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Clinical features and later prognosis of replicable early-life wheeze clusters from two birth cohorts 12 years apart

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Abstract

Background: Clustering techniques can define the heterogeneity of asthma and wheezing. Defining early-life wheezing clusters and associated asthma risk could potentially inform patient management strategies. Clustering models that yield replicable cluster groups will have greater validity and clinical utility. This study sought to identify early-life wheezing clusters that are translatable into clinical practice and assess their stability over time in two whole-population birth cohorts established a decade apart from the same geographical location.

Methods: Nonparametric K-means cluster analysis was performed separately on two birth cohorts from the Isle of Wight, UK; the Isle of Wight Birth Cohort (IOWBC) and Food Allergy and Intolerance Research Cohort (FAIR), using clinically defining variables in wheezing subjects in the first 3–4 years. Associations of resulting clusters with potential early-life risk factors and 10-year asthma outcomes were further assessed.

Results: Five clusters were identified in both cohorts: (1) infantile-onset-transient-non-atopic-wheeze, (2) infantile-onset-persistent-non-atopic-wheeze, (3) infantile-onset-atopic-wheeze, (4) early-childhood-onset-non-atopic-wheeze, and (5) early-childhood-onset-atopic-wheeze. Two atopic wheezing clusters (3 and 5) were associated with greatest early-life wheeze frequency, highest wheeze persistence, and asthma prevalence at 10 years. Cluster 1 was commonest but had lowest early-life wheeze frequency and asthma prevalence at 10 years. Cluster 2, characterized by limited atopy but recurrent infantile respiratory infections and ongoing early-life wheezing, had high 10-year asthma prevalence only in IOWBC.

Conclusions: Early-life wheeze comprises several disease clusters (two more severe and three mild–moderate) with differing relationships to later childhood asthma, which can be replicated over time supporting their potential validity and clinical utility.

KEYWORDS
asthma, atopy, early-life wheezing, wheezing phenotypes

Abbreviations: ANOVA, analyses of variance; BMI, body mass index; CCC, cubic clustering criterion; FAIR, Food Allergy and Intolerance Research birth cohort; IOWBC, Isle of Wight Birth Cohort; NAUW, Non-Atopic Uncontrolled Wheeze; SPT, skin prick test.

1 | INTRODUCTION

There is growing understanding of unique phenotypes of early-life wheezing.[1] Gaining insight into what clinical features predispose a child who wheezes to develop asthma may help in earlier identification, risk modification, and treatment to alter clinical course. Prior longitudinal studies evaluating wheezing patterns in young children identified differences in characteristics and outcomes based on the timing of wheezing onset and duration.[2–8] Further evaluation has identified additional factors, including personal and family history of atopy, lung function, ethnicity, sex, and other environmental exposures that modulate asthma risk.[3,5,9] Better understanding of clinically relevant classifications for both asthma and wheezing has been advanced through unbiased techniques of cluster and latent class analyses.[10–13] Establishing cluster groupings with similar features and outcomes in different populations would increase validity of a clustering model. Similarly, stability among clustering groups over different time periods would indicate longevity of a particular model.

In this study, we employed a cluster analysis using clinically relevant and readily available variables to classify early-life wheezing clusters that reflect real-world clinical practice. Our study utilized two prospectively followed birth cohorts from the Isle of Wight (United Kingdom; UK) that commenced 12 years apart to evaluate the reproducibility of the cluster modeling over time. Following cluster identification, associated clinical characteristics and 10-year outcomes were assessed to gain insight into possible clinical and prognostic implications of each cluster.

Key Message

Replicable early-life wheezing clusters based on clinically relevant parameters, in two birth cohorts established a decade apart, identify distinct patterns of childhood wheezing associated with differing morbidity and persistence risk. This study highlights higher risk childhood wheeze phenotypes that merit close attention in clinical practice.

2 | METHODS

Two whole population birth cohorts established on the Isle of Wight 12 years apart were evaluated in this study. The Isle of Wight Birth Cohort (IOWBC) ($n = 1456$) was established in 1989 and the Food Allergy and Intolerance Research (FAIR) birth cohort ($n = 969$) was established in 2001–2002 as whole population birth cohorts to study the natural history of asthma and allergic disease. The details of methodology and follow-up studies for the IOWBC and FAIR studies have been published previously.[7,14–20] Ethics approval was obtained for the IOWBC from the Isle of Wight NHS Ethics committee (No 05/89; dated 08/22/1988) and for the FAIR cohort from the NRES South Central—Southampton B Research Ethics Committee (REF 10/H0504/11).

In both cohorts, informed consent from the subject's parents and information on first-degree family history of allergy, parental smoking, socioeconomical status, household pets, and birth weight were obtained. Subjects were evaluated at predetermined intervals. Cohort subjects were evaluated at birth and ages 1, 2, 4, and 10 years for the IOWBC and at birth and ages 1, 2, 3, and 10 years for FAIR. Feeding and weaning practices, immunization history, and exposure to relevant environmental factors (e.g., domestic pets and tobacco smoke) were recorded at the 1-year evaluation. At 1, 2, and either 3 or 4 years of age, parents also completed a series of questionnaires to provide information on clinical asthma and allergy status. These questionnaires recorded symptoms of atopy, including features for eczema, rhinitis, and food allergy. The presence of wheezing within the last 12 months, history of recurrent chest infections, the presence of nocturnal cough or sleep disturbance, diagnosis of asthma, and treatment for asthma were also assessed. Specific definitions/questions used in the two cohorts are given in Table E1. Notable differences include different wheezing ranges used for the ordinal scale of wheezing frequency and requirement for three separate episodes of wheezing and/or cough in addition to physician diagnosis of asthma in the IOWBC to meet criteria for diagnosis of asthma at 4 years. Current asthma at 10 years was defined as "physician diagnosed asthma ever" plus "current wheeze." Skin prick testing (SPT) was performed in all consenting subjects at 3 (FAIR) or 4 years (IOWBC) and again at 10 years to a standard aeroallergen panel.[17,19]

2.1 | Statistical methods

All statistical analyses were performed using the SAS statistical package version 9.4 (SAS Institute). The two cohorts were analyzed separately. A nonparametric K-means clustering method (PROC FASTCLUS in SAS) was applied to detect the clusters of subjects. This approach is selected due to its simplicity and robustness to different shapes of data. The cluster analysis was performed in each cohort on subjects with wheezing at any point within the past 12 months at ages 1, 2, 3, or 4 years. Subjects with no recorded wheezing in the first 3 (FAIR study) to 4 years (IOWBC study) of life were excluded. Cluster variables were selected that defined clinical characteristics in the first 3–4 years. These included both questionnaire-derived data and variables from objective testing. Six clinical disease defining variables derived from data obtained in the first 3 (FAIR) to 4 years (IOWBC) were selected for the cluster analyses: age of wheeze onset, wheeze frequency at age 3 or 4 years, atopy (positive SPT) at 3 or 4 years, eczema by 3 or 4 years, food allergy at 3 or 4 years, and rhinitis at 3 or 4 years. We standardized continuous variables to reduce clustering bias due to different scales or units. The final choice for the number of clusters was determined by an overall evaluation of CCC[21] and pseudo F,[22] combined with an R^2 statistic measuring between cluster variation (Appendix A, Table E3).

To evaluate variation of each clustering variable across the clusters, analyses of variance (ANOVA) was used for continuous

variables and chi-squared tests for categorical variables. To test differences between clusters, pairwise *t*-tests were applied to continuous variables, and for categorical variables, pairwise proportion tests were applied. Associations with potential risk factors recorded during the first 4 years were then assessed. These included male sex, family history (parent or sibling) of asthma, lower socioeconomic status at birth, mode of delivery, maternal smoking in pregnancy, exclusively breastfed, recurrent chest infections in infancy (age 1 or 2 years), birthweight, and Body Mass Index (BMI) *z*-score at 2 years. In these assessments, chi-squared tests and ANOVA were applied for categorical and continuous variables, respectively.

3 | RESULTS

Among cohort subjects, 367 (23.9%) had previously recorded wheeze during the first 4 years of life in the IOWBC and 485 (50%) during the first 3 years of life in FAIR. These subjects with a history of wheeze formed the respective populations for cluster analysis.

Variables used in the cluster analysis and additional potential risk factors between the IOWBC and FAIR studies showed significant differences (Table 1). In the respective clustered populations, estimated mean onset of wheeze was later in the IOWBC compared with FAIR (1.5 years vs. 0.8 years, $p < 0.001$). Frequency of wheezing at 3 or 4 years was higher in the IOWBC (1.2 vs. 0.5 on ordinal scale, $p < 0.001$); however, scales used for analysis differed. In the IOWBC, there was also significantly higher prevalence of atopic sensitization (26% vs. 13%, $p < 0.001$) and food allergy (17% vs. 7%, $p < 0.001$), but lower prevalence of eczema (29% vs. 65%, $p < 0.001$) and rhinitis (11% vs. 36%, $p < 0.001$). Diagnosis of asthma was also significantly higher in the IOWBC at both preschool age (49% vs. 17%, $p < 0.001$) and at 10 years of age (29% vs. 13%, $p < 0.001$).

In separate cluster analyses of the IOWBC and FAIR early-childhood wheezers, five clusters were identified: (1) infantile-onset-transient-non-atopic-wheeze, (2) infantile-onset-persistent-non-atopic-wheeze, (3) infantile-onset-atopic-wheeze, (4) early-childhood-onset-non-atopic-wheeze, and (5) early-childhood-onset-atopic-wheeze. These five clusters from the two separate cohorts were paired based on similar characteristics among clustering variables as outlined in Table 2. Age of wheeze onset separated into three early-onset (1, 2, 3) and two late-onset (4, 5) clusters. The overall proportional split of early-onset and late-onset wheeze was similar in the two cohorts, though there were differences in prevalence of individual clusters. Atopy and allergic diseases (eczema, food allergy, and rhinitis) segregated into lower (1, 2, 4) and higher (3, 5) prevalence clusters. At age 3–4, there was significant difference among clusters for prevalence of current wheezing ($p < 0.001$), diagnosis of asthma ($p < 0.001$), and treatment for asthma ($p < 0.001$) with consistently lowest prevalence in Cluster 1 (indicating an early, transient wheeze pattern) but highest for Clusters 3 and 5 in both cohorts (consistent with greater disease severity). Furthermore, Cluster 2 demonstrated moderate-to-high current wheezing, asthma diagnosis, and treatment needs in both cohorts but these trends were more pronounced in IOWBC.

Associations of the early-childhood wheeze clusters with potential early-childhood risk factors were also evaluated. In the IOWBC, no significant differences were observed between clusters for birthweight, BMI *z*-score at 2-year, male sex, maternal smoking during pregnancy, family history of asthma, lower socioeconomic status at birth, vaginal delivery, exclusive breastfeeding for the first 3 months of life, and pet exposure during infancy (Table E2). However, there were significant differences between clusters in the FAIR cohort (Table 3). Cluster 3 had the highest while Cluster 5 had the lowest BMI *z*-scores (0.9 vs. −0.3, $p = 0.017$), prevalence of family history of atopy (76% vs. 35%, $p = 0.0014$). There was also significant difference among clusters based on families with an annual household income less than £50 K with similar trend with higher prevalence in Cluster 3 than in Cluster 5 (49% vs. 20%, $p > 0.001$). There was also a similar nonsignificant trend for maternal smoking in pregnancy in the FAIR cohort data ($p = 0.064$) such that there was higher prevalence in Cluster 3 (31%) than in cluster 5 (16%).

Asthma and wheezing outcomes at 10 years were evaluated for each cluster (Figure 1). Across both cohorts, there were significant differences for both 10-year wheezing frequency ($p < 0.001$) and diagnosis of asthma ($p < 0.001$) among clusters with prevalence lowest in Cluster 1 and highest among Clusters 3 and 5, which were associated with higher prevalence of atopy and greater wheeze frequency in earlier childhood. Discrepancies in asthma outcomes at 10 years of age were noted between cohorts for Cluster 2, with subjects from the IOWBC continuing to exhibit higher asthma prevalence (43% vs. 25%, $p = 0.020$) and treatment need (47% vs 29%, $p = 0.028$) compared to FAIR. Additionally, in the FAIR cohort, while Cluster 2 showed moderate 10-year asthma treatment needs, their asthma and wheeze prevalence was comparably low to that of subjects with persistent nonatopic wheezing seen in Cluster 4. In the IOWBC, Cluster 2 had the highest rates of recurrent respiratory infections at ages 1–2 (54%, $p < 0.001$) plus highest 4-year wheezing frequency among clusters with infantile-onset wheezing (1–3) (100%, $p < 0.001$). This pattern was not observed in FAIR, where 3-year wheeze frequency was low in Cluster 2 (34%).

Key features of each cluster, associated risk factors, and 10-year outcomes are summarized in Figure 2.

4 | DISCUSSION

To our knowledge, this is the first study to characterize early-life wheezing clusters in two longitudinal birth cohorts enrolled within the same geographical location a decade apart. We defined early-life wheeze clusters, their associations with later childhood asthma outcomes, and the stability of these clusters over time, thus providing confidence in their clinical utility. Five distinct wheezing clusters were identified in both. These clusters were distinguished by clinically relevant and easily obtainable variables including age of wheeze onset, wheeze frequency, atopic status, allergic comorbidity, early-life chest infections, plus prevalence of current wheeze, asthma, and asthma treatment at 3 to 4 years. We demonstrated associations among these clusters with later childhood asthma outcomes and the

TABLE 1 Comparison of patient demographics and wheezing characteristics.

	Entire cohort				Population for cluster analysis			
	IOWBC (*N* = 1536)	FAIR (*N* = 969)	Total (*N* = 2505)	*p* Value	IOWBC (*N* = 367)	FAIR (*N* = 485)	Total (*N* = 909)	*p* Value
Estimated age of wheeze onset (years)								
Mean (sd)	1.6 (1.2)	0.8 (0.8)	1.2 (1.1)	<0.0001	1.5 (1.2)	0.8 (0.8)	1.1 (1.0)	<0.001
N-Not collected	1018	450	1468		20	0	20	
Continuous/ordinal wheeze frequency[a]								
Mean (sd)	0.9 (1.2)	0.3 (0.6)	0.5 (0.9)	<0.001	1.3 (1.3)	0.5 (0.8)	0.8 (1.1)	<0.001
N-Not collected	1018	79	1097		20	0	20	
Atopy at 3 or 4 years								
Yes	193 (20%)	70 (10%)	263(16%)	<0.001	81 (26%)	46 (13%)	127 (19%)	<0.001
No	787 (80%)	660 (90%)	1387(84%)		235 (74%)	317 (87%)	552 (81%)	
N-Not collected	556	299	855		51	122	230	
Eczema in the 1st 3- to 4-years								
Yes	263 (18%)	579 (60%)	842 (35%)	<0.001	105 (29%)	314 (65%)	419 (49%)	<0.001
No	1185 (82%)	380 (40%)	1565 (65%)		261 (71%)	170 (35%)	431 (51%)	
N-Not collected	88	10	98		1	1	2	
Food allergy in the first 3- to 4-years								
Yes	127 (9%)	58 (6%)	185 (8%)	0.014	61 (17%)	34 (7%)	95 (11%)	<0.001
No	1292 (91%)	894 (94%)	2186 (92%)		305 (83%)	450 (93%)	755 (89%)	
N-Not collected	117	17	134		1	1	20	
Rhinitis at 3- to 4-years								
Yes	65 (5%)	279 (31%)	344 (16%)	<0.001	39 (11%)	176 (36%)	215 (25%)	<0.001
No	1149 (95%)	611 (69%)	1760 (84%)		327 (89%)	308 (64%)	635 (75%)	
N-Not collected	322	79	401		1	1	2	
Asthma diagnosis at 3 or 4 year								
Yes	181 (15%)	83 (9%)	302 (14%)	<0.001	179 (49%)	83 (17%)	262 (31%)	<0.001
No	1033 (85%)	807 (91%)	1799 (86%)		186 (51%)	401 (83%)	587 (69%)	
N-Not collected	322	79	401		2	1	3	
Asthma diagnosis at 10 year								
Yes	201 (15%)	101 (14%)	302 (14%)	0.62	114 (32%)	60 (13%)	174 (21%)	<0.001
No	1167 (85%)	632 (86%)	1799 (86%)		238 (68%)	411 (87%)	649 (79%)	
N-Not collected	168	236	404		15	14	29	
Gender								
Female	594 (49%)	462 (48%)	1056 (49%)	0.91	154 (42%)	223 (46%)	377 (44%)	0.26
Male	624 (51%)	492 (52%)	1116 (51%)		213 (58%)	261 (54%)	474 (56%)	
N-Not collected	318	15	333		0	1	1	
Lowest socioeconomic level								
Yes	73 (10%)	340 (35%)	413 (24%)	<0.001	32 (14%)	179 (37%)	211 (29%)	<0.001
No	650 (90%)	623 (65%)	1273 (76%)		205 (86%)	302 (63%)	507 (71%)	
N-Not collected	813	6	819		130	4	134	
Family history of asthma								
Yes	595 (47%)	411 (42%)	1006 (45%)	0.021	186 (58%)	255 (53%)	441 (55%)	0.16
No	660 (53%)	558 (58%)	1218 (55%)		135 (42%)	230 (47%)	365 (45%)	
N-Not collected	281	0	281		46	0	64	

TABLE 1 (Continued)

	Entire cohort				Population for cluster analysis			
	IOWBC (*N* = 1536)	FAIR (*N* = 969)	Total (*N* = 2505)	*p* Value	IOWBC (*N* = 367)	FAIR (*N* = 485)	Total (*N* = 909)	*p* Value
Smoking during pregnancy								
Yes	384 (25%)	225 (24%)	609 (25%)	0.52	102 (28%)	131 (28%)	233 (29%)	1
No	1137 (75%)	712 (76%)	1849 (75%)		264 (72%)	342 (72%)	568 (71%)	
N-Not collected	15	32	47		1	12	13	
Exclusively breastfed >3 months								
Yes	419 (33%)	191 (20%)	800 (36%)	<0.001	81 (25%)	80 (17%)	269 (33%)	0.0032
No	865 (67%)	759 (80%)	1434 (64%)		243 (75%)	403 (83%)	538 (67%)	
N-Not collected	252	19	271		43	2	45	

Note: The *p*-values are for the tests comparing the means (for continuous variables) or for comparing the distribution patterns of a categorical variable between the IOWBC and FAIR cohorts.

[a]Wheeze frequency was defined by a categorical scale; For IOWBC: 0—0 episodes in past 12 months, 1—<3 episodes in past 12 months, 2—3 episodes in past 12 months, 3—>3 episodes in past 12 months; For FAIR: 0—0 episodes in past 12 months, 1—<3 episodes in past 12 months, 2—4 to 12 episodes in past 12 months, 3—>12 episodes in past 12 months.

stability of these clusters over time, thus providing confidence in their clinical utility.

Two higher severity atopic clusters were identified: one with onset in infancy (Cluster 3; infantile-onset-persistent-atopic-wheeze) and the other in early childhood (Cluster 5; early-childhood-onset-persistent-atopic-wheeze). These two clusters showed stronger association with asthma in later childhood. Milder nonatopic wheezing clusters (1; infantile-onset-transient-non-atopic-wheeze and 4; early-childhood-onset-transient-non-atopic-wheeze) were also demonstrated that did not show strong associations with later childhood asthma. An infantile-onset-non-atopic-wheeze cluster (2) showed moderate–high wheeze/asthma features in early-life and was associated with later childhood asthma and treatment need.

Similar patterns have been observed in other studies on early-life wheezing. Early-onset, transient wheezing, which resolves by 3–4-years of age as characterized by Cluster 1, is the commonest group of early-life wheezers and have the lowest risk for developing asthma.[2,3,11] This cluster had lowest association to allergic disease among all clusters. Therefore, infantile-onset wheezers with a brief preschool wheezing history and no history of atopy are unlikely to require additional asthma-type management.

In contrast, persistent and later onset wheezing can result in higher rates of asthma later in childhood, and this risk can be further increased by a history of atopy.[1] By differentiating clusters by both timing of onset and presence of atopy, this study's cluster analysis demonstrated that history of atopy, regardless of when onset of wheezing occurred, was a strong predictor of higher prevalence of asthma at 10 years of age. Both Cluster 3 and Cluster 5 resulted in similar higher persistence of asthma at age 10, while Cluster 4 had lower persistent asthma at age 10. These findings further support the inclusion of allergen sensitization and history of eczema as criteria for higher risk of asthma persistence in several childhood prediction models.[23]

While there was strong agreement in 10-year outcomes in Clusters 1, 3, 4, and 5, there were discrepant findings among the two cohorts for Cluster 2 (infantile-onset-persistent-non-atopic-wheeze) with higher rates of persistent asthma among subjects in the earlier established IOWBC. This discrepancy may be associated with an increased history of recurrent respiratory infections among Cluster 2 patients observed in the IOWBC. Data on the history of recurrent respiratory infections were not obtained in the FAIR cohort to corroborate this possible association. Other studies have observed increased risk for asthma with higher frequency of early-life wheezing. Cluster analysis of the Trousseau Asthma Program cohort identified the Non-Atopic Uncontrolled Wheeze (NAUW) cluster, characterized by increased wheezing frequency that persisted beyond early childhood in the absence of atopy and had poorer response to inhaled therapy.[11] Given possible absence of increased respiratory infections in the later FAIR cohort, this may reflect better understanding and mitigation of risk of early life respiratory infections to reduce incidence of asthma. Further studies to understand this trend over time are needed.

Within the FAIR cohort, prevalence of family history of asthma, increased BMI *z*-score, lower household income, and maternal smoking during pregnancy were highest in Cluster 3 and lowest in Cluster 5. These two clusters have high levels of atopy and primarily differed by timing of wheezing onset, so these factors may play a role in earlier onset of wheezing in atopic children. Studies have shown that family history of atopy,[24] low socioeconomic level,[25] infant BMI,[26] and maternal smoking during pregnancy[27] do increase the risk for wheezing and asthma, but there has not been a clear association with earlier onset of wheezing. Maternal smoking during pregnancy also increases the risk for early-life viral infections, including bronchiolitis, which may result in earlier presentation of wheezing in this subset of patients.[28] There were no statistically significant differences in associated early-life risk factors among clusters in the IOWBC, including to any of those identified in the FAIR cohort. Prior analysis of the

TABLE 2 Participant characteristics by early-life wheezing cluster.

		Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	*p*-Value
n (%)	IOWBC	143 (39%)	77 (21%)	29 (7.9%)	56 (15%)	62 (16.9%)	
	FAIR	241 (49.7%)	69 (14.2%)	37 (7.6%)	112 (23%)	26 (5.3%)	
Variables utilized in cluster analysis							
Continuous variables; Mean (SD)							
Age of wheeze onset (years)	IOWBC	***0.57*** (0.42)	0.73 (0.47)	1.72 (0.73)	**2.99** (0.62)	2.78 (0.67)	<0.001
	FAIR	0.4 (0.2)	***0.3*** (0.2)	***0.3*** (0.2)	1.9 (0.5)	**2.2** (0.5)	<0.001
Wheeze frequency	IOWBC[a]	0.13 (0.33)	**2.68** (*0.47*)	1.21 (0.62)	***0.30*** (0.46)	2.63 (0.49)	<0.001
	FAIR[b]	***1.0*** (0.0)	***1.0*** (0.0)	**2.2** (0.4)	***1.0*** (0.0)	**2.2** (0.4)	<0.001
Categorical variables; % (n/N_0)							
Atopy	IOWBC at 4 year	***9.3%*** (11/118)	31.9% (23/72)	**68.0%** (*17/25*)	17.4% (8/46)	40.0% (22/55)	<0.001
	FAIR at 3 year	***7%*** (12/172)	16% (9/58)	21% (6/28)	13% (11/84)	**38%** (8/21)	0.0006
Eczema	IOWBC in first 4 years	22.4% (32/143)	***31.2%*** (24/77)	**82.8%** (*24/29*)	14.6% (8/55)	27.4% (17/62)	<0.001
	FAIR in first 3 years	63% (151/241)	***61%*** (42/69)	**89%** (33/37)	63% (71/112)	68% (17/25)	0.0287
Food allergy	IOWBC in first 4 years	11.9% (17/143)	14.3% (11/77)	**65.5%** (19/29)	***10.9%*** (6/55)	12.9% (*8/62*)	<0.001
	FAIR in first 3 years	***4%*** (10/240)	12% (8/69)	16% (6/37)	***4%*** (5/112)	**19%** (5/26)	0.0019
Rhinitis	IOWBC in first 4 years	***2.1%*** (3/143)	13.0% (10/77)	**48.3%** (14/29)	5.5% (3/55)	14.5% (*9/62*)	<0.001
	FAIR in first 3 years	***29%*** (69/240)	45% (31/69)	**59%** (22/37)	37% (41/112)	50% (13/26)	<0.001
Additional clinical features, % (n/N_0)[c]							
Nocturnal symptoms	IOWBC nocturnal symptom frequency ≥3 at 4 years	82.4% (28/34)	**95.9%** (70/73)	78.3% (*18/23*)	***69.2%*** (27/39)	89.7% (52/58)	0.0013
	FAIR sleep disturbance in 12 months at 3 years	***0%*** (1/241)	30% (21/69)	41% (15/37)	14% (16/112)	**46%** (12/26)	<0.001
Recurrent chest infections	IOWBC at 1–2 years	50.8% (67/132)	**53.9%** (35/65)	32.0% (*8/25*)	***17.0%*** (8/47)	36.5% (19/52)	<0.001
Wheeze in past 12 months	IOWBC at 4 year	***30.1%*** (43/143)	**100%** (77/77)	89.7% (26/29)	94.5% (53/56)	**100%** (*62/62*)	<0.001
	FAIR at 3 year	***2%*** (4/241)	99% (68/69)	**100%** (37/37)	49% (55/112)	**100%** (26/26)	<0.001
Asthma diagnosis	IOWBC at 4 year	***13.4%*** (19/142)	89.6% (69/77)	58.6% (17/29)	29.1% (16/55)	**93.6%** (*58/62*)	<0.001
	FAIR at 3 year	***3%*** (7/241)	34% (23/68)	**62%** (23/37)	17% (19/112)	42% (11/26)	<0.001
Asthma treatment	IOWBC at 4 year	***17.5%*** (25/143)	**77.9%** (60/77)	48.3% (14/29)	51.8% (29/56)	72.6% (*45/62*)	<0.001
	FAIR at 3 year	***9%*** (22/237)	70% (46/66)	**80%** (28/35)	38% (42/111)	76% (19/25)	<0.001

Note: For continuous variables, the analysis of variance (ANOVA) was used to compare means across the clusters. For categorical variables, the chi-squared tests were applied to compare the proportions across the clusters. Significantly different clusters are highlighted in bold (highest)/bold italics (lowest), and are identified based on pair-wise *t*-tests (continuous variables) or proportion tests (categorical variables). Definitions of each variable are detailed in Table E1.

[a]Wheeze frequency was defined by a categorical scale; 0—0 episodes in past 12 months, 1—<3 episodes in past 12 months, 2—3 episodes in past 12 months, 3—>3 episodes in past 12 months.

[b]Wheeze frequency was defined by a categorical scale; 0—0 episodes in past 12 months, 1—<3 episodes in past 12 months, 2—4 to 12 episodes in past 12 months, 3—>12 episodes in past 12 months.

[c]For each variable, the number of subjects in total, denoted by N_0, can be different from the size of each cluster (denoted by *N*).

IOWBC did demonstrate increased risk for persistent wheezing with family history of atopy, parental smoking, and lower social class at birth, but these trends were not observed among studied clusters.[29]

The significant difference in environmental factors on wheezing and asthma outcomes in the FAIR cohort may indicate they are playing a larger role on disease in recent years. Some of these factors, such

TABLE 3 Association of early-life factors with early-life wheeze clusters in FAIR cohort.

	Overall	Total cluster cohort	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	*p*-Value
Continuous variables; Mean (SD)								
Birthweight (kg)	3.4 (0.6)	3.4 (0.6)	3.4 (0.6)	3.4 (0.6)	3.3 (0.5)	3.3 (0.5)	3.3 (0.7)	0.60
BMI *z*-score at 2 years	0.2 (1.1)	0.3 (1.1)	0.1 (1.0)	0.8 (1.2)	**0.9 (2.0)**	0.4 (0.8)	***−0.3 (0.9)***	**0.017**
Categorical variables; % (n/N_0)[a]								
Male	52% (492/954)	54% (261/484)	57% (138/241)	54% (37/68)	57% (21/37)	44% (49/112)	62% (16/26)	0.17
Maternal smoking in pregnancy	24% (225/937)	28% (131/485)	27% (64/237)	41% (27/66)	31% (11/36)	23% (25/109)	16% (4/25)	0.064
Family history of asthma	42% (411/969)	53% (255/485)	48% (116/241)	65% (45/69)	**76% (28/37)**	51% (57/112)	**35% (9/26)**	**0.0014**
Annual household income less than 50 K	35% (340/963)	37% (179/481)	37% (88/238)	51% (35/69)	49% (18/37)	29% (33/112)	20% (5/25)	**>0.001**
Vaginal delivery	78% (755/966)	74% (359/484)	74% (178/240)	77% (53/69)	70% (26/37)	75% (84/112)	69% (18/26)	0.92
Exclusively breastfed >3 months	40% (381/950)	39% (188/483)	39% (93/241)	32% (22/69)	32% (12/37)	45% (50/111)	44% (11/25)	0.39
Pet exposure	58% (563/969)	60% (293/485)	59% (141/241)	70% (48/69)	68% (25/37)	59% (66/112)	50% (13/26)	0.30

Note: The *p*-values are for the tests comparing the means (for continuous variables) across the five clusters or for comparing the distribution patterns of a categorical variable in each cluster. For continuous variables, ANOVA was used, and for categorical variables, chi-square tests were implemented. [#]Significantly differing clusters are highlighted in bold (highest) and bold italics (lowest) (significance = $p < 0.05$), and are identified based on pair-wise proportion tests (categorical variables).

[a]For each variable, the number of subjects in total, denoted by N_0, can be different from the size of each cluster (denoted by *N*).

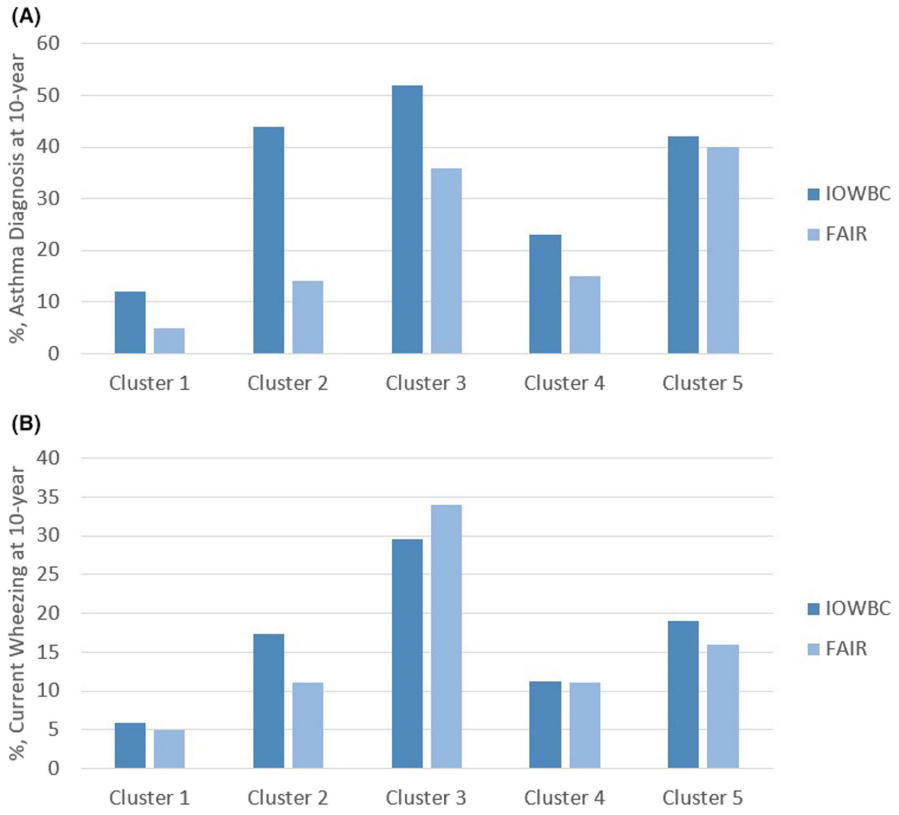

FIGURE 1 Longitudinal asthma characteristics of the early childhood wheeze clusters. (A) Percent of patients by cluster with asthma diagnosis at 10 year. Asthma diagnosis is defined as a history of physician diagnosed asthma plus wheezing in the past 12 months at 10 years of age. (B) Percent of patients by cluster with current wheezing at 10 years of age. Current wheezing is defined as the presence of any wheezing in the past 12 months at 10 years of age.

as low socioeconomic level, infant BMI, and parental smoking, can reflect social disadvantages that are concerningly causing more pronounced effects over time. This could highlight an increasing need to identify and address such disparities with public health measures.

A major strength of this study is the ability to compare the wheezing patterns of children from two different time periods. By studying two cohorts from the same geographical region, many confounding variables were minimized, though significant differences in several characteristics were noted. The prevalence of wheezing between 3 and 4 years of age was significantly higher in FAIR (50% of cohort) than in IOWBC (29% of cohort). Recognition of wheezing may have increased over time causing higher reported wheezing rates in the more recent FAIR cohort. Potentially aligned to that concept, prevalence of milder wheeze (represented by Cluster 1) accounted for a higher proportion of early-childhood wheezing in FAIR than IOWBC.

Additionally, among these subjects with early-life wheezing, 49% met the definition for having asthma in the IOWBC compared to only 17% in FAIR at 3–4 years of age. The definition of asthma at this early age in IOWBC was based on "physician diagnosis plus recurrent wheeze" while in FAIR it was "parentally reported." Such different criteria may partly explain these differences as may the fact that the FAIR early-childhood assessment was 1 year earlier than IOWBC. Furthermore, over time in the UK, it has become widely accepted that making a secure asthma diagnosis before the age of 6 is tenuous and may have led to lower early-childhood asthma labeling in FAIR. Nevertheless, there also remained a higher prevalence of asthma among subjects in the IOWBC at 10 years of age. The FAIR cohort was established in 2001–2002, so this pattern may also reflect the reported decrease in asthma prevalence observed after 2006, though this trend would not account for the entire magnitude of difference between both cohorts.[30] Other early-life factors, such as allergen sensitization, breastfeeding rates, and socioeconomic level, may also contribute to these differences in asthma prevalence.

Limitations in the study include reliance on subjective reports for many variables assessed, including wheezing frequency, other atopic symptoms, and nature of early-life chest infections. Asthma outcomes evaluated were also restricted to subjective reports of ongoing wheezing, asthma diagnosis, and use of asthma therapies. Definitions utilized between the two cohorts were not equivalent and may have accounted for some of the differences in characteristics observed. Further studies to evaluate other objective outcomes, including lung function and response to specific therapies, could better delineate cluster outcomes and provide guidance for management approaches for each cluster. Additionally, a geographically limited population limits wider applicability of these findings due to the homogenous patient population residing on an island. Expansion of this cluster analysis model to other populations can further establish its clinical relevance.

The findings of this cluster analysis on two similar populations adds to the growing understanding of the heterogenicity of early-life wheezing. Clustering patterns observed in this study indicate that early-life wheezing associated with atopy or other allergic comorbidities, regardless of wheezing age of onset, has the highest rates of asthma at age 10. This highlights the importance for the evaluation of allergic comorbid conditions to identify and treat these patients earlier. In children who do not have atopy, early onset of wheezing that persists

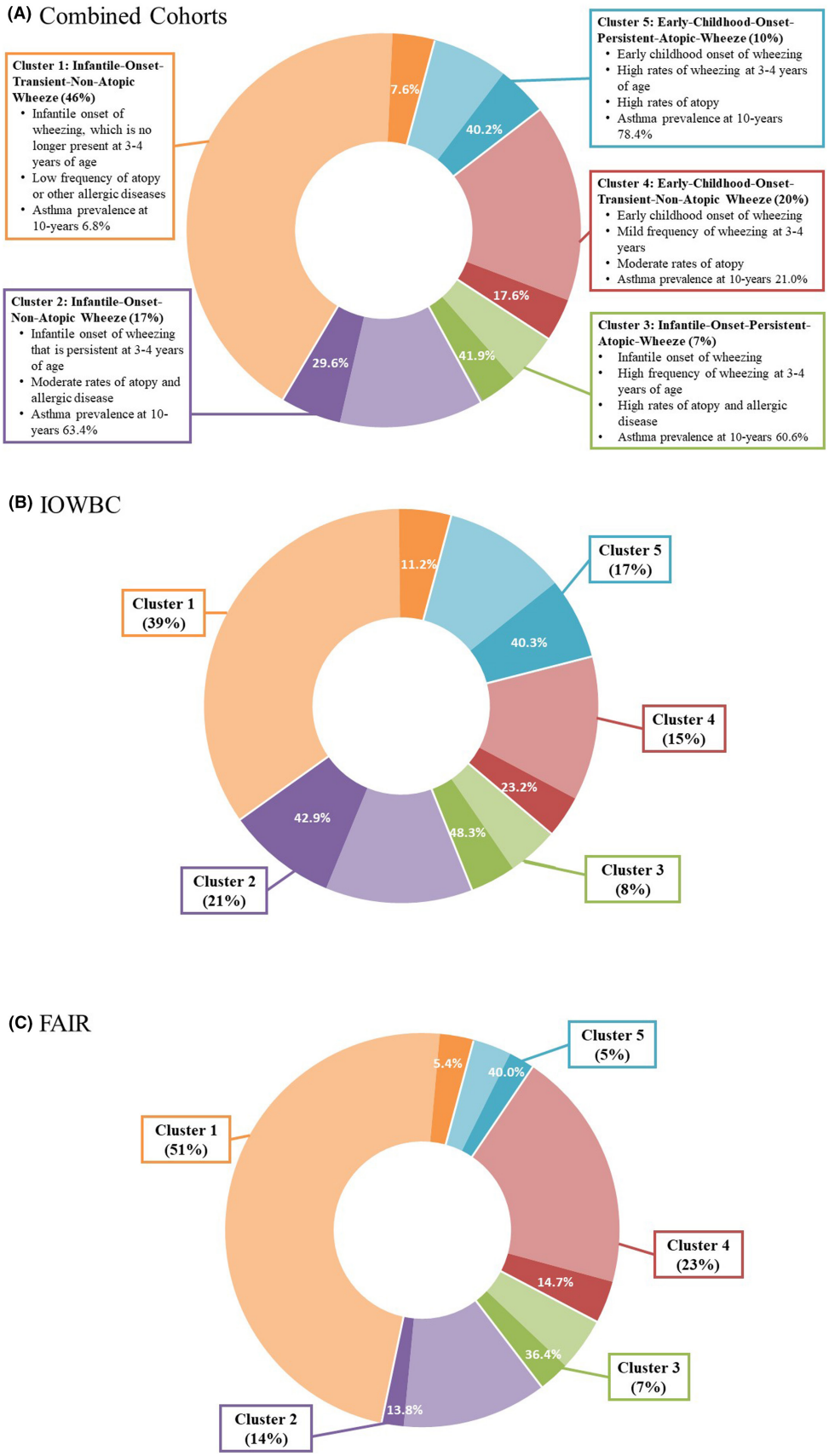

FIGURE 2 Summary of early-life wheezing cluster characteristics and 10 year asthma outcome. Proportion of patients within each of the clusters among (A) combined clusters, (B) IOWBC, and (C) FAIR. Darker shaded area indicates percentage of patients within each cluster who met criteria for a diagnosis of asthma at age 10 years.

beyond 3–4 years of age also have a higher risk of carrying a diagnosis of asthma at 10 years of age. Differences in clusters between cohorts may also indicate longitudinal trends in factors that may affect onset of wheezing and asthma. Specifically, risk increased by higher frequency of early-life respiratory infections may be less pronounced over time with better recognition of their role as a risk factor. Conversely, there is increasing importance of environmental factors including low socio-economic level, infant BMI and maternal tobacco smoking that require addressing. Further study of these childhood wheeze clusters should focus on whether earlier detection and management and mitigation of risk factors has potential to improve longer term health outcomes.

AUTHOR CONTRIBUTIONS

Suzanne Ngo Y: Conceptualization; investigation; writing – original draft; visualization. **Carina Venter:** Conceptualization; investigation; writing – review and editing; funding acquisition; supervision; resources; methodology. **William Anderson C:** Conceptualization; writing – review and editing; supervision. **Kaci Picket:** Investigation; methodology; formal analysis; data curation; writing – review and editing; visualization. **Hongmei Zhang:** Investigation; methodology; formal analysis; data curation; writing – review and editing; conceptualization. **Hasan Arshad S:** Conceptualization; investigation; funding acquisition; writing – review and editing; methodology; supervision; resources. **Ramesh Kurukulaaratchy J:** Conceptualization; investigation; funding acquisition; writing – review and editing; methodology; supervision; resources.

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CONFLICT OF INTEREST STATEMENT

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PEER REVIEW

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SUPPORTING INFORMATION

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

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