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The role of wheezing subtypes in the development of early childhood asthma

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Abstract

Background Early childhood wheezing is associated with asthma risk at later ages, emphasizing the need for understanding wheezing patterns and their implications for asthma development.

Methods Children in the F2-generation ($n=603$) of the Isle of Wight Birth Cohort (IOWBC) were followed-up at 3, 6, 12, 24, 36, and 72 months. Prevalence of wheeze and wheeze type (general, infectious, and non-infectious) were recorded. Group-based trajectory models covering ages 3 to 36 months were used to identify early childhood wheezing trajectories for each type of wheeze. These trajectories were examined for their association with asthma status and lung function at 6 years and later.

Results Distinct trajectories for general ("Persistent", "Transient", "Progressive", and "Infrequent/Never"), infectious ("Persistent", "Transient", and "Infrequent/Never"), and non-infectious ("Progressive", "Early Occurrence", and "Infrequent/Never") wheezing were identified. Compared to the "Infrequent/Never" trajectories, four trajectories were associated with an increased risk of asthma, namely "Progressive" non-infectious, "Early Occurrence" non-infectious, "Persistent" infectious, and "Persistent" general wheeze trajectories.

Conclusions The identification of wheeze trajectories across different etiologies as significant risk factors for asthma may aid in understanding the complex, multifactorial nature of asthma onset. The findings suggest that early identification of specific wheeze patterns, not just occurrence of wheezing, can inform clinical interventions and potentially mitigate the risk of developing asthma.

Background

Allergic respiratory diseases, including asthma and wheezing, are common in early childhood [1]. Globally, asthma is one of the most frequent chronic respiratory diseases with a prevalence of 357.4 million individuals in 2019 [2]. Pediatric asthma is considered to have multiple unclear clinical indications and etiologies [3]. Hence, asthma as a heterogeneous disorder incorporates multiple common conditions and treatments, and thus, there is no "gold standard" for its diagnosis [4]. Studies suggest that there is an association between wheeze events in early childhood and later asthma diagnosis, and that this association may be related to the mode, persistence, and temporality of wheeze [5–9].

Thus, it has been suggested that asthma is best described via the scoring or assessment of signs and symptoms, namely the occurrence of wheezing – its timing, duration, severity, and etiology [10–12]. Previous indexes, such as The Asthma Predictive Index, have used summative occurrence as partial proxies for asthma risk

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[13]. However, to produce a more robust assessment, the patterns of wheezing temporality and occurrence have been investigated through group-based trajectory modeling. This approach condenses onset and duration of wheezing into classifications that may aid and hasten clinical interventions compared to observations of wheeze alone. Phenotypic trajectories of childhood wheeze have been developed previously [14–16] and were described in a meta-analysis that identified consistent allocation of children into five wheeze trajectories in early childhood: "Never/Infrequent", "Early-Transient", "Early-Persistent", "Intermediate-Onset", and "Late-Onset" [17]. In the thirteen studies described by the meta-analysis, asthma was the most prevalent among children exhibiting persistent wheeze with an early onset, but later onset was important for children with already known risk factors for asthma.

However, previous studies have only assessed wheezing irrespective of potential differences in biological mechanisms of wheezing derived from infection or in the absence of infection. These wheezing types may differentially impact the development and pattern of wheeze and asthma in early childhood. This study addresses a gap in the literature by assessing not only non-specific wheezing (general), but also wheezing in the presence or absence of infection (i.e. infectious and non-infectious wheeze). In addition, this study provides evidence relating phenotypic trajectories to lung function and biomarker tests such as the fraction of exhaled nitric oxide (FeNO) and forced expiratory volume (FEV1), which have both been proven useful in the discrimination of wheeze and asthma [18, 19].

Methods

Study population

In 1989–1990, a whole birth cohort was established on the Isle of Wight (IOWBC), United Kingdom wherein 1,456 newborns were enrolled (F1 generation). This cohort was extended to three generations: F0, grandparents; F1, parents; and F2, grandchildren [20]. Recruitment in the F2 generation occurred among offspring of F1 parents (F2: $n = 611$ from 2010 to 2022). Extensive descriptions of the IOWBC F1 and F2 generations can be found elsewhere [21, 22]. Wheeze information was collected via questionnaires from the F2 generation at 3, 6, 12, 24, 36, and 72 months (or later) with information collected for 603 children. Data on asthma and other covariates were obtained from the F2 generation questionnaires and clinical documents. Ethical considerations were approved by NRES Committee South Central, Hampshire B, UK upon enrollment and during follow-up and at the University of Memphis (IRB ID: 2423).

Data collection and covariates

Questionnaire data collected at follow-ups approximately at ages 3, 6, 9, 12, 24, 36, and 72 months (or later due to the COVID-19 pandemic) were used to determine the presence and condition of wheezing at each timepoint. At each follow-up, we distinguished three wheezing responses: general, infectious, and non-infectious wheezing (Table 1). Children were classified as having general wheeze if questionnaire data indicated a positive response to the child having "wheezing or whistling in the chest". In children with general wheeze, questionnaire data were used to further distinguish between infectious and non-infectious wheezing at each timepoint. If the wheezing was described occurring "between colds or chest infections" then the wheezing was classified as non-infectious wheezing. When parents identified wheeze "in association with chest infection" or "in association with a cold," wheeze for that time point was assigned as infectious. Wheeze statuses (yes or no) up to 36 months were used as dependent variables in trajectory analyses separate for cause of wheezing (infectious, non-infectious, general). This approach was previously used in the assignment of the wheeze status in the first 12 months of life [23].

Asthma in offspring at 72 months (or later) was the primary outcome of interest for this study. Children were defined as asthmatic either through a doctor's diagnosis or via the presence of non-infectious wheezing or dry cough in the night at 72 months in conjunction with the prescription of either bronchodilators or inhaled corticosteroids. This definition of asthma has been successfully used previously and, importantly, in this young age included a tentative definition by clinicians [24]. Several other covariates were considered as potential confounding factors. Associations of wheezing trajectories and asthma were adjusted for gender [25–27], birth weight

Table 1 Prevalence of wheeze responses by month of wheeze assessment ($n = 603$)

	3 Months	6 Months	12 Months	24 Months	36 Months	72 Months	*p*-value[1]
General Wheeze	135 (26%)	71 (37%)	142 (37%)	94 (35%)	111 (47%)	41 (34%)	< 0.001
Missing	93	409	220	336	368	481	
Infectious Wheeze	108 (22%)	65 (34%)	133 (35%)	90 (34%)	103 (44%)	39 (32%)	< 0.001
Missing	106	409	221	336	368	481	
Non-Infectious Wheeze	54 (11%)	27 (14%)	35 (9.2%)	19 (7.2%)	21 (8.9%)	12 (9.9%)	0.3
Missing	94	410	222	340	368	482	

[1]Pearson's Chi-squared test comparing assessments

[28–30], birth height [31], maternal and paternal history of atopic disease [32–34], exposure to domestic pets [35, 36], and living on farms [37–39].

In addition, to explore whether wheezing trajectories are associated with respiratory or immune markers, we additionally investigate associations of different wheezing trajectories with lung function and allergic markers. These include forced expiratory volume in the first second (FEV_1), and fractional exhaled nitric oxide (FeNO) assessed at about 6 years of age. Forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), and forced expiratory flow when 25 and 75% of the FVC has been expired (FEF25–75) were measured using a Koko Spirometer and software with a portable desktop device (both PDS Instrumentation, Louisville, KY, USA). Spirometry was performed and evaluated according to the American Thoracic Society (ATS) criteria. The children were required to be free of respiratory infection for 2 weeks and not to be taking any oral steroids and were advised to abstain from any β-agonist medication for 6 h and from caffeine intake for at least 4 h [40]. Sex-stratified linear regression models of lung function tests (FVC, FEV_1, FEF25-75%, FEV_1/FVC, and FeNO) and their association to wheezing subtype trajectories were calculated, adjusting for maternal *in utero* smoking, birth order, birthweight, and birth height. The models were stratified by sex since the sex of the child has a strong influence on lung function [41].

Group-based trajectory modeling

Discrete group-based trajectory models were estimated using the wheeze status at the 3 to 36 month follow-up points. This time-window facilitates the detection of wheezing trajectories that precede the onset of asthma determined at age 6 years (or later). The procedure TRAJ in SAS [42] was applied to perform trajectory analyses. This procedure probabilistically assigns specific wheeze trajectories to individual children based on which trajectory is most probable based on that child's signs of wheezing. It retains participants with missing longitudinal data and the model parameters are estimated using the maximum likelihood method [42]. The best-fitting model was determined based on Bayesian Information Criterion values (BIC). For each wheeze group (general, infectious, and non-infectious), models were fit up to the fifth polynomial order with a maximum of five trajectories assessed. To assess all possible combinations of trajectories (up to 6) and polynomial orders, a SAS macro, AutoTRAJ, was written to automate this process [43]. Trajectory names for our analyses were selected in agreement with previous studies and proposed standardized naming practices [17, 44]. The current analyses establish separated models and trajectories for different types of wheezing (general, infectious, non-infectious). In a next step, log-binomial models in SAS procedure GLIMMIX were used to assess the association between membership in etiology-specific wheeze trajectories and asthma status.

When assessing the role of different wheezing conditions for asthma assessed at age 72 months (or later), all covariates were included in the initial log-binomial models. Covariates were considered as confounders if their presence changed the odds ratio of statistically significant trajectories by 10% or more. Culling of covariates was performed via backwards selection to produce the most parsimonious model. Offspring gender and familial history of asthma were considered a priori and were retained throughout. Based on the finally selected model, receiver operating characteristic curves (ROC) were used to assess the quality of using wheeze trajectories to predict asthma status at 72 months.

Additionally, the sum of reported wheeze occurrences of individual children was used as a proxy of severity and temporality to distinguish trajectories via a readily identifiable clinical measure. By utilizing the summation of reported wheeze occurrences through 3 years, we hope to mirror the counts of wheeze often included in indices that predict and diagnose atopic diseases, such as The Asthma Predictive Index [13]. Kruskal-Wallis were performed using SAS procedure NPAR1WAY to determine if the average sum of wheeze occurrences was different among trajectories identified as risk factors for asthma and baseline measures. These sums of wheeze were also used in log-binomial models to provide comparisons between trajectories and raw counts of wheezing as indicators of childhood asthma.

In all association analyses, p-values of ≤ 0.05 were considered statistically significant. All data were analyzed with SAS version 9.4 (SAS Institute, Cary, NC). Summary tables were made in R using the package gtsummary [45].

Results

Table 1 shows the prevalences and missing information for 3 to 72 months. Prevalences of general and infectious wheeze were higher than non-infectious wheeze for every time point (Table 1). The prevalences of general and infectious wheeze varied between follow-up periods, which was not observed for non-infectious wheezing.

Trajectory models were fit for general, infectious, and non-infectious wheezing based on individual classification of wheezing type at follow-up. Regarding the trajectories for general wheeze, four distinct trajectories were detected: "Persistent", "Transient", "Progressive", and "Infrequent/Never" (Fig. 1). The "Infrequent/Never" trajectory exhibited a low occurrence of general wheeze throughout and was therefore used as a reference group in further analyses. Trajectories of infectious wheeze showed the best fit for three trajectories: "Persistent",

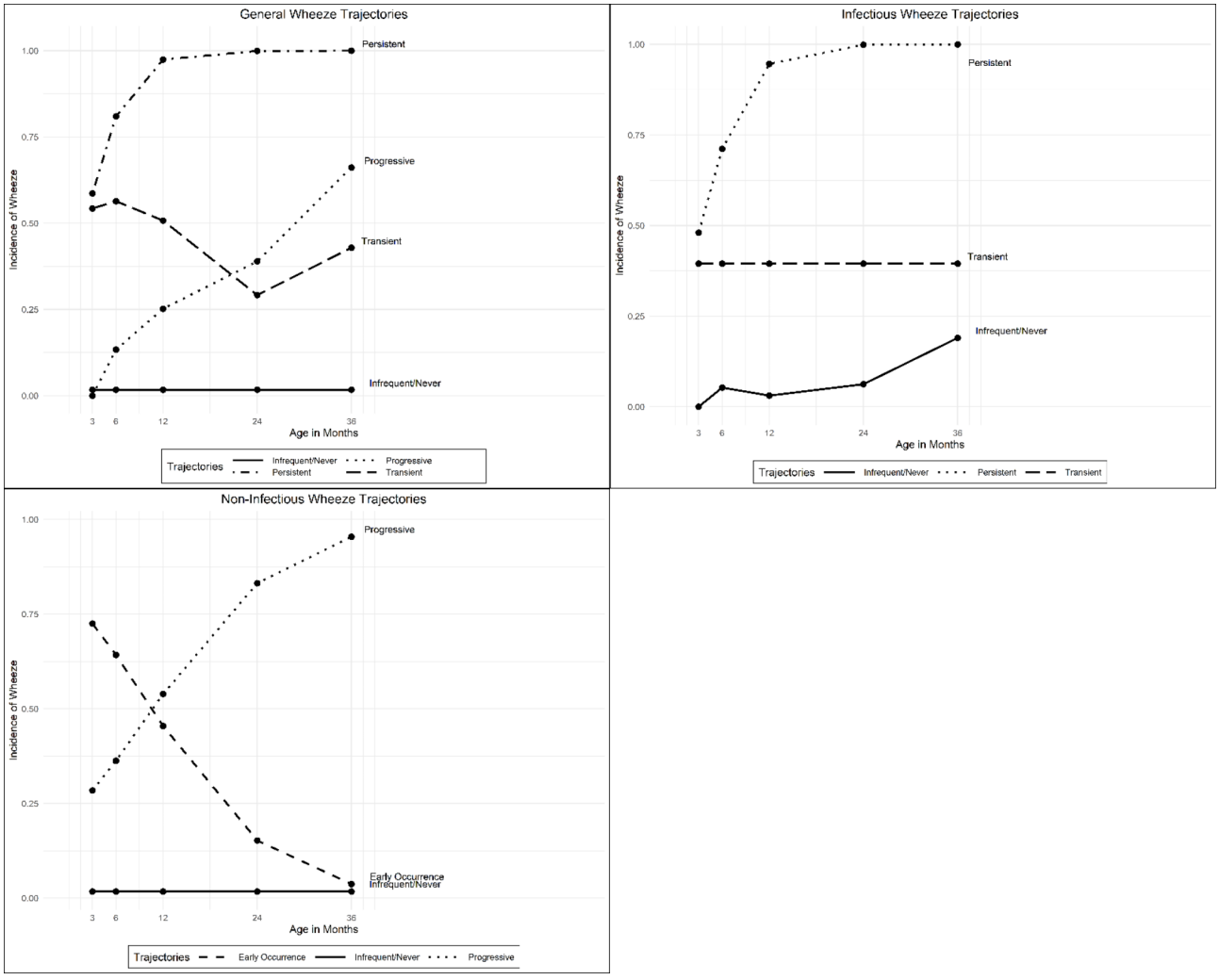

Fig. 1 Wheeze type specific trajectory models to 36 months

"Transient", and "Infrequent/Never" (Fig. 1). Three trajectories of non-infectious wheezing were detected: "Progressive", "Early Occurrence", and "Infrequent/Never" (Fig. 1). Most children were assigned membership to the "Infrequent/Never" trajectory regardless of wheeze type (non-infectious wheeze "Infrequent/Never": 88%; infectious wheeze "Infrequent/Never": 60%; general wheeze "Infrequent/Never": 52%). Given that all wheeze subtypes exhibited a similar "Infrequent/Never" trajectory, this trajectory was selected as a reference for all trajectories.

Regarding potential confounders, pet ownership, farm residence, and family history of allergic disease did not show any differences among the groups (Tables 2a, 2b, 2c). There are significant differences between the sex of the child for non-infectious wheeze trajectories with boys being more representative of the non-infectious "Early Occurrence" and "Progressive" trajectories. The mean number of reported wheeze was significantly higher for children that were not in the "Infrequent/Never" group across all wheezing types (Tables 2a, 2b, 2c; all p-values < 0.001).

The trajectory of progressive or persistent wheezing exists in all identified wheeze trajectory classifications (infectious, non-infectious, general), and further, these phenotypes of wheeze – progressive or persistent – significantly increase the risk of asthma at 72 months or later regardless of wheeze type (NIW "Progressive" OR 33.33; IW "Persistent" OR: 26.04; GW "Persistent" OR: 13.11). Investigating whether the trajectory sources overlap, we found that despite exhibiting a similar pattern of wheeze and increased asthma risk, there was no large overlap between general, infectious, and non-infectious persistent and progressive trajectories (Fig. 2).

Associations of general wheeze trajectories with asthma were controlled for gender, paternal and maternal history of allergic disease, birth height, and birth weight (Fig. 3). "Persistent" wheezing increased the odds of asthma at 6 years or later by 13.11 (95% CI: 1.35-127.57).

Table 2a General wheeze trajectory summary statistics

	Overall	Infrequent/ Never, *N* = 315[1]	Persistent, *N* = 105[1]	Progressive, *N* = 66[1]	Transient, *N* = 117[1]	*p*-value[2]
Gender						0.061
Female	262 (44%)	149 (49%)	36 (35%)	30 (45%)	47 (40%)	
Male	330 (56%)	156 (51%)	68 (65%)	36 (55%)	70 (60%)	
Asthma Diagnosis at 72 Months or later	15 (2.5%)	1 (0.3%)	8 (7.6%)	1 (1.5%)	5 (4.3%)	< 0.001
Maternal History of Allergic Disease	352 (72%)	183 (72%)	62 (74%)	36 (62%)	71 (75%)	0.4
Paternal History of Allergic Disease	235 (66%)	115 (68%)	46 (69%)	33 (69%)	41 (56%)	0.3
Resides on Farm	11 (1.9%)	8 (2.8%)	0 (0%)	1 (1.5%)	2 (1.8%)	0.4
Pet in the Home	316 (54%)	166 (56%)	53 (50%)	38 (58%)	59 (50%)	0.6
Parental Reports of General Wheeze from 3–72 Months (Mean (SD))	1.10 (1.33)	0.02 (0.14)	2.84 (1.31)	1.55 (0.71)	1.62 (0.86)	< 0.001

[1]n (%); Mean (SD)

[2]Pearson's Chi-squared test; Fisher's exact test; Kruskal-Wallis rank sum test

Table 2b Infectious wheeze trajectory summary statistics

	Overall	Infrequent/Never, *N* = 359[1]	Persistent, *N* = 104[1]	Transient, *N* = 140[1]	*p*-value[2]
Gender					0.091
Female	262 (44%)	167 (48%)	38 (37%)	57 (41%)	
Male	330 (56%)	182 (52%)	65 (63%)	83 (59%)	
Asthma Diagnosis at 72 Months or later	15 (2.5%)	1 (0.3%)	9 (8.7%)	5 (3.6%)	< 0.001
Maternal History of Allergic Disease	352 (72%)	211 (72%)	61 (74%)	80 (68%)	0.6
Paternal History of Allergic Disease	235 (66%)	137 (67%)	42 (67%)	56 (62%)	0.7
Resides on Farm	11 (1.9%)	8 (2.4%)	0 (0%)	3 (2.3%)	0.3
Pet in the Home	316 (54%)	195 (57%)	52 (50%)	69 (49%)	0.2
Parental Reports of Infectious Wheeze from 3–72 Months (Mean (SD))	1.00 (1.28)	0.11 (0.34)	2.72 (1.29)	1.60 (0.76)	< 0.001

[1]n (%); Mean (SD)

[2]Pearson's Chi-squared test; Fisher's exact test; Kruskal-Wallis rank sum test

Table 2c Non-infectious wheeze trajectory summary statistics

	Overall	Early Occurrence, *N* = 51[1]	Infrequent/Never, *N* = 529[1]	Progressive, *N* = 23[1]	*p*-value[2]
Gender					< 0.001
Female	262 (44%)	13 (25%)	246 (47%)	3 (13%)	
Male	330 (56%)	38 (75%)	272 (53%)	20 (87%)	
Asthma Diagnosis at 72 Months or later	15 (2.5%)	7 (14%)	3 (0.6%)	5 (22%)	< 0.001
Maternal History of Allergic Disease	352 (72%)	30 (79%)	309 (72%)	13 (59%)	0.3
Paternal History of Allergic Disease	235 (66%)	17 (63%)	206 (66%)	12 (71%)	0.9
Resides on Farm	11 (1.9%)	0 (0%)	11 (2.2%)	0 (0%)	0.8
Pet in the Home	316 (54%)	22 (43%)	280 (55%)	14 (61%)	0.2
Parental Reports of Non-Infectious Wheeze from 3–72 Months (Mean (SD))	0.31 (0.76)	1.71 (0.88)	0.06 (0.24)	2.35 (0.98)	< 0.001

[1]n (%); Mean (SD)

[2]Pearson's Chi-squared test; Fisher's exact test; Kruskal-Wallis rank sum test

This translated to decreases in lung function for the male "Persistent" general wheezers (17% of children) of -0.41 L for FVC, -0.38 L for FEV1, and − 0.47 L for FEF25-75% lung function tests (Table 3). Likewise, for infectious "Persistent" wheezing (17% of children), there was an increased risk of asthma at or after 6 years (OR: 26.04, 95%CI: 2.59-261.77) that further corresponded to a -0.23 L decrease in FEV1 and a -0.38 L decrease in FEF25-75% test in males. There was no "Persistent" non-infectious wheezing trajectory.

Although the "Progressive" general wheeze (11% of children) was associated with a -0.31 L decrease in FVC for male offspring (Table 3), membership in that trajectory did not significantly increase the odds of asthma at or after 72 months (OR: 2.32; 95%CI: 0.12–44.46). Similarly, "Progressive" non-infectious wheezing (4% of

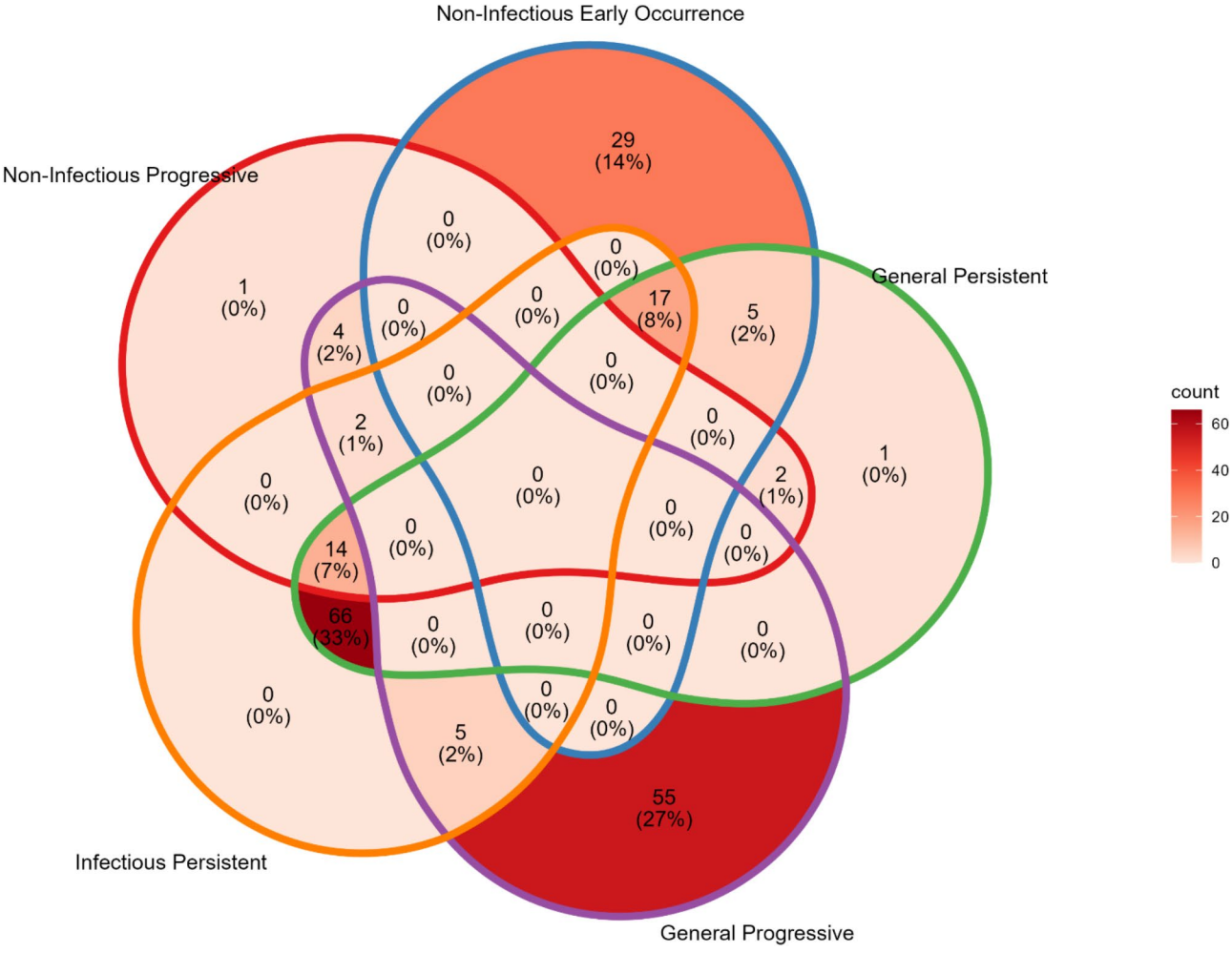

Fig. 2 Associations between wheezing subtype and F2-offspring asthma

children) had 33.33 times the odds of asthma compared to "Infrequent/Never" non-infectious wheezing (95%CI: 4.40-252.38), yet this trajectory was not associated with any changes in lung function.

Transience of general wheezing was not associated with lung function or asthma diagnosis at 6 years of age (Fig. 3). The "Transient" infectious wheeze trajectory did not show a significant risk of asthma with an increase in odds of 1.71 for those children compared to children in the "Infrequent/Never" trajectory (95%CI: 0.09–30.95). However, for male children, membership in the "Transient" infectious wheezing trajectory was associated with a -0.28 L decrease in FVC, a -0.25 L decrease in FEV1, and a -0.37 decrease in FEF25-75%.

The non-infectious "Early Occurrence" trajectory showed increased odds of asthma at or after 72 months (OR: 16.91; 95%CI: 1.90-150.20). This was the only trajectory for which the lung function of girls was impacted with a decrease in FEV1/FVC ratio of -0.08 (Table 3).

The predictability of wheeze trajectory on asthma status at or after 72 months was assessed using ROC (receiver operating characteristics) curves for the three wheezing subtypes. To compare and evaluate these ROC curves, the area under the curve (AUC) was evaluated. AUC values above 0.7 suggest the trajectories have a high proportion of correctly predicting asthma diagnoses at or after 72 months (Fig. 4). The Mann-Whitney AUC for the general wheeze trajectory model was 0.84 (95%: 0.66–1.00). The infectious wheeze model had a similar AUC (0.87, 95%: 0.70–1.00). Non-infectious wheeze presented a somewhat higher predictive accuracy with an AUCs of 0.91 (95% CI: 0.80–1.00).

Further, to compare wheezing trajectories to counts of wheezing occurrence (as would be used in the present clinical setting via wheezing indices), we assessed differences in wheezing occurrence by trajectory using Kruskal-Wallis tests (Tables 2a, 2b, 2c). For children with "Persistent" general wheeze, on average, 2.71 periods of wheeze were reported in the five follow-ups. Children without "Persistent" general wheezing exhibited significantly less wheeze occurrences over five follow-up periods (mean: 0.62, p-value < 0.0001). This was also observed

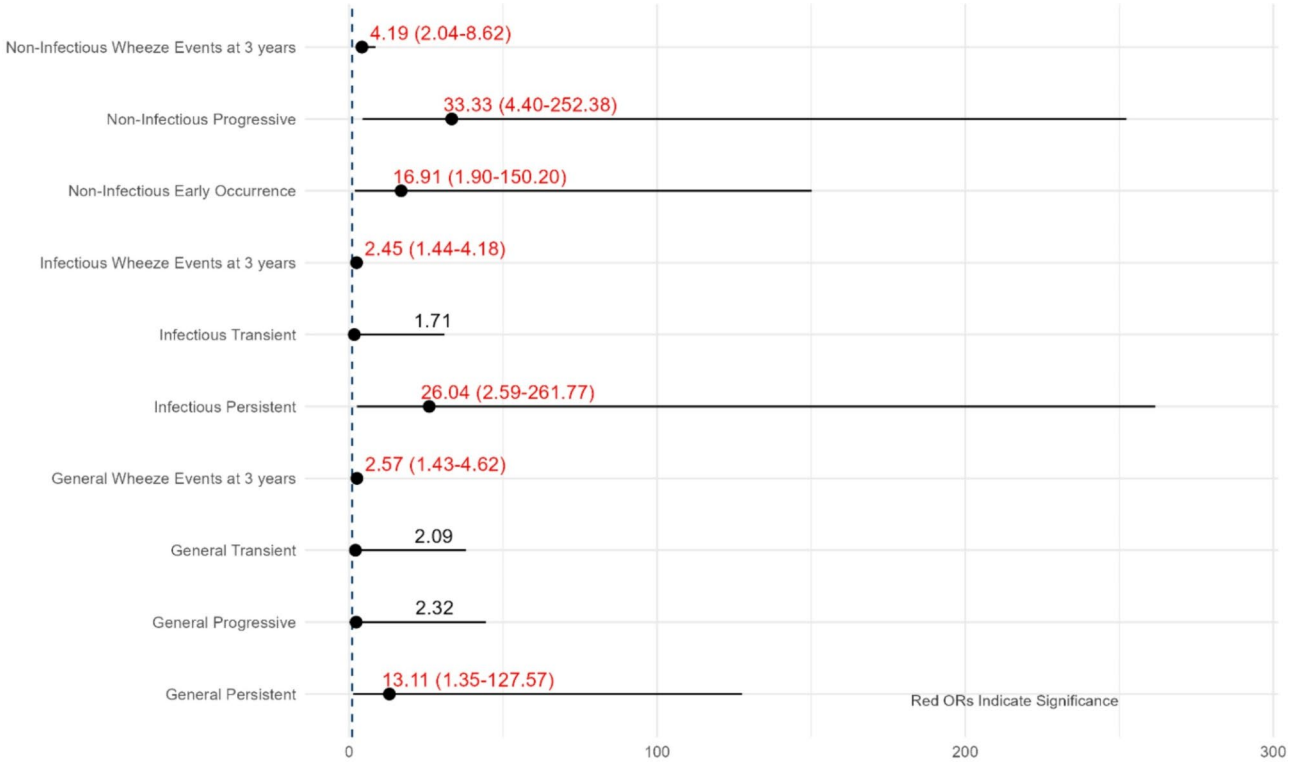

Fig. 3 Associations between wheezing subtype and F2-offspring asthma

Table 3 Parameter estimates of lung function tests by wheezing subtype trajectory (estimate (*p*-value))

		FVC in Liters		FEV1 in Liters		FEV1/FVC Ratio		FEF 25–75% in Liters		FeNO in log(Liters)	
		Males *n* = 43	Females *n* = 43	Males *n* = 43	Females *n* = 43	Males *n* = 43	Females *n* = 43	Males *n* = 43	Females *n* = 43	Males *n* = 44	Females *n* = 38
General	Persistent	***-0.41 (0.0033)***	0.06 (0.5184)	***-0.38 (0.0019)***	-0.03 (0.7079)	-0.02 (0.5245)	-0.06 (0.0701)	***-0.47 (0.0211)***	-0.26 (0.2182)	0.07 (0.6918)	-0.07 (0.7227)
	Transient	-0.17 (0.1886)	0.06 (0.5194)	-0.11 (0.3276)	-0.06 (0.4394)	0.02 (0.5751)	0.003 (0.9053)	-0.09 (0.6577)	-0.10 (0.6074)	-0.07 (0.7465)	0.21 (0.3737)
	Progressive	***-0.31 (0.0443)***	0.04 (0.6854)	-0.21 (0.1130)	-0.05 (0.5664)	0.04 (0.37)	-0.01 (0.888)	-0.01 (0.9545)	-0.17 (0.4678)	-0.07 (0.7188)	-0.02 (0.9090)
Infectious	Persistent	-0.23 (0.0736)	-0.01 (0.9362)	***-0.23 (0.0437)***	-0.06 (0.4396)	-0.02 (0.5189)	-0.04 (0.2462)	***-0.38 (0.0433)***	-0.22 (0.2662)	0.19 (0.2639)	-0.09 (0.6262)
	Transient	***-0.28 (0.0331)***	0.01 (0.9466)	***-0.25 (0.0227)***	-0.01 (0.8388)	-0.02 (0.6688)	-0.01 (0.8555)	***-0.37 (0.046)***	-0.08 (0.6378)	-0.04 (0.8022)	-0.05 (0.7400)
Non-infectious	Early Occurrence	-0.04 (0.8057)	-0.02 (0.9044)	-0.04 (0.7810)	-0.13 (0.2264)	-0.02 (0.5700)	***-0.08 (0.0429)***	-0.06 (0.7847)	-0.47 (0.0833)	0.07 (0.7346)	-0.31 (0.1198)
	Progressive	0.02 (0.9015)	N/A	0.02 (0.8851)	N/A	-0.01 (0.8074)	N/A	-0.15 (0.5760)	N/A	-0.06 (0.7959)	N/A

Bolded estimates have *p*-values less than 0.05

for "Persistent" infectious wheeze, which had a mean of 2.72 reports while members of other infectious wheeze trajectories had a mean of 0.59 reports of wheeze across five questionnaires (p-value < 0.0001). Non-infectious "Early Occurrence" wheeze averaged 1.71 reported wheezing periods over the follow-up compared to 0.17 for all other non-infectious trajectories (p-value < 0.0001). Similarly, "Progressive" non-infectious wheeze reported 2.35 periods during the follow-up compared to 0.22 for all other non-infectious wheeze types.

One increase of reported general wheeze events by 36 months was significantly associated with asthma (OR: 2.57; 95%CI: 1.43–4.62). This was similarly seen for reported infectious wheeze (OR: 2.45; 95%CI: 1.44–4.18). The magnitude was increased for non-infectious wheeze. One additional reported non-infectious wheeze event

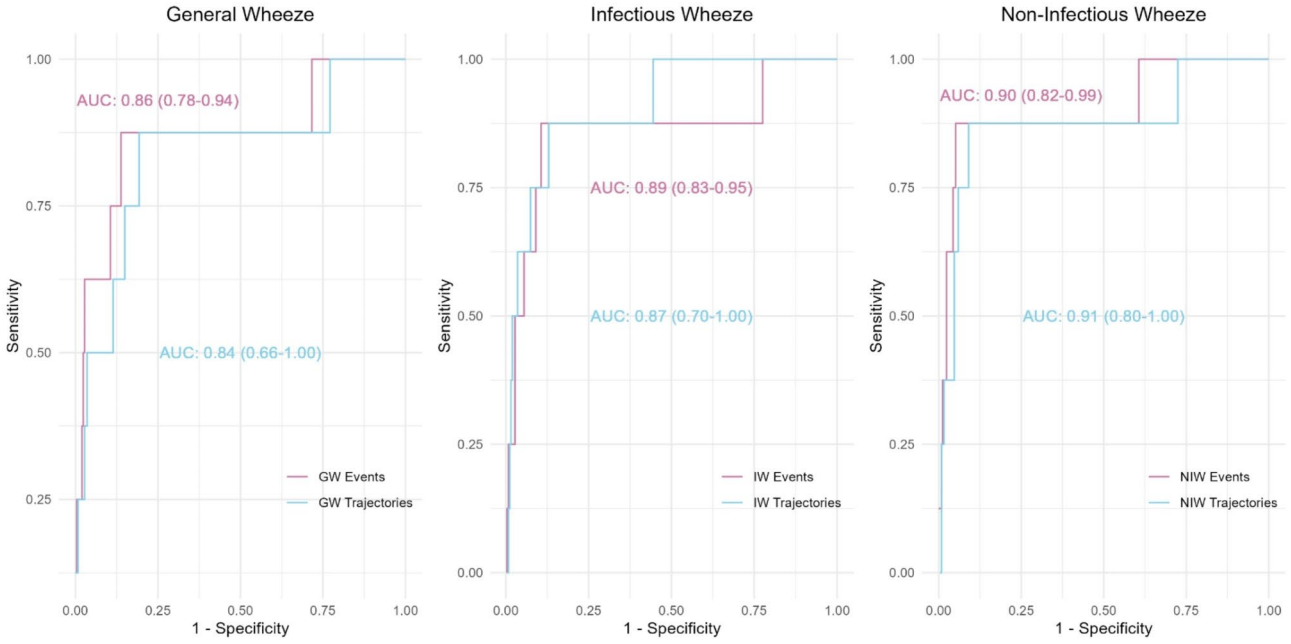

Fig. 4 ROC Curves for Models of Subtype Trajectories and Reported Events

was associated with 4.19 times higher odds of asthma (95%CI: 2.04–8.62). Reported general, infectious, and non-infectious wheeze events exhibited similar AUC and predictability for asthma diagnosis as wheezing trajectories (Fig. 4).

Discussion

Trajectory models of the symptoms of wheeze based on questionnaires from 3 to 36 months yielded three non-infectious (NIW), three infectious (IW), and four general wheeze (GW) trajectories. A comparable study assessing eight wheeze assessments from 3 to 60 months utilizing the same methodology based on general wheeze found four trajectories [46]. Two other studies, in addition to the previously mentioned study, looking at general wheeze from infancy to adolescence consistently detected persistent and infrequent wheeze trajectories with the remaining trajectories being variations of transient wheeze of various onsets, incidents, and durations [46–48]. A "Persistent" non-infectious wheeze trajectory did not emerge despite being present in general and infectious wheezing (Fig. 1). The lack of a "Persistent" non-infectious wheeze trajectory suggests that previously identified generalized wheeze models from the literature fail to capture the effect of non-infectious wheeze since the emphasis is often placed on persistent general wheeze in these studies. Yet in this study, non-infectious wheeze presents a significantly higher risk for asthma at 72 months without a "Persistent" wheeze trajectory. This suggests that prior studies focused on only general wheeze and the importance of persistence may overlook the impact of non-infectious wheeze.

Four trajectories showed significant associations with an asthma diagnosis at 6 years or later: GW "Persistent", IW "Persistent", NIW "Persistent", and NIW "Progressive". Regarding general wheeze, "Persistent" general wheeze led to a 13.11-fold increase in odds of later asthma diagnosis. While previous studies have shown the increased risk of asthma due to persistent wheeze, the trajectory analysis suggests that the risk may be greater than previously assessed [49]. Furthermore, "Persistent" general wheeze comprises a substantial number of children (17.4%). Also, infectious "Persistent" wheezing trajectory was associated with later asthma diagnoses (OR: 26.04). The importance of persistent wheezing as an indicator of asthma is well documented [17, 50]. We found no indication that general or infectious transient wheezing increased the odds of later asthma diagnosis at 6 years.

Regarding the non-infectious group, "Progressive" wheeze increases the odds for asthma compared to "Infrequent/Never" (OR: 33.33; 95%CI: 4.40-252.38). In the "Progressive" trajectory, the occurrence of non-infectious wheeze continued to rise over time. Wheeze among the "Early Occurrence" non-infectious trajectory exhibited high levels during infancy that quickly declines later in life – the inverse of the "Progressive" trajectory. The "Early Occurrence" trajectory increased the odds of asthma as well (OR: 16.91), which is supported by another study showing that early onset of wheezing is a risk factor for asthma [51]. All phenotypic

trajectories with non-infectious wheeze was associated with increased odds of developing asthma at or after 72 months.

The lack of a non-infectious "Persistent" trajectory represents a departure from the previously identified understanding of wheezing in early childhood – previous studies, utilizing only general wheeze detected and identified the importance of persistent general wheezing in the development of asthma [46–48]. However, these studies were unable to detect non-infectious wheezing due to their methodology. Therefore, they could not identify the importance of non-infectious wheezing, which does not exhibit a persistent wheeze trajectory.

Moreover, this study has identified two trajectories of non-infectious wheeze that both increase the risk of asthma but provide different phenotypes of wheezing. "Progressive" non-infectious wheezing may represent increased non-infectious wheezing occurring as asthma develops. Conversely, "Early Occurrence" non-infectious wheezing may represent non-infectious wheezing that occurs as a precursor, or possible cause, of asthma.

Regarding wheezing trajectories and measurable markers, "Persistent" infectious and general wheezing was also associated with decreased lung function (Table 3). FEV_1 and FEF25-75% in male offspring were significantly associated with reduction in lung capacity for any phenotype of infectious wheezing and "Persistent" general wheezing. Declining FEV_1 function is strongly linked with increased risk of pediatric asthma attacks [52]. Moreover, FEF25-75% has been shown to be a possible early marker of asthma and asthma severity [53, 54]. FVC was significantly negatively associated with "Persistent" infectious and general wheeze as well as "Progressive" general wheezing in male offspring. Male children with mild to moderate asthma have significantly lower FVC [55]. The results identify that among two trajectories associated with asthma ("Persistent" infectious and general wheeze), there are significant reductions in FEV_1, FEF25-75%, and FVC. In girls, the ratio of FEV_1 and FVC was lower for "Early Occurrence" non-infectious wheezing. The FEV_1/FVC ratio has been found to be lower in children with persistent asthma; however, these results indicate that the ratio of FEV_1 and FVC is lower among a specific phenotype of non-infectious wheezing that is associated with increased asthma risk [56].

Our findings disagree with a previous study that emphasizes transient or intermittent infectious wheeze as significant risk factors for the development of asthma [17]. We find that general and infectious wheezing is most impactful for asthma risk when it is progressive or persistent. Our findings suggest that any presence of non-infectious wheeze greatly increases the risk of asthma diagnosis at 72 months or later. Moreover, general and infectious "Persistent" wheezing were significant risk factors for later asthma diagnosis.

Depending on the wheeze type, children reporting two or three wheezing events in the first three years were associated with membership in wheezing trajectories with higher odds of later developing asthma (Tables 2a, 2b, 2c). Moreover, in all wheezing subtypes, increased reports of wheeze at 36 months were risk factors for asthma at or after 72 months – increased wheezing was a risk factor for asthma. However, the mean number of reported wheezing periods does not vary among trajectories leading to asthma, which makes differentiation between at-risk and benign trajectories impossible through the counting of wheezing episodes alone.

For example, a child exhibiting two reports of general wheezing at 36 months could be categorized as either "Persistent", "Progressive", or "Transient". Yet only the "Persistent" general wheeze trajectory increases asthma odds, which suggests that there is additional value to considerations of temporality and frequency in the differentiation of phenotypes into trajectories beyond just counts of wheeze episodes. Similarly, the mean reported level of wheeze by 72 months in "Early Occurrence" (1.71 events) and "Progressive" (2.35 events) non-infectious wheeze are indistinguishable, yet their phenotypes exhibit opposite timing – the count of reported wheeze could not differentiate the "Early Occurrence" and "Progressive" non-infectious wheeze without the added benefit of the temporality.

Moreover, this study assesses general wheeze using two subtypes. From this analysis we see that general and infectious wheeze are only risk factors for asthma when there is persistence of those wheeze types, while any non-infectious wheeze is a risk factor for asthma. This granularity may describe different biological pathways of the atopic march that are missed when only considering counts of general wheeze. Therefore, the combined consideration of wheeze type, temporality, and frequency of reported wheeze as described through trajectories provides additional context in the clinical setting.

Conclusions

The utilization of wheezing subtype to establish phenotypic trajectories of early childhood wheeze is a novel approach. Due to being identified at 36 months, wheezing phenotype trajectories provide insight into the development of asthma prior to diagnosis at 72 months. As in previous studies, we identify that persistence of general and infectious wheezing is an important indicator of asthma risk; however, we establish that there is no persistent phenotype of non-infectious wheezing. These non-infectious wheeze trajectories are not adequately described in the literature since there is no persistent non-infectious wheeze. Yet, we show that non-infectious

wheezing of any phenotype increases asthma risk. Because these wheeze type specific trajectories consider the temporality, type, and frequency of wheeze, they can better describe a child's phenotype of wheeze prior to the diagnosis of asthma when compared to merely counting wheeze episodes. Clinicians should utilize not just frequency, but also wheeze type and temporality to assess wheezing as a risk factor for asthma. This may provide critical time to administer prophylaxis, treatment, or other interventions.

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Author contributions
DW and WK conceived the design of the study, interpreted the data, and drafted the manuscript. YJ and HZ helped with the statistical analysis. HA supervised the data and sample collection. All authors critically revised the manuscript for important intellectual content. The manuscript has been read and approved by all authors.

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Data availability
The datasets analyzed during the current study are not publicly available but are available from the corresponding author on request.

Declarations

Ethics approval and consent to participate
Ethics approval was obtained from the Isle of Wight Local Research Ethics Committee at recruitment of this birth cohort born on the Isle of Wight, United Kingdom, between January 1989 and February 1990. Parents and children also consented for their data to be used at a later stage to identify asthma. Written informed consent was obtained from all children and parents before they participated in the study. For the F2 generation, we received ethics approval from the Isle of Wight, Portsmouth, and SE Hampshire Local Research Ethics Committee (Study Title: A study of epigenetic driven immunological changes in the development of Asthma and Allergy in infancy). Research Ethics Committee Reference Number: 09/H0504/129; Protocol number: 1; 4 December 2009. The latest renewal was on 14 October 2021, by the NRES Committee South Central—Hampshire B (09/H0504/129). At the University of Memphis, the Institutional Review Board approved the investigation (#2423).

Consent for publication
Not applicable.

Informed consent
Written informed consents were obtained from the parents until age 10 and at 18 and 26 years from the participants at each follow-up. The ethical principles for medical research involving humans with identifiable data followed the Declaration of Helsinki. For participants assessed by phone interview, consent was documented on the consent form with the name of the person giving consent, and the name and signature of the person taking the form were recorded.

Clinical trial number
Not applicable.

Competing interests
The authors declare no competing interests.

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