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ORIGINAL ARTICLE

Epidemiology of Allergic Disease

Trajectories of cough without a cold in early childhood and associations with atopic diseases

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Abstract

Background: Although children can frequently experience a cough that affects their quality of life, few epidemiological studies have explored cough without a cold during childhood.

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Objectives: The objective of the study was to describe the latent class trajectories of cough from one to 10 years old and analyse their association with wheezing, atopy and allergic diseases.

Methods: Questions about cough, wheeze and allergic diseases were asked at 1, 1.5, 2, 3, 4, 5, 6 and 10 years of age in the European prospective cohort of Protection against Allergy: STUdy in Rural Environment (PASTURE). Specific IgE assays were performed at 10 years of age. Questions regarding a cough without a cold were used to build a latent class model of cough over time.

Results: Among the 961 children included in the study, apart from the never/infrequent trajectory (59.9%), eight trajectories of cough without a cold were identified: five grouped acute transient classes (24.1%), moderate transient (6.8%), late persistent (4.8%) and early persistent (4.4%). Compared with the never/infrequent trajectory, the other trajectories were significantly associated with wheezing, asthma and allergic rhinitis. For asthma, the strongest association was with the early persistent trajectory (OR_a = 31.00 [14.03–68.51]), which was inversely associated with farm environment (OR_a = 0.39 [0.19–0.77]) and had a high prevalence of cough triggers and unremitting wheeze. Late and early persistent trajectories were also associated with food allergy. Atopic sensitization was only associated with the late persistent trajectory.

Conclusion: Late and early persistent coughs without a cold are positively associated with atopic respiratory diseases and food allergy. Children having recurrent cough without a cold with night cough and triggers would benefit from an asthma and allergy assessment. Growing up on a farm is associated with reduced early persistent cough.

KEYWORDS
allergic diseases, asthma, atopy, childhood, cough

1 | INTRODUCTION

Cough is a frequent and non-specific respiratory symptom in children that may considerably reduce their quality of life.[1] In the majority of otherwise healthy children, cough is a symptom related to a self-limiting viral upper respiratory tract infection that resolves within a week.[2]

However, children with coughs that are not associated with a respiratory infection but are often triggered by normally innocuous stimuli are commonly seen in paediatric practice. This type of cough is more frequent in children who also wheeze and the presence of the two concomitant symptoms is well documented in asthma. Regardless of associated asthma, coughs triggered by normally non-tussigenic stimuli highly suggest cough hypersensitivity, where dysregulated afferent neural pathways and/or the central processing of the cough are likely mechanisms[3,4] with atopy as one of the aetiological mechanisms.[5]

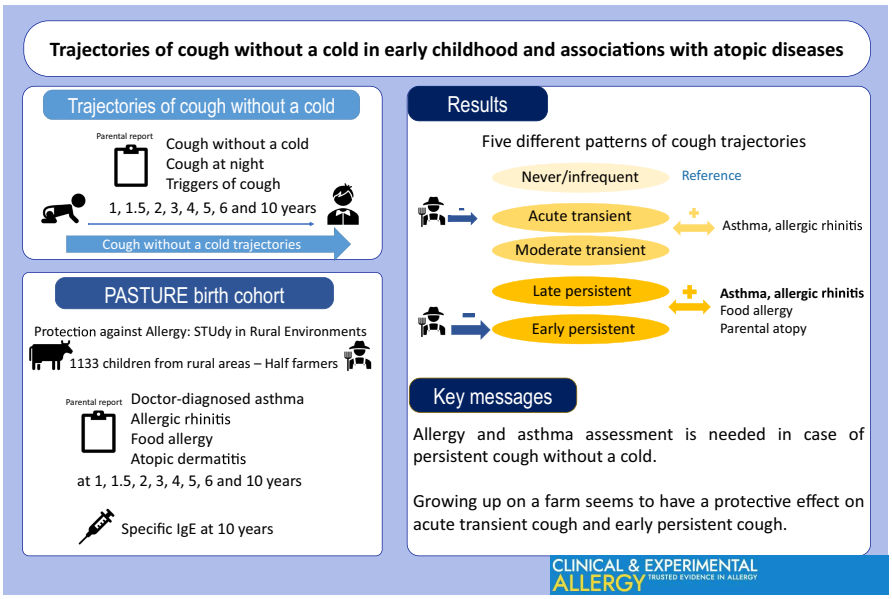
Understanding of the mechanisms behind the transition to chronic cough is still a great challenge. Recently published European Respiratory Society guidelines on the diagnosis and treatment of chronic cough refer to its predominant causes in children.[6]

Key messages

- Age at onset, triggers and persistence of symptoms are important to better characterize cough.
- Recurrent cough with night cough and triggers should lead to allergy and asthma assessment.
- Growing up on a farm is associated with reduced early persistent cough.

Systematic reviews and studies reveal that cough aetiology, frequency and sensitivity differ in many ways throughout childhood[5,7] and between children and adults,[8,9] so these guidelines recommend exploring the natural history of cough over time through observational cohort studies.

A data-driven approach, based on unsupervised statistical methods such as (LCA), has increasingly been used to explore the natural course of respiratory symptoms. Most studies using this approach focus on asthma,[10,11] and a few focus on allergic rhinitis and atopic sensitization.[12,13] Cough data have been mostly used to



GRAPHICAL ABSTRACT

Five different patterns of cough trajectories during early childhood have been highlighted. Recurrent cough without a cold, with night cough and triggers should lead to allergy and asthma assessment. Growing up on a farm seems to have a protective effect on acute transient cough and early persistent cough.

determine wheeze and asthma phenotypes.[14] While atopy and Th2 cell-mediated inflammation have been considered one of the aetiological mechanisms of cough hypersensitivity syndrome, no study has explored the relationship between cough and all atopic diseases, including food allergy and atopic dermatitis. In most studies that have investigated respiratory symptoms' trajectories throughout childhood, cough, wheezing and asthma were grouped together. Thus, cough is always explored as an asthma symptom and no studies focus on cough patterns.

The European prospective birth cohort PASTURE (Protection against Allergy STUdy in Rural Environment) involves children from rural areas and aims to evaluate risk and protective factors for allergic diseases, offering the opportunity to explore trajectories of cough without a cold in childhood and investigate their link with atopic diseases.

This study aims to assess trajectories of cough without a cold in childhood from 1 to 10 years old in the PASTURE cohort and their associations with atopic diseases, including asthma and the farming environment.

2 | METHODS

2.1 | Study design and population

The PASTURE/EFRAIM (Mechanisms of early protective exposures on allergy development) study focuses on a prospective birth cohort involving children born in 2002 and 2003 in rural areas in five European countries (Austria, Finland, France, Germany and Switzerland) to evaluate risk factors and protective factors for allergic diseases. The design of the PASTURE study has been described in detail elsewhere[15] and the inclusion and exclusion criteria of this study, detailed in online supplements, were those of the overall PASTURE study.[16] To briefly summarize, pregnant women were recruited during their third trimester of pregnancy and divided into two groups: women who lived on family-run farms where livestock was kept (farm group) and women from the same rural areas who did not live on a farm (non-farmer group). In total, 1133 children were included in this birth cohort. The study was approved by the local research ethics committee in each country, and written informed consent was obtained from the parents.

2.2 | Questionnaires

Questionnaires were self-administered by the parents when the children were 12, 18, 24, 36, 48, 60 and 72 months old and then at 10 years of age. The questionnaires were based on items from the International Study of Asthma and Allergies in Childhood,[17] the Asthma Muti-centre Infants Cohort Study[18] and the American Thoracic Society.[19] At all time-points, parents were asked "How often has your child had a cough without a cold during the last 12 months?" (or during the last 6 months at the 18- and 24-month follow-ups). The possible answer categories were "never," "less than once a month," "once a month" and "at least twice a month." The same question was asked for "cough at night without a cold." When the children reached 2 years of age, parents were also asked "Has your child ever had an attack of cough without a cold caused by one of the following factors: physical exercise, excitation, change of temperature?"

The length and characteristics of cough are described in the Appendix S1.

Unremitting wheeze was defined by the prevalence of wheeze without a cold or symptoms between wheezes reported by the parents at least once between 18 months and 10 years of age. Children were considered as having unremitting wheeze if the parents answered "one or more" to the question "How many attacks of wheezing has your child had in the last 12 months apart from a cold?" or "no" to the question "Is your child completely cured (without any respiratory complaints) between these episodes?"

Children were defined as having doctor-diagnosed asthma if the parents reported that the child had been diagnosed with asthma by a doctor at least once or if the child had had at least two doctor-diagnosed spastic, obstructive or asthmatic bronchitis in questionnaires at age 4, 5, 6 and 10, independent of a diagnosis reported in the first 3 years of life.

Allergic rhinitis was defined by the simultaneous presence of nasal and eye symptoms without a cold (itchy, runny or blocked nose and red, itchy eyes) and/or a doctor-diagnosed allergic rhinitis from 3 to 10 years of age.

Definitions of atopic dermatitis, food allergy, parental history of atopy and specific IgE (sIgE) measurements are provided in the Appendix S1.

2.3 | Statistical analysis

A LCA was used to identify subtypes of cough symptoms over time.[20] The variables "cough without a cold" and "cough without a cold at night" were coded in binary variables "never" versus "at least once during the last 12 months" at each visit. Cough triggered by physical exercise, change of temperature and/or excitation was coded in binary variables "no trigger" versus "at least one trigger" at each visit. The three defined variables were incorporated into the LCA model. As we decided to focus on the three items that supported the diagnosis of asthma as described by the Global Initiative for Asthma (GINA), we did not incorporate the length and characteristics of cough without a cold into the LCA model.

Children with data on cough symptom at less than six of the eight visits were excluded ($n = 172$). Bayesian information criterion (BIC), consistent Akaike information criterion (cAIC), and entropy were used to define the number of classes that best fit the data.[21] BIC was considered as the most reliable fit statistic and bootstrapped likelihood ratio test was performed in case of discordance between two statistical parameters.[22] The probability of an individual belonging to each class was estimated based on conditional probabilities of cough symptoms at each time given a class membership.[23] For sensitivity analyses, a LCA was performed on children with information on cough symptoms at all eight time-points and among the entire PASTURE population.

Multinomial logistic regression was used to investigate the associations between latent class trajectories of cough (outcomes) and the characteristics of the population (exposures). Logistic regression was used to investigate the associations between atopic diseases (outcomes) and the trajectories of cough (exposures). Multivariable models were adjusted for centre, parental history of atopy, gender and farming status, as there were known associations with allergic diseases and the centres used in the study population selection. Stratified analyses were performed to investigate the associations between respiratory atopic diseases and trajectories of cough according to unremitting wheeze. A data analysis was performed using SAS software version 9.4 (SAS Institute Inc.).

3 | RESULTS

3.1 | Study population

Of the 1133 children enrolled in the PASTURE birth cohort, 961 (84.8%) participated in at least six visits and 80.1% of them ($N = 770$) had a follow-up at the 10-year visit. Population characteristics are presented in Table S1.

Regarding allergic diseases, 815 subjects presented available data for atopic dermatitis, 781 for food allergy, 773 for allergic rhinitis and 775 for doctor-diagnosed asthma. sIgE assays were performed on 521 children at the age of 10.

The point prevalence of cough symptoms during the first 10 years of life is presented in Table 1.

3.2 | Selection of the class solution that best fit the data

According to BIC and entropy, the nine-class solution was identified as the best model to fit the data (Table 2). cAIC was the lowest for the eight-class solution but the bootstrapped likelihood ratio test was significant in favour of the nine-class solution ($p = .01$). Apart from one large class ($n = 576$; 59.9%), the eight other classes represented 4.4% ($n = 42$) to 6.8% ($n = 65$) of the population. Sensitivity analyses are described in the online supplements.

3.3 | Trajectories of cough without a cold

Out of the nine classes of cough without a cold (called cough from now on), five were identified as acute transient trajectories, because only one time-point had >50% of children with a cough (Figure S1). Assuming that having a cough once at 3, 4, 5, 6 or 10 years old is similar, these five classes have been grouped into one trajectory called acute transient ($n = 232$; 24.1%). Together with this acute transient trajectory, the four other classes served to define five different cough trajectories (Figure 1; Figure S2). The never/infrequent (reference) trajectory ($n = 576$; 59.9%) had a low prevalence of a cough and a cough at night during the first 2 years, and then no symptoms after 2 years, and no triggers. The

TABLE 1 Point prevalence of cough symptoms up to 10 years of age.

	1 year	1.5 year	2 years	3 years	4 years	5 years	6 years	10 years
Cough[a]								
N	NA	670/931	675/947	802/938	804/953	837/950	784/920	563/770
% (95%CI)		72 (69–75)	71 (68–74)	85 (83–88)	84 (82–87)	88 (86–90)	85 (83–87)	73 (70–76)
Cough without a cold[a]								
N	197/947	111/925	136/947	162/938	164/953	182/950	138/919	104/758
% (95%CI)	21 (18–23)	12 (10–14)	14 (12–17)	17 (15–20)	17 (15–20)	19 (17–22)	15 (13–17)	14 (11–16)
Cough without a cold at night[a]								
N	29/948	73/926	97/947	11/938	114/933	114/921	106/918	68/758
% (95%CI)	3 (2–4)	8 (6–10)	10 (8–12)	12 (10–14)	12 (10–14)	12 (10–14)	11 (9–14)	9 (7–11)
At least one trigger of cough without a cold								
N	NA	NA	51/944	50/937	61/953	72/950	56/918	41/755
% (95%CI)			5 (4–7)	5 (4–7)	6 (5–8)	8 (6–9)	6 (4–8)	5 (4–7)
Cough triggered by sport								
N	NA	NA	24/945	26/937	41/953	49/950	40/919	33/756
% (95%CI)			2 (1–3)	3 (2–4)	4 (3–6)	5 (4–7)	4 (3–6)	4 (3–6)
Cough triggered by excitation								
N	NA	NA	21/946	18/937	24/953	26/950	19/918	12/756
% (95%CI)			2 (1–3)	2 (1–3)	2 (1–3)	3 (2–4)	2 (1–3)	2 (1–2)
Cough triggered by change of temperature								
N	NA	NA	27/945	23/937	31/953	33/950	37/919	19/757
% (95%CI)			3 (2–4)	2 (1–3)	3 (2–4)	3 (2–5)	4 (3–5)	2 (1–4)
Out of children with cough without a cold								
Duration of cough (more than 2 weeks)								
N	NA	5/106	19/117	13/161	13/164	18/134	14/138	9/104
% (95%CI)		4 (1–8)	14 (8–20)	8 (4–12)	8 (4–12)	12 (7–17)	10 (5–15)	9 (3–14)
Dry cough								
N	NA	57/107	83/132	120/159	104/144	106/153	100/138	87/104
% (95%CI)		53 (44–63)	63 (55–71)	75 (69–82)	72 (65–79)	69 (62–77)	72 (65–80)	84 (77–91)
Productive cough								
N		50/107	49/132	42/159	44/144	51/153	41/138	21/104
% (95%CI)	NA	47 (37–56)	37 (29–45)	26 (20–33)	31 (23–38)	33 (26–41)	30 (22–37)	20 (12–28)

Abbreviations: CI, confidence interval; NA, not applicable.

[a]At least once in the last 12 months (6 months at the 1.5- and 2-year follow-up).

moderate transient trajectory ($n = 65$; 6.8%) had the highest prevalence of a cough, a cough at night, and triggers at 2 years of age, and then decreased, with 15% of children still having a cough at 10 years old. The late persistent trajectory ($n = 46$; 4.8%) had the highest prevalence of a cough, a cough at night, and triggers at 5 years of age, with >50% of children having a cough at 10 years old but only 20% of children reporting triggers. The early persistent trajectory ($n = 42$; 4.4%) had a high prevalence of a cough and a cough at night increasing from 1 to 5 years of age, and more than a 60% prevalence rate of a cough at 10 years old. The early persistent trajectory had the highest prevalence of triggers (from 30% to 60%).

In all trajectories, most coughing episodes lasted less than a week (Figure S3). In both persistent trajectories, about 50% of children with a cough had episodes lasting a week or more and about 10% had coughing episodes lasting more than 2 weeks. Apart from the reference, dry cough was predominant (Figure S4).

3.4 | Association of cough trajectories with the characteristics of the study population

Growing up on a farm was inversely associated with the acute transient and early persistent cough trajectories (Table 3). These associations persisted after adjustment for the centre and parental history of atopy. Parental history of atopy was positively associated with the acute transient, late and early persistent trajectories. Gender was not associated with cough trajectories.

3.5 | Association of cough trajectories with atopic diseases and sensitization

Unremitting wheeze was associated with all cough trajectories, with the strongest association for the persistent trajectories (Table 4).

Both doctor-diagnosed asthma and allergic rhinitis were positively associated with all cough trajectories, with the strongest associations for early persistent. Regarding pooling asthma or allergic rhinitis diagnosis, 40.5% of children in the early persistent trajectory had neither allergic rhinitis nor asthma (vs. 89.8% in the reference trajectory).

Of all children with doctor-diagnosed asthma, 87% provided information about their age when they were first diagnosed. Among those, 57.5% were first diagnosed before or at the age of three and 8.0% were diagnosed aged six or over. There was no statistical difference in age at the first diagnosis of asthma according to cough trajectories ($p = .2225$). The cumulative prevalence of asthma according to the different cough trajectories is presented in Figure 2. Most asthma diagnoses were reported by the age of five, even in the late persistent trajectory. However, the early persistent trajectory had the highest proportion of reported asthma diagnoses after the age of five (22.7%).

Food allergy was associated with late and early persistent trajectories (Table 4). Atopic dermatitis was not associated with any cough trajectories. sIgE sensitization to seasonal and perennial aeroallergens was associated with the late persistent trajectory.

TABLE 2 Model parameters of performed with the population that participated in at least 6 visits ($N = 961$).

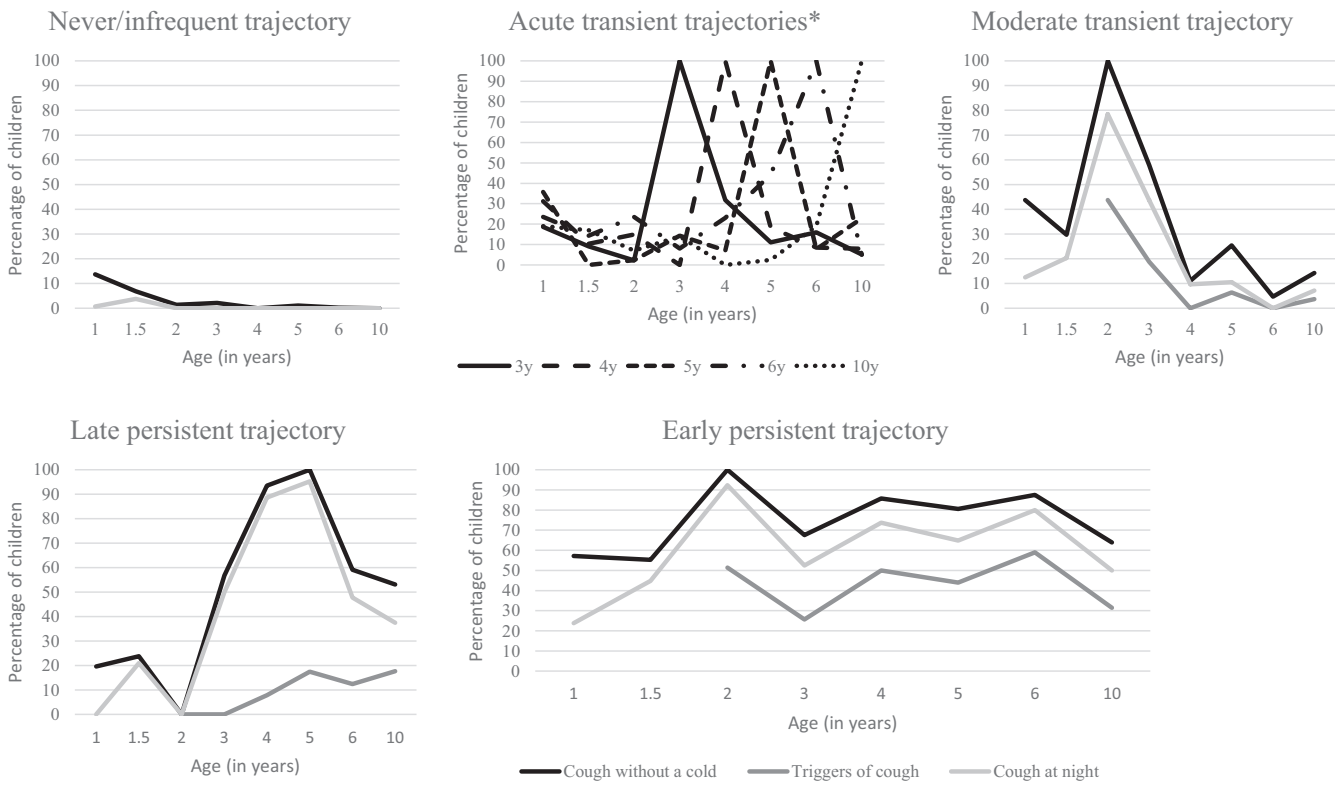
Number of classes	BIC	cAIC	Entropy
2	4906	4951	0.92
3	4545	4613	0.92
4	4329	4420	0.91
5	4222	4336	0.94
6	4149	4286	0.93
7	4099	4259	0.94
8	4069	**4252**	0.95
9	**4066**	4272	**0.96**
10	4100	4329	**0.96**

Note: Bold values are the lowest values for BIC and cAIC and the highest value for entropy.

Gray shade: selected model.

3.6 | Stratified analyses according to unremitting wheeze

In children with unremitting wheeze (Table 5), doctor-diagnosed asthma was positively associated only with persistent trajectories whereas in children without unremitting wheeze only the association



*Triggers of cough and cough at night for acute transient trajectories are described in Figure E1

FIGURE 1 Description of the five latent classes of cough (after grouping acute transient trajectories together): trajectories of the prevalence of a cough without a cold, a cough without a cold at night and a cough triggered by at least one factor from one to 10 years of age.

TABLE 3 Association between farming status, parental atopy, centre, gender and the latent class trajectories of cough without a cold.

		LCA trajectories of cough without a cold					
	All	**Reference ($n = 576$)**	**Acute transient ($n = 232$)**	**Moderate transient ($n = 65$)**	**Late persistent ($n = 46$)**	**Early persistent ($n = 42$)**	***p*-value**
Farmer							
No./Total no. (%)	464/960 (48.3)	308/576 (53.5)	91/232 (39.2)	29/64 (45.3)	23/46 (50.0)	13/42 (30.9)	**.0007**
OR (95% CI)	NA	1 (reference)	**0.56 (0.41–0.77)**	0.72 (0.43–1.21)	0.87 (0.48–1.59)	**0.39 (0.20–0.77)**	
OR[a] (95% CI)	NA	1 (reference)	**0.58 (0.42–0.80)**	0.69 (0.40–1.17)	1.02 (0.54–1.91)	**0.39 (0.19–0.77)**	
Parental atopy							
No./Total no. (%)	507/957 (53.0)	273/574 (47.6)	138/231 (59.7)	35/65 (53.8)	31/45 (68.9)	30/42 (71.4)	**.0003**
OR (95% CI)	NA	1 (reference)	**1.64 (1.20–2.23)**	1.29 (0.77–2.15)	**2.44 (1.27–4.69)**	**2.76 (1.38–5.49)**	
Centre							**.0043**
Finland							
No./Total no. (%)	173/961 (18.0)	80/576 (13.9)	48/232 (20.7)	17/65 (26.1)	12/46 (26.1)	16/42 (38.1)	
OR (95% CI)	NA	1 (reference)	1.31 (0.81–2.11)	1.36 (0.67–2.78)	1.41 (0.61–3.24)	**2.71 (1.14–6.43)**	
Austria							
No./Total no. (%)	192/961 (20.0)	127/576 (22.0)	45/232 (19.4)	9/65 (13.8)	9/46 (19.6)	2/42 (4.8)	
OR (95% CI)	NA	1 (reference)	0.77 (0.48–1.23)	0.45 (0.20–1.04)	0.66 (0.27–1.61)	0.21 (0.04–1.01)	
Switzerland							
No./Total no. (%)	204/961 (21.2)	137/576 (23.8)	41/232 (17.7)	9/65 (13.8)	8/46 (17.4)	9/42 (21.4)	
OR (95% CI)	NA	1 (reference)	0.65 (0.41–1.04)	**0.42 (0.18–0.97)**	0.55 (0.22–1.37)	0.89 (0.34–2.31)	
France							
No./Total no. (%)	173/961 (18.0)	110/576 (19.1)	42/232 (18.1)	11/65 (16.9)	4/46 (8.7)	6/42 (14.3)	
OR (95% CI)	NA	1 (reference)	0.83 (0.52–1.34)	0.64 (0.29–1.41)	0.34 (0.11–1.08)	0.74 (0.25–2.14)	
Germany							
No./Total no. (%)	219/961 (22.8)	122/576 (21.2)	56/232 (20.7)	19/65 (28.3)	13/46 (28.3)	9/42 (21.4)	
OR (95% CI)	NA	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	
Gender (girls vs. boys)							
No./Total no. (%)	466/961 (48.6)	291/575 (50.6)	104/232 (44.8)	33/64 (51.6)	23/46 (50.0)	15/42 (35.7)	.2641
OR (95% CI)	NA	1 (reference)	0.79 (0.58–1.08)	1.04 (0.62–1.74)	0.98 (0.53–1.78)	0.54 (0.28–1.04)	

Note: Values in bold: $p < .05$.

Abbreviation: OR[a], odds ratio adjusted for centre and parents with a history of allergy.

TABLE 4 Association between the latent class trajectories of cough without a cold and unremitting wheeze, atopic diseases up to 10 years of age (asthma, allergic rhinitis, atopic dermatitis and food allergy) and sensitization to food and inhalant allergens at 10 years of age (>0.7 IU/ml).

		LCA trajectories of cough without a cold					
	All	Reference ($n = 576$)	Acute transient ($n = 232$)	Moderate transient ($n = 65$)	Late persistent ($n = 46$)	Early persistent ($n = 42$)	*p*-value
Unremitting wheeze							
No./Total no. (%)	194/933 (20.8)	55/558 (9.9)	59/227 (24.3)	30/63 (47.6)	25/43 (58.1)	25/42 (59.5)	**<.0001**
OR[a] (95% CI)	NA	1 (reference)	**3.03 (1.20–4.60)**	**9.18 (5.10–16.52)**	**13.21 (6.64–26.3)**	**12.50 (6.22–25.14)**	
Asthma							
No./Total no. (%)	100/939 (10.6)	21/561 (3.7)	30/229 (13.1)	11/64 (17.2)	14/43 (32.6)	24/42 (57.1)	**<.0001**
OR[a] (95% CI)	NA	1 (reference)	**3.48 (1.93–6.30)**	**5.41 (2.41–12.14)**	**12.90 (5.78–28.81)**	**31.00 (14.03–68.51)**	
Allergic rhinitis							
No./Total no. (%)	143/938 (15.2)	45/561 (8.0)	50/228 (21.9)	15/64 (23.4)	15/43 (34.9)	18/42 (42.9)	**<.0001**
OR[a] (95% CI)	NA	1 (reference)	**2.65 (1.69–4.17)**	**3.08 (1.56–6.08)**	**5.70 (2.77–11.72)**	**5.99 (2.92–12.30)**	
Asthma or allergic rhinitis							
No./Total no. (%)	180/939 (19.2)	57/561 (10.2)	65/229 (28.4)	17/64 (26.6)	16/43 (37.2)	25/42 (59.5)	**<.0001**
OR[a] (95% CI)	NA	1 (reference)	**2.96 (1.97–4.47)**	**2.94 (1.54–5.60)**	**4.91 (2.44–9.90)**	**9.85 (4.85–20.02)**	
Atopic dermatitis							
No./Total no. (%)	328/933 (35.2)	175/555 (31.5)	85/141 (37.6)	27/65 (41.5)	20/45 (44.4)	21/42 (50.0)	.1920
OR[a] (95% CI)	NA	1 (reference)	1.23 (0.88–1.72)	1.37 (0.79–2.38)	1.58 (0.83–3.01)	1.91 (0.98–3.72)	
Food allergy							
No./Total no. (%)	76/930 (8.2)	28/555 (5.0)	21/226 (9.3)	5/60 (7.7)	11/42 (26.2)	11/42 (26.2)	**<.0001**
OR[a] (95% CI)	NA	1 (reference)	1.71 (0.93–3.14)	1.29 (0.47–3.53)	**5.71 (2.51–13.00)**	**5.17 (2.25–11.87)**	
Sensitization to perennial aeroallergens							
No./Total no. (%)	105/521 (20.1)	48/296 (16.2)	30/136 (26.1)	7/38 (18.4)	11/22 (50.0)	9/29 (31.03)	.0550
OR[a] (95% CI)	NA	1 (reference)	1.32 (0.78–2.24)	1.10 (0.45–2.24)	**3.79 (1.50–9.62)**	2.06 (0.86–4.91)	
Sensitization to seasonal aeroallergens							
No./Total no. (%)	158/521 (30.3)	71/296 (24.0)	49/136 (36.0)	13/38 (34.2)	12/22 (54.5)	13/29 (44.8)	**.0423**
OR[a] (95% CI)	NA	1 (reference)	1.53 (0.97–2.43)	1.50 (0.71–3.17)	**3.33 (1.31–8.41)**	1.95 (0.88–4.35)	
Sensitization to food allergens							
No./Total no. (%)	112/521 (21.5)	59/296 (19.9)	29/136 (21.3)	11/38 (28.9)	6/22 (27.3)	7/29 (24.1)	.8061
OR[a] (95% CI)	NA	1 (reference)	0.95 (0.56–1.60)	1.62 (0.73–3.56)	1.15 (0.42–3.15)	1.07 (0.43–2.71)	

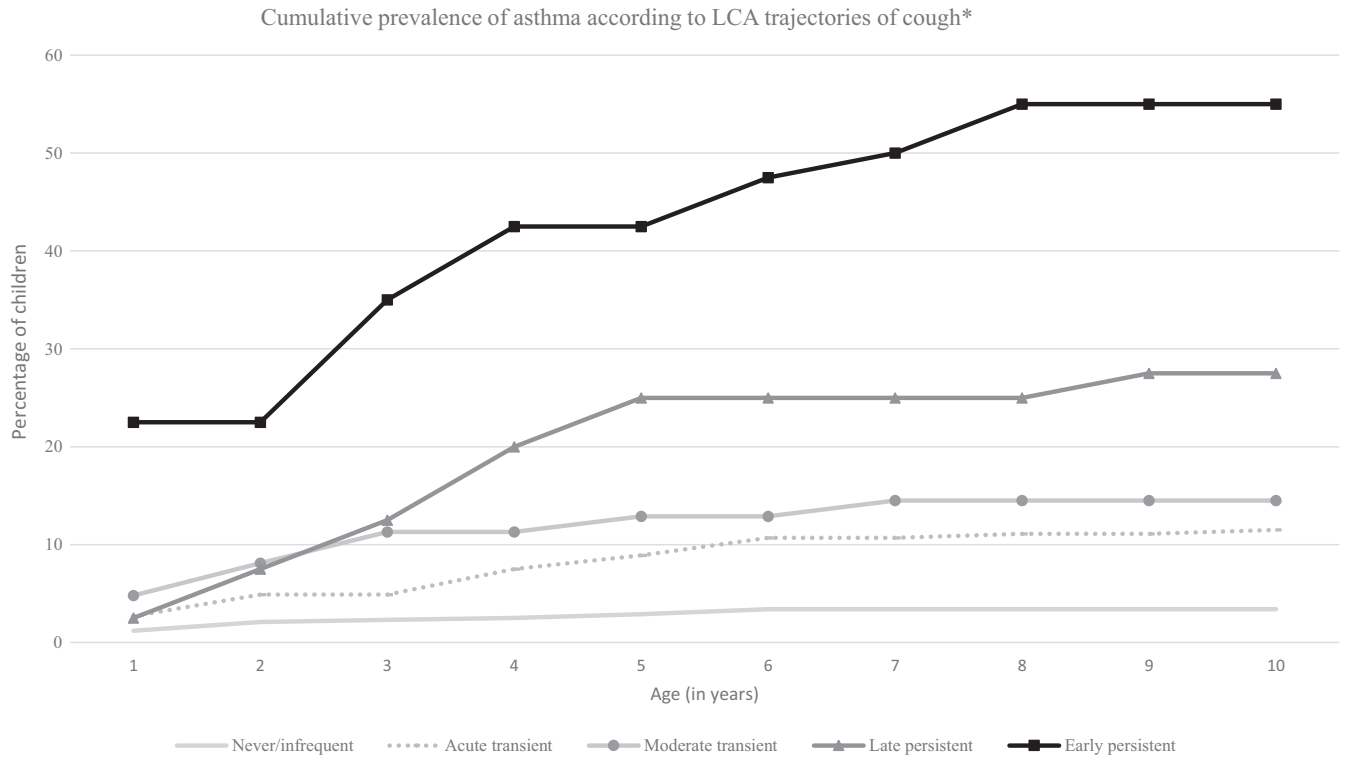
Note: Values in bold: $p < .05$.

Abbreviation: OR[a], odds ratio adjusted for farmer, centre, sex and parents with a history of allergy.

with the late persistent trajectory remained significant. Allergic rhinitis was positively associated with all trajectories only in children with unremitting wheeze and remained associated only with the acute transient trajectory in children without unremitting wheeze. Prevalence of other atopic diseases and sensitization according to unremitting wheeze are presented in Table S2.

4 | DISCUSSION

To the best of our knowledge, this study is the first to assess trajectories of cough without a cold during the first 10 years of life using statistical methods without a priori assumptions. Apart from children who never or infrequently suffered from a cough in the absence



*Cumulative prevalence of asthma was defined as the cumulative prevalence of doctor-diagnosed asthma during the follow-up

FIGURE 2 Age at first diagnosis of asthma according to latent class trajectories of cough.

of infection (59.9%), eight types of trajectories were identified: five with acute transient cough, two with an early-onset cough that differed thereafter by the degree of resolution, and one with a late-onset cough. Doctor-diagnosed asthma and allergic rhinitis were positively associated with all these trajectories. The strongest associations were found for the late and early persistent trajectories, and both were associated with food allergy and parental history of atopy. Farming status was associated with a lower risk of acute transient and early persistent trajectories.

Even though it was not designed to explore cough, the PASTURE study allowed the present research to study the longitudinal course of cough without a cold in almost 1000 children. The eight measures repeated over time with identical questions at each follow-up, the non-selected nature of this prospective birth cohort, and the high number of participants with available cough data in at least six of the eight follow-ups allowed us to minimize major bias. Multivariable models were used to investigate the association between atopic diseases and cough trajectories and were adjusted for several confounders to minimize confounding bias.

However, one limitation of our study, as in most epidemiological studies, is the reported nature of the symptoms and medical diagnoses. Collected data did not allow us to differentiate chronic from acute cough nor explore other symptoms sought during cough assessment.[6] A cough without a cold was defined as having such a cough at least once in the past 12 months because of the low number of children having a cough once a month or more. This criterion could be perceived as too broad. However, almost 60% of children did not report such a cough in the absence of infection. Due to the relatively small size for persistent trajectories, confidence intervals for logistic regressions are wide, reflecting some incertitude in the value of odd ratios for these trajectories. For these reasons, stratified analyses should be interpreted with caution.

Regarding statistical and theoretical decisions for the LCA, indicator variables were selected to explore the trajectories over time of the three items that supported asthma diagnosis as described by the GINA. Class-solution selection based on multiple fit statistics and sensitivity analyses were performed. The differences in fit statistics found in the population with no missing data could be explained by the reduction in sample size. Finally, the decision to group the five acute transient classes was based on the absence of theoretical and clinical sense to differentiate a cough reported only once by the age of occurrence. Replication in other cohorts would be of interest to validate this model.

Regarding the point-prevalence of a cough without a cold during the first 10 years of life, it ranged from 12% to 21%, with the highest prevalence at 1 year of age. That might be explained by physiological gastro-oesophageal reflux disease in the early infancy, as this aetiology of cough apart from colds has been described as frequent.[24] In our cohort, dry cough was predominant except in the reference trajectory. A predominant wet cough in this trajectory suggests a post-viral cough. The prevalence of a cough without a cold, a cough at night and cough triggers were lower than in the Leicestershire cohort (from 34% to 55% from a cough without a cold, 20% to 31% for a night cough and 18% to 26% for triggers).[25] This difference could

TABLE 5 Association between the latent class trajectories of cough without a cold, asthma and allergic rhinitis up to 10 years of age in children according to unremitting wheeze.

In children with unremitting wheeze	All ($n = 194$)	LCA trajectories of cough without a cold					
		Reference ($n = 55$)	Acute transient ($n = 59$)	Moderate transient ($n = 30$)	Late persistent ($n = 25$)	Early persistent ($n = 25$)	*p*-value
Asthma							
No./Total no. (%)	71/190 (37.4)	9/52 (17.3)	19/58 (32.8)	9/30 (30.0)	12/25 (48.0)	22/25 (88.0)	**.0001**
OR[a] (95% CI)	NA	1 (reference)	2.28 (0.86–6.06)	1.76 (0.56–5.53)	**4.00 (1.25–12.74)**	**35.38 (7.81–160.28)**	
Allergic rhinitis							
No./Total no. (%)	61/189 (32.3)	3/52 (5.8)	17/57 (29.8)	10/30 (33.3)	14/25 (56.0)	17/25 (68.0)	**<.0001**
OR[a] (95% CI)	NA	1 (reference)	**7.45 (1.86–29.86)**	**7.52 (1.73–32.71)**	**25.18 (5.63–112.74)**	**28.56 (6.12–133.17)**	
Asthma or allergic rhinitis							
No./Total no. (%)	86/190 (45.3)	8/52 (15.4)	30/58 (51.7)	11/30 (36.7)	15/25 (60.0)	22/25 (88.0)	**<.0001**
OR[a] (95% CI)	NA	1 (reference)	**6.62 (2.43–18.02)**	2.98 (0.96–9.24)	**7.74 (2.42–24.80)**	**33.38 (7.41–150.32)**	
In children without unremitting wheeze	**All ($n = 739$)**	**Reference ($n = 503$)**	**Acute transient ($n = 168$)**	**Moderate transient ($n = 33$)**	**Late persistent ($n = 18$)**	**Early persistent ($n = 17$)**	***p*-value**
Asthma							
No./Total no. (%)	29/738 (3.9)	12/490 (2.4)	11/168 (6.5)	2/33 (6.1)	2/18 (11.1)	2/17 (11.8)	**.0472**
OR[a] (95% CI)	NA	1 (reference)	**2.55 (1.09–5.99)**	2.73 (0.57–13.07)	**6.47 (1.24–33.62)**	4.97 (0.99–25.05)	
Allergic rhinitis							
No./Total no. (%)	82/738 (11.1)	42/502 (8.4)	33/168 (19.6)	5/33 (15.1)	1/18 (5.6)	1/16 (5.9)	**.0282**
OR[a] (95% CI)	NA	1 (reference)	**2.19 (1.31–3.65)**	1.79 (0.64–5.05)	0.60 (0.08–4.78)	0.53 (0.07–4.18)	
Asthma or allergic rhinitis							
No./Total no. (%)	94/738 (12.7)	49/502 (68.0)	35/133 (20.8)	6/33 (18.1)	1/18 (5.6)	3/17 (17.6)	.0633
OR[a] (95% CI)	NA	1 (reference)	**1.97 (1.21–3.23)**	1.89 (0.72–4.98)	0.50 (0.06–3.94)	1.59 (0.42–5.99)	

Note: Values in bold: $p < .05$.

Abbreviation: OR[a], odds ratio adjusted for farmer, centre, sex and parents with a history of allergy.

be due to population characteristics: rural in the PASTURE cohort and mostly urban in the Leicestershire cohort. The prevalence of a night cough in the Leicestershire cohort was even higher than in the PARIS birth cohort (14%–18%), including children born in the area of Paris.[26]

The comparison with other cohorts highlights the originality of our prospective study, which includes several repeated questions about coughing throughout the first 10 years of life. In the PARIS birth cohort,[26] apart from the never or infrequent phenotype, two dry night cough phenotypes were identified from one to 4 years old: transient and rising. Due to the difference in age assessment, the rising phenotype might correspond to early persistent or moderate transient trajectories; a late persistent trajectory could not be identified. In the Leicestershire cohort, five phenotypes of cough and wheeze were identified with only two follow-ups (8–13 and 13–18 years): transient (with and without wheeze) and persistent (with and without wheeze/with atopy).[14] A replication in another English cohort with earlier follow-up ages led to differences in three of the five phenotypes,[27] highlighting the importance of symptom assessment age.

The protective effect of the farm environment on atopic diseases has already been demonstrated in several studies.[28–30] Here, we found an inverse association between growing up on a farm and the acute transient and early persistent cough trajectories. The strongest association was for the early persistent trajectory, suggesting that growing up on a farm can protect children from developing an early persistent cough. Studying the different exposures specific to the farm environment could help to better understand the relationship between the farm environment and different cough trajectories.

The association of all the cough trajectories with doctor-diagnosed asthma and allergic rhinitis demonstrates the close relationship between cough, asthma and allergic rhinitis. The association between these atopic diseases, parental history of atopy and acute transient trajectories is contradictory to previous studies.[14,24,25] Even in children without unremitting wheeze, the acute transient trajectory was associated with doctor-diagnosed asthma and allergic rhinitis. These results suggest that a cough without a cold, even acute, is not physiological and could be related to an allergic hypersensitivity.

The highest prevalence of doctor-diagnosed asthma and allergic rhinitis was found in children with the early persistent trajectory. About 40% of children presenting this cough trajectory did not have a diagnosis of asthma or allergic rhinitis at 10 years of age. These results confirm that an isolated cough without a cold, even at night, is not always asthma.[31] In our study, doctor-diagnosed asthma was mostly reported before the age of three. At this young age, an asthma diagnosis is clinical based on the child's history of wheezing,[32] and we cannot exclude that some children outgrow their asthma later in life. In the presence of unremitting wheeze, almost 90% of children in the early persistent trajectory had doctor-diagnosed asthma. Association of persistent trajectories with doctor-diagnosed asthma was stronger in children with unremitting wheeze, but it remained positive in children without unremitting wheeze. On the other hand, allergic rhinitis remained significantly associated with all cough trajectories only in children with unremitting wheeze. Even if these analyses need to be interpreted with caution due to the small size of some classes, it confirms that a persistent cough trajectory (with early or late onset) should lead to asthma and allergic investigations, especially if associated with unremitting wheeze.

The late persistent trajectory was the only trajectory associated with aeroallergens sensitization. Sensitization to seasonal and perennial aeroallergens has already been described as positively associated with allergic rhinitis and late-onset symptoms,[12,33] but sensitization to perennial aeroallergens is also frequently associated with severe and early profiles of allergic rhinitis and asthma,[34] which we did not find in the early persistent trajectory.

Finally, the new finding is the positive association of both persistent trajectories with food allergy. Atopy and Th2 inflammation have been considered one of the aetiological mechanisms of cough hypersensitivity syndrome in which the immune system initiates neuroimmune crosstalk. The involvement of neuromodulation, described in numerous studies for cough,[35] has also been explored in a few studies for allergic diseases.[36,37] The association of persistent trajectories with all atopic diseases (except atopic dermatitis), especially if associated with unremitting wheeze, suggests the need to explore atopy with asthma and allergy assessment in case of a persistent cough without a cold and with a high prevalence of night cough and triggers. An isolated cough even with night cough and triggers is not sufficient to diagnose asthma; a history of wheezing should be sought, and objective tests should be performed from the age of five.[38] The screening and management of allergic diseases associated with a persistent cough should be part of cough management and could help reduce the burden of a cough. Associated atopic diseases could be a predictive factor for a persistent cough, helping to identify high-risk subgroups likely to benefit from early treatment of atopic diseases in order to avoid instauration of cough hypersensitivity syndrome.

5 | CONCLUSION

We investigated trajectories of cough without a cold from one to 10 years old in a rural prospective birth cohort non selected for risk of atopy. In this population, we identified nine different cough trajectories. The late and the early persistent trajectories, which represent 9.2% of children in our cohort, had the strongest association with asthma and allergic rhinitis and were also associated with food allergy and parental atopy. In clinical practice, these results allow to conclude that children having recurrent cough without a cold and with night cough and triggers should benefit from an asthma and allergy assessment. The strong inverse association between farm environment and an early persistent cough deserves further exploration to seek the prevention of severe cough phenotypes.

AUTHOR CONTRIBUTIONS

A.D-C. was involved in acquisition of data, was responsible for statistical analysis and interpretation of data and drafted the manuscript; F.M., A.H. and M.D. were involved in statistical analysis and interpretation; M-L.D., V.K., C.B., B.S., A.M.K., M.T., C.R. and D-A.V. were involved in acquisition and interpretation of data; E.S.-H. was involved in data management; H.R. was responsible for laboratory analyses; S.D.-A. was involved in interpretation of data and first draft of the manuscript; E.v.M., J.R., J.P. and R.L. obtained funds, set up the PASTURE birth cohort and were responsible for data collection and management of the study, and all authors reviewed the article critically and approved the final version of the manuscript. The PASTURE study group was involved in the acquisition, management and interpretation of data in Austria, Finland, France, Germany and Switzerland. The members of the PASTURE study group contributed substantially to the design, conception and conduct of the study or the acquisition or analysis of data.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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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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