically meaningful wheeze trajectory groups that appear to be programmed by modifiable and non-modifiable factors, and are useful for predicting asthma risk. Early-life interventions can alter some wheeze trajectories (ie, Early-Persistent) in infancy and reduce wheezing prevalence in mid-childhood.

KEYWORDS
childhood asthma, latent class, phenotype, primary prevention, wheezing

1 | INTRODUCTION

Evidence on the clinical relevance of early-life wheeze trajectories is growing, but findings remain contradictory, particularly on the interplay between associated risk factors and implications for asthma development.[1] Our understanding of disease etiology is complicated by the mixed results on wheeze trajectory risk factors and their ability to predict asthma.[2-7] This is partly due to the differences in the

2 methods (ie, investigator-defined[2,4,8] and data-driven methodology[3,5-7,9,10]) often used to identify and define wheeze trajectories during childhood through to adulthood.

Using investigator-defined methodology, the Tucson Children's Respiratory Study (TCRS)[4] proposed 4 clinically distinct wheezing trajectories ("never," "early-transient," "late-onset," and "persistent" wheezing from birth to 6 years). Additional studies[2,8] have applied similar descriptions and linked them to clinical outcomes such as lung function,[2,8] atopy,[2,8] bronchial responsiveness,[2,8] and viral respiratory tract infections[2] throughout childhood and adolescence.

Using data-driven methodology, the Columbia Center for Children's Environmental Health study (CCCEH)[3] identified similar trajectory groups as the TCRS study. However, other cohort studies have yielded larger numbers and different shapes of trajectory groups using different data-driven methods: cluster analysis,[11] factor analysis,[9,10,12] and latent class-based methods.[3,5-7] The latent class-based methods, in particular, model wheeze history to determine the number and shape of trajectory groups without making subjective assumptions about defining features.

The use of different methodologies across studies has likely influenced the identification of trajectory-associated risk factors (eg, smoking was a risk factor for Early-Transient wheezing in TCRS[4] but not CCCEH[3]). Whether these discrepancies persist when the aforementioned methodologies are applied in the same study population is yet to be examined. Moreover, little is known about whether belonging to a particular wheeze trajectory group differentially impacts the effectiveness of primary preventive efforts that target modifiable asthma risk factors.

We recently applied the investigator-defined TCRS trajectories to our Canadian Asthma Primary Prevention Study (CAPPS) of children at high genetic risk of asthma, finding significant associations with respiratory health in adolescence.[2] A child's sex, city of residence, exclusive breastfeeding duration, and atopy during infancy predicted wheeze trajectory group membership ($P < .05$). In the same study population, we now apply a data-driven latent class growth analysis approach to identify wheeze trajectories and explore their association with suspected etiologic factors and asthma diagnoses over time, from birth through 15 years of age. We hypothesize that the number and shapes of latent trajectories in a high-risk population are different from that identified in a general population of children. We also hypothesize that the CAPPS intervention effect on wheezing and asthma differs by trajectory group.

2 | METHODS

2.1 | Study population

We performed a secondary analysis of data from the CAPPS study, which has been described previously.[13] Briefly, 545 mothers from 2 centers (Winnipeg and Vancouver) were recruited in 1995 during the third trimester of pregnancy and randomized to a multifaceted intervention or usual care recommended by their physician (control). After delivery, we followed their children until their 15th birthday or until the family was lost to follow-up. All participants had an immediate family history of asthma or 2-first-degree relatives with classical IgE-mediated allergy. Intervention measures implemented during the third trimester and first post-partum year included avoidance of house dust, pets, and environmental tobacco smoke and encouragement of exclusive breastfeeding with delayed introduction of solid foods. Intervention compliance is discussed in previous papers;[13-15] briefly, the CAPPS intervention was successful in (i) reducing exposure to mite allergen levels by encasement of mattresses and pillows, (ii) increasing duration of breastfeeding, and (iii) reducing daycare enrollment rates. However, there was poor compliance with pet removal. We did not account for the intervention exposures later in childhood because our study focused on prenatal and early postnatal life as the critical period of exposure for childhood asthma pathogenesis.[13-15] Ethics committees at the University of British Columbia and the University of Manitoba approved the study, and parents provided written consent.

2.2 | Wheezing and asthma outcome assessment

Briefly, wheezing was reported by parents at ages 2 weeks, 4, 8, 12, 18, 24 months, and 7 years, and by children at age 15 years. A modified version of the International Study of Asthma and Allergy in Childhood questionnaire[16] was used, capturing "any wheezing episodes" from birth to 24 months, and "wheezing or whistling in the chest" at 7 and 15 years. A pediatric allergist or respirologist (blinded to participant intervention group assignment and healthcare services) conducted structured interviews with parents to record symptoms and physical findings of each child. Spirometry and methacholine challenge (PC20 cutoff <8 mg/mL) testing at 7 and 15 years were performed at the 7th- and 15th-year follow-up. We operationally defined asthma and atopic disorders based on these clinical diagnoses at the 1st-, 2nd-, 7th- and 15th-year follow-up.[13-15] Diagnoses were based on symptoms of wheeze and cough, use of medications, and physical findings without knowledge of the results of allergy skin tests.

2.3 | Risk factors

The presence or absence of suspected childhood asthma risk factors was determined from questionnaires; these included the following: maternal race (White or not), maternal asthma, maternal atopy, postsecondary education, birth order (firstborn or not), child's sex and birth mode (cesarean or vaginal), smoking or pets in the home at the time of birth, exclusive breastfeeding (≥4 months), and daycare attendance (at 24 months). Child atopy was determined based on an epicutaneous skin test at 12 and 24 months.[15]

2.4 | Statistical analysis

Latent class growth analysis (LCGA)[17] was used to identify trajectories of wheeze symptoms and associated risk factors among children from birth through to 15 years. Final model selection

involved an iterative estimation of (i) the number of trajectory groups and (ii) the shape of each trajectory group using both statistical[18] (Bayesian information criteria [BIC], Akaike's information criteria [AIC] and entropy) and non-statistical considerations (reasonable group sizes with non-overlapping posterior probability confidence intervals).[19]

Multinomial logistic regression was used to evaluate potential predictors of wheeze trajectories by estimating the probability of belonging to each group depending on participant characteristics. A 6-step directed acyclic graph (DAG)[20] approach was used to control for confounding (Figure S1).

Generalized linear mixed models (GLMM)[21] were used to examine whether (i) intervention effect varied between and within trajectory groups, and (ii) group membership predicted future asthma diagnosis.

All statistical models adjusted for missing data bias under the assumption that data were missing at random[22] using a full information maximum-likelihood (FIML)–based approach.[23] Sensitivity LCGA and GLMM analyses examining subjects with at least 2, 3, or 4 wheezing/asthma assessments were not different; therefore, only FIML results involving participants with at least 2 wheezing/asthma assessments are presented for conciseness. Four-trajectory group model results are provided in our Supporting Information for interested readers. All statistical analyses were implemented using SAS 9.4 (SAS Institute Inc., Cary, North Carolina); TRAJ procedure was used for LCGA.[24]

3 | RESULTS

3.1 | Wheezing and asthma prevalence

Overall, 525 mothers completed at least 2 wheeze questionnaires during follow-up; 51% were randomly assigned to the intervention group during pregnancy. The prevalence of wheezing differed by intervention group, maternal asthma and education, child's sex, birth order, city of residence, household pets, and daycare attendance at different assessment time-points (Table 1). The prevalence of asthma at the 1st-, 2nd-, 7th- and 15th-year follow-up was 18% (N = 493), 23% (N = 476), 19% (N = 378), and 16% (N = 335), respectively. Comparisons between baseline characteristics and asthma diagnoses at the 1st-, 2nd-, and 7th-year asthma assessments have been summarized previously.[13-15]

3.2 | Latent wheezing trajectories

In LCGA analyses, a 3-trajectory group solution was found to be the most parsimonious model (Figure 1). This model had the lowest (best) BIC, AIC, and highest entropy based on sequential estimation involving 1-6 trajectory models. The 3 distinct wheeze trajectories were described as Low-Progressive (n = 365, 69%), Early-Transient (n = 52, 10%), and Early-Persistent (n = 108, 21%). In the Low-Progressive group, wheezing was infrequent (<5% probability) in the first 24 months and increased slowly over time to approximately 16% by age 15 years. For the Early-Transient group, wheezing probability peaked at 34% at 12 months and remained below 1% for the remainder of follow-up. The Early-Persistent group had a 58% prevalence of wheezing at 12 months, peaking at 63% at 24 months, and slightly declined to 50% at the 15th year. Table S1 summarizes the distribution of participant characteristics by wheeze trajectory group.

3.3 | Predictors of latent wheezing trajectories

Multivariable multinomial logistic regression results (Table 2) showed that the CAPPS intervention was associated with wheeze trajectory group membership ($P < .01$); children in the intervention group had lower odds of Early-Transient (adjusted odds ratio [aOR]: 0.58; 95% CI: 0.38, 0.89) and Early-Persistent (aOR: 0.46; 95% CI: 0.32, 0.68) than Low-Progressive group membership. In addition, modifiable factors targeted by the CAPPS intervention (household smoking, daycare attendance, breastfeeding, and household pets) as well as non-modifiable factors (child's sex, atopy at 12 months, maternal race, asthma, post-secondary education, and study site) were independent predictors of trajectory group membership ($P < .05$).

3.4 | Intervention effect on latent wheezing trajectories

Overall, GLMM results showed that the study intervention effect on wheezing did not vary between trajectory groups ($P = .16$). However, within the Early-Persistent group, the probability of wheezing at the 7th and 15th year was lower among intervention than control group children (Figure 2). The odds of wheezing were 54% lower among intervention than control children at 7 years (aOR: 0.46; 95% CI: 0.20, 0.98) after controlling for maternal race, asthma, post-secondary education, child's sex, and city of residence.

3.5 | Latent wheezing trajectories and clinical outcomes

The odds of an asthma diagnosis were three to six-fold higher in the Early-Persistent group compared with the Low-Progressive group at the 1st-, 2nd-, 7th-, and 15th-year follow-up assessments (Table 3). In contrast, Early-Transient wheezing was not associated with asthma diagnosis at any time point. Similarly, Early-Persistent (but not Early-Transient) wheezing was associated with higher odds of airway hyperresponsiveness at the 15th year (aOR: 1.91; 95% CI: 1.06, 3.45; Table 3). Mean forced expiratory volume in 1-second (FEV1) was 0.09 L lower in the Early-Persistent than Low-Progressive group at 7 years (95% CI: −0.15, −0.04) but was not different between groups at 15 years (Table 3). Early-Transient wheezing was not associated with FEV1.

4 | DISCUSSION

Our results using data-driven methodology in a population at high genetic risk of asthma have identified 3 distinct wheeze trajectory groups:

TABLE 1 Prevalence of wheezing at each assessment by participant characteristics

Characteristics (N per group)	Prevalence of Wheezing (%) by Assessment Month							
	0.5 months n = 520	4 n = 511	8 n = 504	12 n = 498	18 n = 505	24 n = 480	84 n = 472	180 n = 390
Overall	5	10	16	14	16	17	21	25
Study group								
Control (256)	5	11	15	15	18	18	**26***	26
Intervention (264)	6	10	17	13	14	17	**17**	23
Modifiable factors (targeted by the CAPPS intervention)								
Smokers in home								
Yes (119)	7	14	20	17	18	18	25	24
No (400)	5	9	15	13	15	17	20	25
Pets in home								
Yes (180)	**8***	11	19	15	15	17	24	26
No (339)	**4**	10	14	13	16	18	19	24
Exclusive breastfed (≥4 mo)								
Yes (185)	5	7	**11***	12	15	16	**16***	24
No (324)	5	12	**19**	15	16	18	**24**	25
Daycare (24 mo)								
Yes (352)	5	11	16	14	16	**19***	21	25
No (127)	6	7	15	10	14	**12**	19	21
Non-modifiable factors								
Maternal race								
White (431)	6	10	14	14	15	16	22	25
Non-White (89)[a]	2	10	21	15	18	24	17	21
Maternal asthma								
Yes (223)	5	13	18	**18***	18	20	23	**31***
No (293)	5	8	14	**11**	14	15	19	**20**
Maternal atopy								
Yes (405)	6	9	16	15	16	18	23	**27***
No (111)	2	15	15	10	15	15	15	**15**
Post-secondary education								
Yes (396)	5	**9***	**14***	13	15	**15***	20	**21****
No (120)	8	**16**	**21**	16	16	**24**	26	**37**
Child's sex								
Male (266)	5	11	18	**17***	17	19	**26***	24
Female (254)	5	9	13	**10**	14	15	**16**	26
Firstborn								
Yes (229)	5	**8***	15	14	**12***	15	21	**19***
No (287)	6	**13**	16	14	**18**	19	20	**28**
City								
Winnipeg (256)	5	**16***	**21***	16	**20***	**22***	**25***	**30***
Vancouver (264)	5	**5**	**10**	11	**12**	**12**	**17**	**19**
Atopy at 12 mo								
Yes (107)	3	8	14	17	17	**25***	**31***	**31***
No (382)	6	11	17	13	15	**15**	**18**	**21**

(Continues)

TABLE 1 (Continued)

Characteristics (N per group)	Prevalence of Wheezing (%) by Assessment Month							
	0.5 months n = 520	4 n = 511	8 n = 504	12 n = 498	18 n = 505	24 n = 480	84 n = 472	180 n = 390
Birth mode								
Cesarean (109)	4	8	17	14	17	17	19	25
Vaginal (405)	5	11	15	14	15	17	22	25

CAPPS, Canadian Asthma Primary Prevention Study.

[a]Non-Whites (89): Blacks—1%, East Indian—2%, First people—2%, Oriental—10%, Other—3%.

*$P \leq .05$, **$P < .01$ proportion difference (Z) test (Bold font).

Low-Progressive, Early-Transient, and Early-Persistent. The multifaceted CAPPS intervention and the modifiable lifestyle factors it targeted during the prenatal and post-natal periods predicted trajectory membership. Consistent with previous studies, non-modifiable factors such as a child's sex, atopy at 12 months, maternal asthma, and city of residence also predicted group membership. The CAPPS intervention was effective in decreasing the risk of wheezing during mid-childhood in the Early-Persistent group, but had no effect in the other trajectory groups where wheezing was transient or infrequent. Overall, the odds of asthma from birth through adolescence were higher in the Early-Persistent than the Low-Progressive trajectory group.

Our findings support some, but not all, of the conclusions in existing literature about the number and shape of wheeze trajectories and their relationship to asthma diagnoses. Perhaps the most striking difference between our findings and those of comparable LCGA-based studies is the smaller number of trajectory groups in our data, despite the longer duration of follow-up (15 years) compared with previous studies (7-9 years).[3,5,6] In comparison with the 3 wheeze trajectory groups identified in our CAPPS cohort of 525 children, larger studies have identified more groups (CCCEH [N = 689; 4 groups],[3] Millennium Cohort Study [N = 11 632; 4 groups],[5] Avon Longitudinal Study of Parents and Children [N = 5760; 6 groups],[6,25] and Prevention and Incidence of Asthma and Mite Allergy [N = 2810; 5 groups][6]). However, in addition to the larger sample sizes, the different source populations examined in these studies may explain this finding. While previous studies targeted general populations, ours focused on high-risk children (ie, those with an immediate family history of asthma or with 2-first-degree relatives with classical IgE-mediated allergy). This may explain why the "never-wheeze" trajectory found in previous general population cohorts[3,5,6] was not observed. Indeed, the fact that the comparably sized CCCEH study[3] identified 4 distinct trajectory groups suggests the number of trajectory groups may have more to do with population heterogeneity than sample size (confirmed by entropy, BIC, and AIC criteria for model fit). Also, the fact that the 3-trajectory shapes observed in our 3-group solution are replicated in the 4-group solution (sensitivity analysis: Supporting Information) lends credence to their unique existence in this high-risk population vs general populations examined in previous studies. Nonetheless, it cannot be ruled out that our smaller study sample size (N = 525) compared with previous trajectory studies may have limited the identification of less prevalent trajectory groups.

Compared to the direct application of the investigator-defined TCRS wheeze phenotypes in our previous analysis of the CAPPS population,[2] more children were classified in the data-driven "Early-Persistent" trajectory group in the current study (108; 21%) than the TCRS-based "persistent" phenotype in our previous study (59; 13%). Also, the TCRS-based "never-wheeze" (234; 51%) and "late-onset" (39; 9%) phenotypes appear to be combined in the data-driven Low-Progressive trajectory group (365; 69%). These differences likely reflect the different classification methods applied, as well as the different time periods considered, as the TCRS-style phenotyping was based on wheezing in the first 7 years, while our current LCGA study classified wheeze trajectories uses data from birth to 15 years. It is notable that a considerable proportion of children in the Low-Progressive trajectory group do not wheeze from birth to 15 years. The fact that they were not identified as a separate group suggests that occasional wheezing may not be clinically important, even in a high-risk population, underscored by the lower prevalence of asthma in this group compared with the Early-Persistent group.

Our findings also highlight predictors of trajectory membership that have not been identified in previous LCGA-based wheeze trajectory studies[3,5,6] (eg, post-secondary education and city of residence). The association of higher maternal education with lower

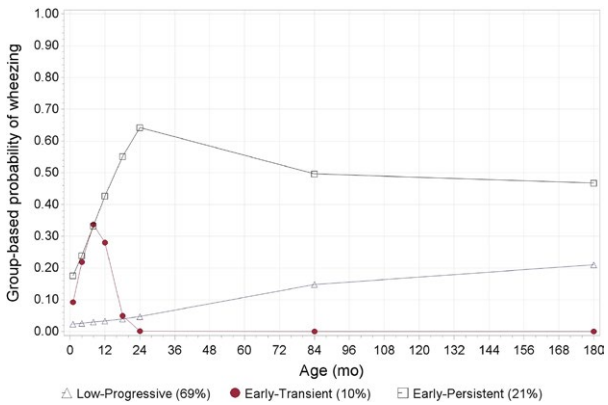

FIGURE 1 Wheeze trajectories identified from CAPPS birth cohort using latent group-based trajectory modeling (N = 525). The proportion of wheezing at each observation month was estimated as a cubic function of age. Lines represent the predicted probability of wheezing at each observation month for each trajectory group, respectively. CAPPS, Canadian Asthma Primary Prevention Study

TABLE 2 Multivariable multinomial logistic regression results showing factors associated with wheeze trajectory group membership in the CAPPS cohort

	Wheeze trajectory group		
Exposure/Risk factor	**Low-progressive Reference group**	**Early-transient Odds ratio (95% CI)**	**Early-persistent Odds ratio (95% CI)**
Intervention[a]	1	0.38 (0.21; 0.68)[b]	0.25 (0.14; 0.46)
		0.58 (0.38; 0.89)[c]	**0.46 (0.32; 0.68)**
Non-modifiable factors			
Maternal race (White)[a]	1	1.13 (0.57; 2.26)[b]	0.79 (0.40; 1.55)
		4.22 (0.76; 13.46)[c]	**0.38 (0.24; 0.57)**
Maternal asthma[a]	1	0.28 (0.12; 0.68)[b]	0.63 (0.25; 1.55)
		1.68 (1.12; 2.53)[c]	**2.72 (1.91; 3.86)**
Maternal atopy[a]	1	2.09 (1.29; 3.39)[b]	1.93 (1.30; 2.86)
		1.66 (0.98; 2.83)[c]	1.26 (0.79; 1.99)
Post-secondary education[a]	1	0.44 (0.24; 0.79)[b]	0.29 (0.18; 0.46)
		0.57 (0.33; 0.95)[c]	**0.39 (0.26; 0.60)**
Child's sex (male)[a]	1	1.15 (0.78; 1.70)[b]	2.06 (1.51; 2.86)
		1.16 (0.78; 1.73)[c]	**2.39 (1.68; 3.39)**
Firstborn[a]	1	1.14 (0.62; 2.08)	0.78 (0.43; 1.40)
		0.87 (0.38; 1.97)	0.58 (0.26; 1.30)
City (Winnipeg)[a]	1	6.05 (3.53; 10.38)[b]	3.35 (1.95; 5.75)
		1.49 (0.92; 2.41)[c]	**3.67 (2.56; 5.26)**
Atopy at 12 mo[a]	1	3.60 (1.27; 10.18)[b]	3.46 (1.20; 9.97)
		2.59 (1.52; 4.39)[c]	**2.86 (1.75; 4.66)**
Cesarean birth[a]	1	1.93 (0.01; 3.72)[b]	0.96 (0.13; 14.4)
		1.07 (0.66; 1.75)[c]	0.96 (0.62; 1.49)
Modifiable factors (targeted by CAPPS intervention)			
Smokers in home[d]	1	2.32 (1.35; 3.97)[b]	2.10 (1.20; 3.67)
		1.66 (0.99; 2.80)[c]	1.31 (0.84; 2.03)
Pets in home[d]	1	1.92 (1.02; 3.60)[b]	2.05 (1.05; 4.01)
		0.58 (0.33; 1.01)[c]	**1.63 (1.07; 2.48)**
Exclusive breastfeeding ≥4 mo[d]	1	0.95 (0.62; 1.46)[b]	0.48 (0.34; 0.68)
		0.20 (0.08; 0.47)[c]	0.79 (0.52; 1.19)
Daycare at 24 mo[d]	1	0.77 (0.47; 1.27)[b]	1.55 (1.05; 2.29)
		1.82 (0.99; 3.32)[c]	1.35 (0.90; 2.03)

CAPPS, Canadian Asthma Primary Prevention Study; CI, confidence interval; OR, odds ratio.
Significant adjusted ORs in bold.
Odds ratios compare the odds having an exposure/risk factor given Early-Transient (column 3) or Early-Persistent (column 4) wheeze trajectory membership vs odds of having an exposure/risk factor given Low-Progressive wheeze trajectory membership (column 2).
[a]Model covariates adjusted for potential confounding: intervention, maternal asthma, post-secondary education, child's sex, city, and atopy at 12 mo. Adjusted effects of (i) maternal asthma and atopy and (ii) race and city (study site) were examined in separate models as informed by the directed acyclic graph procedures for covariate selection; final model results were similar (with coefficient estimates differing by <2%).
[b]Crude odds ratio.
[c]Adjusted odds ratio.
[d]Model covariates adjusted for potential confounding: smoking in home, pets in home, exclusive breastfeeding ≥4 mo, daycare at 24 mo, maternal asthma, post-secondary education, child's sex, city, and atopy at 12 mo.

odds of Early-Transient and Early-Persistent vs Low-Progressive group membership may reflect a lower prevalence of early respiratory infections (a common cause of early wheezing), consistent with previous studies showing reduced infections among infants of higher socioeconomic status.[26] The relevance of study site as a predictor of trajectory group membership may relate to climate or genetic/ethnic differences between cities (24% of Vancouver mothers were non-White vs only 9% of Winnipeg mothers) or reflect higher levels of

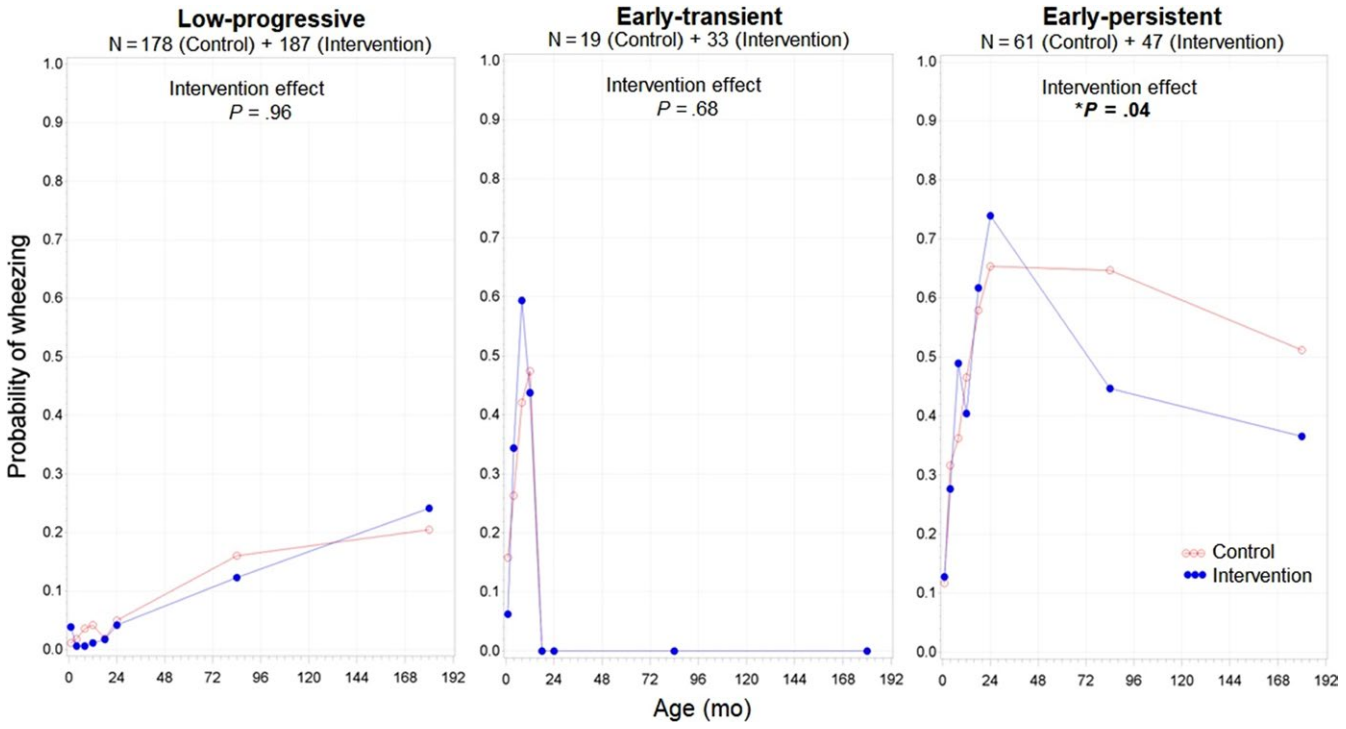

FIGURE 2 Intervention effect within latent group-based wheeze trajectories in the CAPPS cohort. CAPPS, Canadian Asthma Primary Prevention Study

aeroallergen exposure and sensitization to Alternaria in Winnipeg (a prairie city with an agricultural environment).[27]

Additionally, our findings show that compared to investigator-defined wheeze phenotypes, some different predictors and consequences of wheezing are identified and others are missed when the data-driven trajectory approach is applied to the same study population. For example, household pets and maternal asthma predicted Early-Persistent trajectory group membership in our current study, but not the "persistent" TCRS-style phenotype in our previous study.[2] However, both approaches identified male sex, short duration of exclusive breastfeeding (<4 months), atopy at 12 months of age, and living in Winnipeg as predictors of Early-Persistent or "persistent" wheezing.

Regarding clinical prognosis, the TCRS "transient early" phenotype (defined as wheezing in the first 2 years but not at 7 years) was associated with increased asthma risk in adolescence, whereas the data-driven "Early-Transient" trajectory group in our current study (where wheezing occurred in the first year only) was not associated with asthma risk. This suggests that wheezing in the first and second years of life have different physiological consequences and prognostic value, with wheezing in the second (but not the first) year predicting increased asthma risk later in childhood. This clinically important distinction was obscured in previous analyses using traditional investigator-defined phenotypes because they combine the first 2 years in a single "early" period. Overall, these classification methodologies probably result in different approximations of complex realities that need to be interpreted cautiously.

Our study reveals intriguing differences between wheeze trajectory groups regarding their responsiveness to the multifaceted prenatal CAPPS intervention. For the Early-Persistent trajectory group, our results show that intervening during early life to address modifiable risk factors lowered the odds of wheezing during mid-childhood but not during infancy (the intervention period). In addition, the intervention had no effect in the Early-Transient group, where wheezing only occurred during infancy. Together, these results suggest the intervention prevented the pathogenesis of wheezing that occurs later in childhood, which is more likely related to asthma, but did not affect wheezing that occurs during infancy, which is more likely related to respiratory infections.

Some limitations of our study need to be considered. Wheeze trajectories were determined based on parent or self-report of wheezing, and such reports are prone to recall bias. Even if we assume non-differential misclassification among trajectory groups, the direction of bias on trajectory-asthma odds ratio estimates is not predictable since more than 2 trajectory groups are involved.[28] Given our study sample size (N = 525), the differences between the 3 and 4-trajectory group solutions warrant a cautious interpretation and require replication in larger studies among high-risk populations. This also applies to our findings and discussion regarding clinical prognosis of wheezing in the first vs second year of life. Finally, it is important to note that while the CAPPS intervention included avoidance of pets and allergenic foods (in alignment with pediatric and allergy societies' recommendations in the 1990s), these recommendations have been challenged or reversed based on more recent evidence.[29,30]

TABLE 3 Generalized linear mixed model (GLMM) results: associations[a] between wheeze trajectories, asthma diagnosis, and respiratory outcomes in the CAPPS cohort

Outcome	Year of follow-up							
	1 y N = 493		2 y N = 476		7 y N = 378		15 y N = 335	
Wheeze trajectory	n/N (%)	OR (95% CI)	n/N (%)	OR (95% CI)	n/N (%)	OR (95% CI)	n/N (%)	OR (95% CI)
Asthma diagnosis								
Low-Progressive	44/340 (13)	1.0 (reference)	52/329 (16)	1.0 (reference)	31/259 (12)	1.0 (reference)	23/227 (10)	1.0 (reference)
Early-Transient	7/51 (14)	1.17 (0.50; 2.75)	7/49 (14)	0.90 (0.39; 2.11)	0/39 (0)	–	5/35 (14)	1.66 (0.59; 4.72)
Early-Persistent	36/102 (35)	**3.16 (1.87; 5.33)**	52/98 (53)	**5.28 (3.19; 8.75)**	40/80 (50)	**6.33 (3.52; 11.36)**	26/73 (36)	**4.39 (2.27; 8.48)**
Airway hyperresponsiveness[b]								
Low-Progressive					181/242 (75)	1.0 (reference)	53/205 (26)	1.0 (reference)
Early-Transient					28/34 (82)	1.54 (0.61; 3.91)	8/30 (27)	1.03 (0.43; 2.44)
Early-Persistent					59/72 (82)	1.54 (0.79; 3.01)	26/65 (40)	**1.91 (1.06; 3.45)**
					Mean (SD)	Mean difference (95% CI)	Mean (SD)	Mean difference (95% CI)
Lung function: FEV1 (L)								
Low-Progressive					1.41 (0.22)	0.0 (reference)	3.57 (0.70)	0.0 (reference)
Early-Transient					1.36 (0.25)	−0.03 (−0.13; 0.06)	3.49 (0.69)	−0.02 (−0.09; 0.04)
Early-Persistent					1.28 (0.16)	**−0.09 (−0.15; −0.04)**	3.49 (0.64)	−0.02 (−0.07; 0.03)

CAPPS, Canadian Asthma Primary Prevention Study; CI, confidence interval; OR, odds ratio.
Significant adjusted ORs in bold.
[a]All comparisons are adjusted for study group.
[b]Methacholine PC20 <8 mg/mL at 7 and 15 y. Lung function and airway hyperresponsiveness were not measured at 1 and 2 years.

In summary, our results show that data-driven methodology can be used to classify children into clinically meaningful wheeze trajectory groups that are population-specific. These trajectories appear to be programmed by a combination of modifiable and non-modifiable factors. Our results also show that early-life interventions can ameliorate some wheeze trajectories (ie, Early-Persistent), while other trajectories appear to be unaffected by the same interventions. Finally, our data-driven analysis uniquely reveals that wheezing in the second (but not the first) year of life is a strong risk factor for asthma—a clinically important distinction that was not evident using classic investigator-defined wheeze phenotypes.

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AUTHOR CONTRIBUTION

A.H.O and M.B.A. contributed to the design of the work, data analysis and interpretation, and drafting and revising of the manuscript. A.B.B., M.C-Y., E.S.C., R.C., C.R., and W.T.A.W. contributed to the data acquisition, interpretation, and critical revision of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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