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Phenotypic characteristics, healthcare use, and treatment in children with night cough compared with children with wheeze

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Abstract

Objectives: Population-based studies of children with dry night cough alone compared with those who also wheeze are few and inconclusive. We compared how children with dry night cough differ from those who wheeze.

Methods: LuftiBus in the school is a population-based study of schoolchildren conducted between 2013 and 2016 in Zurich, Switzerland. We divided children into four mutually exclusive groups based on reported dry night cough (henceforth referred as "cough") and wheeze and compared parent-reported symptoms, comorbidities, exposures, FeNO, spirometry, and healthcare use and treatment.

Results: Among 3457 schoolchildren aged 6–17 years, 294 (9%) reported "cough," 181 (5%) reported "wheeze," 100 (3%) reported "wheeze and cough," and 2882 (83%) were "asymptomatic." Adjusting for confounders in a multinomial regression, children with "cough" reported more frequent colds, rhinitis, and snoring than "asymptomatic" children; children with "wheeze" or "wheeze and cough" more often reported hay fever, eczema, and parental histories of asthma. FeNO and spirometry were similar among "asymptomatic" and children with "cough," while children with "wheeze" or "wheeze and cough" had higher FeNO and evidence of bronchial obstruction. Children with "cough" used healthcare less often than those with "wheeze," and they attended mainly primary care. Twenty-two children (7% of those with "cough") reported a physician diagnosis of asthma and used inhalers. These had similar characteristics as children with wheeze.

Conclusion: Our representative population-based study confirms that children with dry night cough without wheeze clearly differed from those with wheeze. This suggests asthma is unlikely, and they should be investigated for alternative aetiologies, particularly upper airway disease.

A list of the LUIS study group members can be found in the acknowledgments section.

KEYWORDS
asthma, FeNO, healthcare, spirometry

1 | INTRODUCTION

Cough is a common symptom affecting children's and their families' quality of life and burdening healthcare systems.[1] Respiratory tract infections are the most common cause of cough, followed by asthma which is characterized by cough and wheeze.[2,3] Cough is also present in rare lung diseases, such as cystic fibrosis, primary ciliary dyskinesia or interstitial lung diseases.[4] Many children have a dry cough occurring in the absence of an obvious respiratory infection or an underlying severe disease,[2] which is a diagnostic conundrum for physicians and a source of parental worries.[5] Underlying causes of recurrent dry cough can include environmental exposures, (e.g., tobacco smoke, allergens), ear, nose, and throat (ENT) problems, postinfectious cough, or atypical asthma.[4,6–9] Although wheezing is a key symptom of asthma,[10] some researchers proposed that children can have "cough variant asthma" without audible wheeze,[11] yet others fear this construct may lead to asthma overdiagnosis, unnecessary treatments such as corticosteroids, side effects, and increased costs.[5,12–14]

Previous studies on unclear cough were small, included selected participants from specialist clinics[15–17] or relied only on self-reported data.[13,18,19] Few were population-based and included information on measurable asthma traits.[20–23] Only two studies distinguished between children with wheeze alone or cough alone from those with both symptoms.[20,24] Our LuftiBus in the school (LUIS) study of unselected schoolchildren obtained information on parent-reported wheeze, cough, upper respiratory symptoms, environmental exposures, asthma diagnosis and treatment, and healthcare visits; we also measured fractional exhaled nitric oxide (FeNO) and spirometry, which are important asthma-related traits.[25] We, therefore, aimed to determine how frequently schoolchildren reported dry night cough (henceforth referred as "cough"), wheeze alone and in combination with cough, and neither cough nor wheeze and compare how these four groups ("cough," "wheeze," "wheeze and cough," and "asymptomatic") differed. We assessed differences in sociodemographic and environmental information, family history, parent-reported symptoms and comorbidities, FeNO and spirometry, healthcare utilization, and parent-reported physician diagnosis of asthma and treatments. Our underlying motivation was to gain insight into the etiology of unclear cough and investigating possibilities that some children presenting with cough may have a variant form of asthma.

2 | METHODS

2.1 | Study design and population

We conducted LUIS from 2013 to 2016 in the canton of Zurich, Switzerland, as a cross-sectional population-based study of 6–17-year-old schoolchildren (ClinicalTrials.gov: NCT03659838).[26] All schools were invited, and whole classes recruited. Parents completed questionnaires about respiratory symptoms, diagnoses and treatments, lifestyle, and household characteristics. Trained lung function technicians measured FeNO and performed spirometry in a mobile bus with lung function equipment. The ethics committee of the canton of Zurich approved the study (KEK-ZH-Nr: 2014-0491); written informed consent was obtained from parents, and verbal and, where appropriate, written consent was obtained from children.

2.2 | Outcomes: Definition of cough and wheeze

Previous studies used different definitions to assess unclear cough, describing it as persistent cough, recurrent cough, nonspecific cough, dry night cough, or cough apart from cold.[12,13,18–22,24,27] For our study, we used the question from the International Study of Asthma and Allergy in Childhood (ISAAC): "In the last 12 months, has your child had a dry cough at night, apart from a cough associated with a cold or a chest infection?" (Table S1). We also used a question from ISAAC to assess wheeze: "Did your child have wheezing or whistling in the chest in the past 12 months?"[28] Based on answers to these two questions, we defined four mutually exclusive groups: "cough," "wheeze," "wheeze and cough," and "asymptomatic."

2.3 | Characteristics: Socioeconomic, environmental, comorbidities, healthcare utilization, and treatment

Based on a literature search, we selected a range of exposures associated with cough, wheeze, or asthma, including (a) sociodemographic factors (sex, age, country of origin, socioeconomic status [Swiss socioeconomic position (SSEP) index]); (b) environmental exposures (urbanization degree, household pets, siblings, and parental smoking); (c) comorbidities (body mass index [BMI], frequency of colds, family history of asthma and chronic cough, personal history of atopy [eczema and hay fever]), and ENT problems, such as rhinitis apart from colds, otitis media, snoring (apart from colds and almost every night), and adenotonsillectomy. We also investigated potential triggers for cough or wheeze, asking specifically about exercise, respiratory infections, aeroallergens (house dust, pollen, and pets), physical factors (cold air/fog, laughter, weather/temperature changes), and certain foods and drinks.[13,19,20,29] We include the questions in Table S1. We also compared how different types of healthcare utilization, frequency of parent-reported physician asthma diagnosis ever, and asthma treatment in the past 12 months differed across the four groups.

2.4 | Measurements: FeNO and spirometry

Trained technicians measured FeNO (expressed in parts per billion [ppb]) with the single-breath online method according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) recommendations[30] using a chemiluminescence analyser (CLD88; Eco Medics). Spirometry was performed using Masterlab, Jaeger, according to ATS/ERS guidelines and pediatric pulmonologists did a post hoc quality control of flow-volume curves.[31] Using Global Lung Initiative (GLI) reference values,[32] we derived z-scores for forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1), and forced expiratory flow between the 25% and 75% of the FVC (FEF_{25-75}). We also calculated the FEV_1/FVC ratio.

2.5 | Statistical analysis

We compared sociodemographic information, environmental factors, family history, and symptoms between the four groups of children first using descriptive statistics and in a second step, using multinomial logistic regression with "asymptomatic" as the reference group. We report unadjusted and adjusted odds ratio (OR) and 95% confidence intervals (95% CI). In the adjusted model, we included all variables that were associated with either "cough," "wheeze," or "wheeze and cough" in the univariable analysis ($p < .05$), and then we applied stepwise backward selection. We performed likelihood ratio tests between the full model and reduced models and only kept variables if the likelihood ratio test had a $p < .05$. Sex and age were kept a priori.

We then investigated how FeNO and lung function parameters differed between the four groups using descriptive statistics and then regression analyses, with the "asymptomatic" children as reference. As FeNO was not normally distributed, we used quantile regression analysis with FeNO as an outcome and the four groups as exposure. We adjusted for age, sex, hay fever, inhaled corticosteroids (ICS), use of beta-2 receptor antagonist and smoking—factors potentially influencing FeNO.[33–35] As the spirometry outcome parameters were normally distributed, we computed four linear regression models. Each had a spirometry index as outcome (z-scores of FEV_1, FVC, FEV_1/FVC, and FEF_{25-75}) and the four groups as exposure, and we adjusted for BMI z-score.

We compared types of healthcare utilization, frequency of parent-reported physician asthma diagnosis ever, and asthma treatment in the past 12 months between groups by calculating proportions and 95% CI.

In a post hoc analysis to investigate accurate asthma diagnosis and treatment, we compared characteristics of 22 children with "cough" who reported physician diagnosis of asthma and use of asthma inhalers (short-acting bronchodilators [SABA] or ICS) in the past 12 months with children reporting "wheeze," "wheeze and cough," and the remaining 272 children with "cough."

We recorded missing values for symptom questions as "no"; we assumed absent or mild symptoms when parents had not answered with "yes" (Table S1). As a sensitivity analysis, we did a complete case analysis and the overall conclusion remained the same (data available from the authors on request). We used STATA (Version 15.1, StataCorp LLC., College Station, TX) for statistical analysis.

3 | RESULTS

We included 3457 children (50% male) from 37 schools (Figure S1) with a median age of 13 years (range 6–17) (Table 1). Parents reported children with dry night cough alone ("cough") for 294 (9%); wheeze alone ("wheeze") for 181 (5%); "wheeze and cough" for 100 (3%); and neither symptom ("asymptomatic") for 2882 (83%) (Figure 1A). Twenty-two children with "cough" (7% of 294) were diagnosed with asthma by physicians and reported using asthma inhalers (SABA or ICS) in the past 12 months (Figure 1B).

3.1 | Characteristics of children with "cough," "wheeze," "wheeze and cough," and "asymptomatic"

The four groups differed in regard to environmental exposures, parental history, symptoms, and symptom triggers (Tables 1, S2, and Figure 2).

Children with "cough" were less often male (OR 0.79, 95% CI 0.61–1.02) and younger (OR 0.91, 95% CI 0.86–0.96) with lower SSEP (OR 0.77, 95% CI 0.68–0.88) than "asymptomatic" children. They also reported more colds in the past 12 months (OR 2.22, 95% CI 1.66–2.97), more rhinitis apart from colds (OR 2.65, 95% CI 1.98–3.53), and more snoring (OR 1.58, 95% CI 1.20–2.07). There were no differences between children with "cough" and "asymptomatic" children regarding tobacco exposure and personal or family history of atopic diseases (Figure 2 and Table S2).

Children either with "wheeze" or "wheeze and cough" reported more frequent colds and rhinitis than asymptomatic children, and there were strong associations with parental history of asthma (OR 4.15, 95% CI 2.93–5.87 for "wheeze" and OR 2.58, 95% CI 1.58–4.20 for "wheeze and cough") and a personal history of hay fever (OR 1.94, 95% CI 1.31–2.85 for "wheeze" and OR 2.04, 95% CI 1.25–3.31 for "wheeze and cough"). BMI was associated with both outcomes—the association was stronger for "wheeze and cough" (OR 1.17, 95% CI 1.01–1.36 for "wheeze" and OR 1.41, 95% CI 1.17–1.70 for "wheeze and cough"). A report of otitis media was associated with "wheeze and cough" (OR 2.23, 95% CI 1.29–3.83) but not with "wheeze" (OR 0.81, 95% CI 0.43–1.51) (Figure 2 and Table S2).

All trigger factors for cough or wheeze were reported more often among children with "wheeze" or "wheeze and cough" when compared with children with "cough" (Table 1). House dust as a trigger was reported more often for children with "wheeze and cough" (33%) than for children with "wheeze" (22%, $p = .046$), and some physical triggers also differed between the two groups (cold air: 39% for "wheeze and cough" vs. 26% for "wheeze" [$p = .023$]; weather/temperature change, 29% vs. 15% [$p = .005$]) (Table S3).

Direct comparisons between "cough" versus "wheeze," "cough" versus "wheeze and cough," and "wheeze" versus "wheeze and cough" are provided in Table S3.

TABLE 1 Characteristics of asymptomatic children, children with cough alone ("cough"), wheeze alone ("wheeze"), and "wheeze and cough" in the LuftiBus in the school study ($N = 3457$).

	Total ($N = 3457$) *n* (%)	Asymptomatic[a] ($N = 2882$) *n* (%)	Cough[a] ($N = 294$) *n* (%)	Wheeze ($N = 181$) *n* (%)	Wheeze and cough ($N = 100$) *n* (%)	*p*-Value
Sociodemographic factors						
Male sex	1719 (50)	1446 (50)	132 (45)	85 (47)	56 (56)	.162
Median age in years (IQR)	13 (10–14)	13 (10–14)	12 (9–14)	13 (11–14)	12 (9–14)	.011[f]
Child, country of birth CH	3042 (89)	2527 (88)	266 (91)	167 (93)	82 (82)	.019
Swiss SEP median[b] (IQR)	69.7 (62.2–76.6)	69.9 (62.5–76.9)	68.9 (59.3–75.1)	70.2 (62.7–76.1)	68.8 (62.5–75.1)	.036[f]
Environmental exposures						
Large urban area	1674 (48)	1400 (49)	157 (53)	77 (43)	40 (40)	.040
Household pets	1469 (43)	1244 (44)	105 (36)	82 (46)	38 (38)	.055
Maternal smoking	571 (17)	483 (17)	52 (18)	17 (9)	19 (19)	.055
Paternal smoking	757 (22)	634 (22)	68 (24)	36 (20)	19 (20)	.746
Parental history of						
Asthma	486 (14)	347 (12)	43 (15)	69 (39)	27 (27)	<.001
Chronic cough	180 (6)	130 (5)	20 (7)	20 (11)	10 (11)	<.001
Symptoms and comorbidities/clinical factors						
Median BMI z-score[c] (IQR)	−0.01 (−0.70–0.80)	−0.03 (−0.71–0.76)	0.04 (−0.65–0.86)	0.26 (−0.71–0.96)	0.29 (−0.4–1.00)	.005[f]
Eczema[d]	249 (7)	184 (6)	22 (7)	30 (17)	13 (13)	<.001
Rhinitis[d]	1048 (30)	726 (25)	139 (47)	115 (64)	68 (68)	<.001
Hay fever	766 (22)	549 (19)	74 (25)	94 (52)	49 (49)	<.001
Frequent colds (> 3/year)[d]	587 (17)	407 (14)	91 (31)	50 (28)	39 (39)	<.001
Otitis media at least once[d]	333 (10)	262 (9)	36 (12)	13 (7)	22 (22)	<.001
Snoring[d,e]	888 (26)	697 (24)	105 (36)	53 (29)	33 (33)	<.001
Triggers for wheeze or cough[d]						
Exercise	614 (18)	373 (13)	85 (29)	94 (52)	62 (62)	<.001
Dust	217 (6)	106 (4)	38 (13)	40 (22)	33 (33)	<.001
Pollen	383 (11)	208 (7)	51 (17)	78 (43)	46 (46)	<.001
Pets	128 (4)	54 (2)	15 (5)	37 (20)	22 (22)	<.001
Cold air	334 (10)	200 (7)	48 (16)	47 (26)	39 (39)	<.001
Food and drink	100 (3)	64 (2)	17 (6)	12 (7)	7 (7)	<.001
Laughter	284 (8)	193 (7)	37 (13)	34 (19)	20 (20)	<.001
Weather/temperature change	267 (8)	159 (6)	52 (18)	27 (15)	29 (29)	<.001
Colds/infections	2138 (62)	1703 (59)	214 (73)	136 (75)	85 (85)	<.001

Abbreviations: BMI, Body Mass Index; CH, Switzerland; IQR, interquartile range; SEP, socioeconomic position.

[a]For simplicity, we refer to "dry night cough" as "cough" and to "asymptomatic" for children who report neither dry night cough nor wheeze, but these children could report other types of cough.

[b]Swiss SEP ranges from 0-lowest (worse) to 100-highest (better).

[c]We calculated BMI z-scores using references values from the World Health Organization.

[d]Refer to symptoms in the past 12 months.

[e]Snoring includes those who snore sometimes without cold or almost every night.

[f]*p*-Values calculated using Kruskal-Wallis; other *p*-Values calculated using chi-square test.

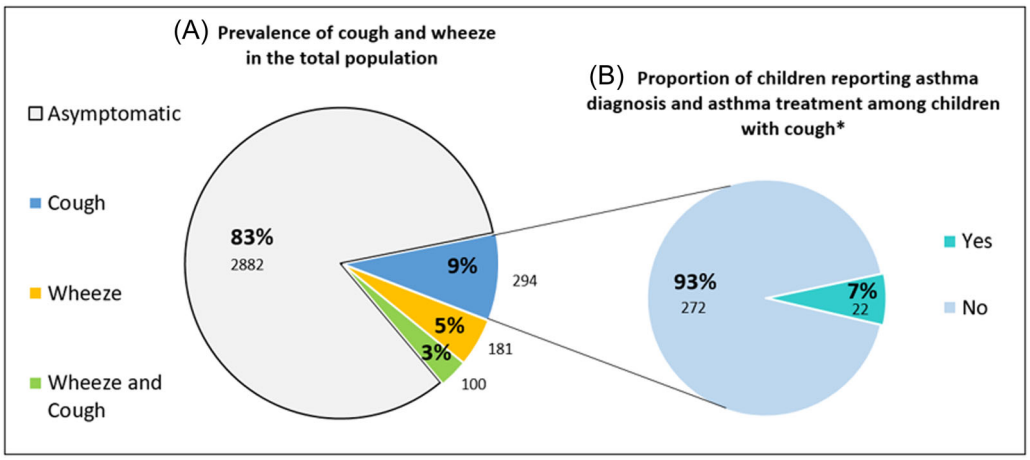

FIGURE 1 (A) Reported prevalence of cough, wheeze, wheeze and cough, and asymptomatic in the LuftiBus in the school study ($N = 3457$) (B) Proportion of children with physician-diagnosed asthma and asthma medication among children with cough ($N = 294$). For simplicity, we refer to "dry night cough" as "cough" and to "asymptomatic" for children who report neither dry night cough nor wheeze, but some of these children have reported cough at daytime after certain triggers. *Reported physician diagnosis of asthma ever and use of asthma medication (either inhaled corticosteroid or short-acting bronchodilators) in the past 12 months.

3.2 | FeNO and spirometry tests

Children with "cough" had similar FeNO levels (median 11.5 ppb, IQR 6.6–20.6) as asymptomatic children (median 11.8, IQR 7.0–19.9) (Table 2), which we confirmed in the adjusted regression model (Figure 3 and Table S4). FEV_1, FEV_1/FVC, and FEF_{25-75} z-scores were comparable among children with "cough" and "asymptomatic" children (Table 2, Figure 4, and Table S4). FVC was higher among children with "cough" (+0.170 z-scores, 95% CI 0.020–0.320), even after adjustment for BMI (+0.143 z-scores, 95% CI 0.000–0.286).

Children with "wheeze" tended to have a higher median FeNO (24.5 ppb [IQR 12.8–48.8]) compared to children with "wheeze and cough" (19.7 ppb [IQR 9.4–45]), although the difference was not statistically significant ($p = .120$) (Tables 2 and S5). Children with "wheeze" and "wheeze and cough" had higher FeNO than "asymptomatic" children and children with "cough." Differences remained after adjusting for potential confounders in the quantile regression (Figure 3 and Table S4). Compared with "asymptomatic" children and those with "cough," children with "wheeze," and "wheeze and cough" also had lower z-scores for FEV_1, FEV_1/FVC, and FEF_{25-75}, but these parameters did not differ between the two groups (Figure 4 and Tables S4 and S5).

3.3 | Healthcare utilization

Children with "wheeze and cough" used healthcare more than children with "wheeze" or "cough" (Tables 2, S5, and Figure S2A). Only 13% of children with "cough" reported two or more visits to pediatricians, and 7% required emergency consultations in primary care in the last 12 months. Visits to pulmonologists or allergologists were mainly reported by children with "wheeze" (15%) or "wheeze and cough" (22%). Hardly any children (< 1%) with "cough" reported emergency hospital visits or hospitalizations for respiratory problems.

3.4 | Asthma diagnosis and treatment

A physician diagnosis of asthma ever was reported among 8% of children overall (Table 2 and Figure S2B) and the frequency of diagnosis differed between children with "cough" and children with "wheeze" and children with "wheeze and cough" (Table S5). Half of the children with "wheeze and cough" and 43% of those with "wheeze" reported physician diagnosis of asthma compared with 11% of children with "cough" and 5% of asymptomatic children. Asthma inhalers were prescribed most often for children with "wheeze and cough" (SABA: 58%; any ICS: 43%) and "wheeze" (SABA: 45%; any ICS: 33%); 11% of children with "cough" received SABA and 8% ICS in the last year (Table 2, Figure S2B).

3.5 | Subgroup analysis: Children with "cough" who were diagnosed with and treated for asthma

For a small fraction (7%, $N = 22$) of children with "cough," parents reported a diagnosis of asthma and current treatment with SABA or ICS (Figure 1B). These children resembled in all aspects children with "wheeze" or "wheeze and cough" (Table S6) and were distinct from other children reporting "cough" alone. They frequently had positive family histories of asthma (43%), personal histories of atopic dermatitis (14%), and hay fever (50%); they reported respiratory symptoms triggered by exercise (59%) or pollen (41%). Their median (IQR) FeNO values (24.7 [8.8–52.7] ppb) and mean (SD) spirometry z-scores (FEV_1: −0.78 [0.78]; FEV_1/FVC: −0.68 [1.20]; FEF_{25-75}: −0.99 [1.02]) were similar to children with "wheeze."

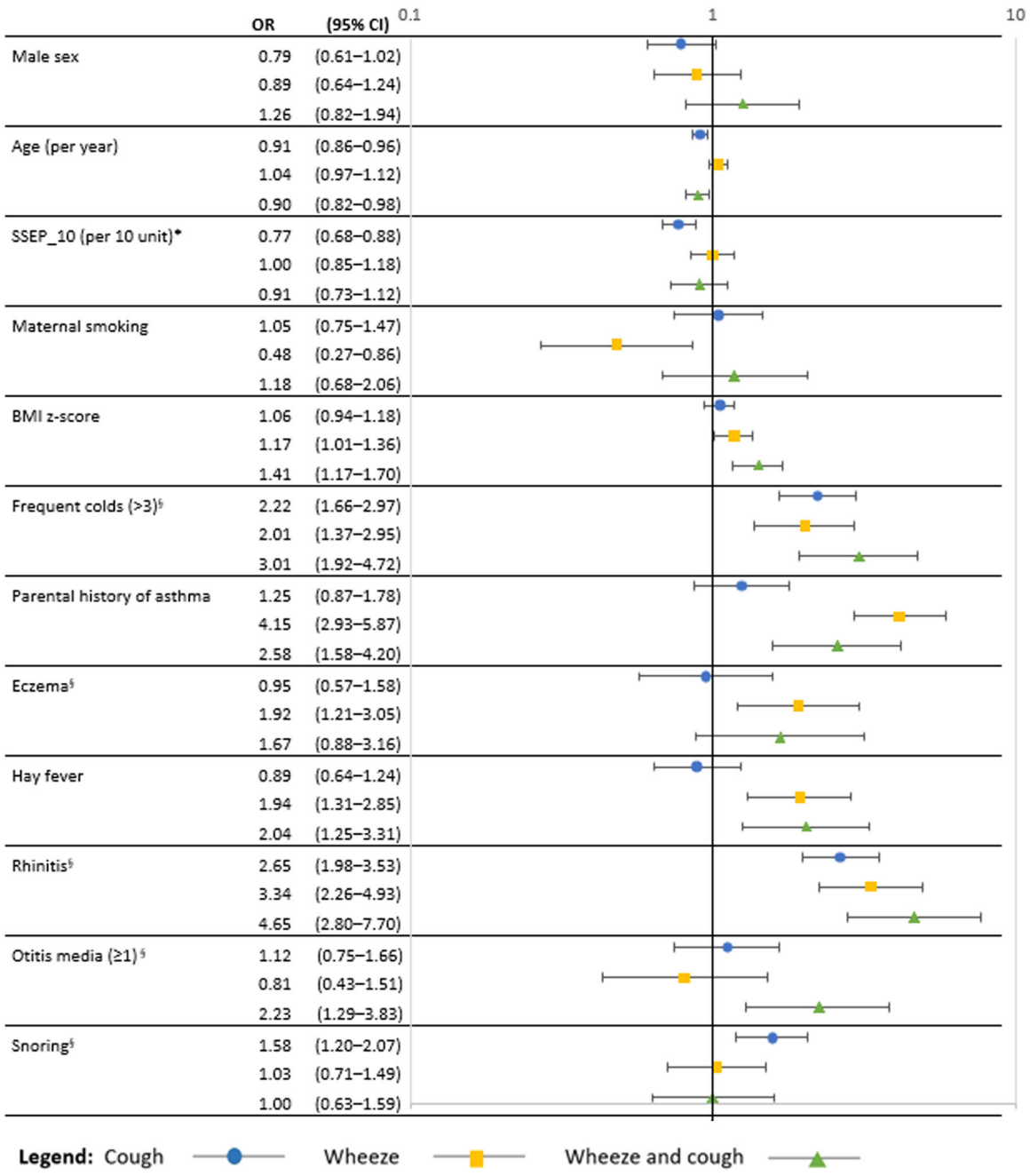

FIGURE 2 Adjusted odds ratios of factors associated with cough ($N = 294$), wheeze ($N = 181$), and wheeze and cough ($N = 100$) compared with asymptomatic children ($N = 2882$) (reference group). For simplicity, we refer to "dry night cough" as "cough" and to "asymptomatic" for children who report neither dry night cough nor wheeze, but some of these children have reported cough at daytime after certain triggers; we calculated BMI z-scores using references values from the World Health Organization; *Swiss SEP ranges from 0-lowest (worse) to 100-highest (better); §refer to symptoms in the past 12 months; OR was adjusted for all the factors in the table; snoring includes those who snore sometimes without cold or almost every night. BMI, Body Mass Index; CH, Switzerland; 95% CI, 95% confidence interval; SEP, socioeconomic position index; OR, odds ratio.

4 | DISCUSSION

Our population-based study found children reporting dry night cough without wheeze ("cough") are distinct from children with "wheeze" or "wheeze and cough" in terms of clinical characteristics, family history, FeNO, spirometry, healthcare use, and asthma diagnosis and treatment. Only a small subgroup (7%) of children reporting "cough" were diagnosed with asthma and treated with inhalers; their features were similar to children with "wheeze."

TABLE 2 Comparison of measured traits (FeNO and spirometry), healthcare pattern, asthma diagnosis, and treatment between asymptomatic children, children with cough, wheeze, and wheeze and cough in the LuftiBus in the school study (*N* = 3457).

	Total (*N* = 3457)	Asymptomatic[a] (N = 2882) *n* (%)	Cough[a] (*N* = 294) *n* (%)	Wheeze (*N* = 181) *n* (%)	Wheeze and cough (*N* = 100) *n* (%)	Overall *p*-value
FeNO (ppb) (*N* = 3030)						
Median (IQR)	12.3 (7.1–21.1)	11.8 (7.0–19.9)	11.5 (6.6–20.6)	24.5 (12.8–48.8)	19.7 (9.4–45.9)	<.001[b]
Mean (SD)	19.7 (24.0)	18.1 (21.4)	18.9 (22.8)	37.9 (41.0)	33.5 (36.4)	<.001[c]
Spirometry parameters						
Mean (SD) FEV_1 z-score (*N* = 2803)	−0.54 (0.99)	−0.53 (0.99)	−0.43 (0.97)	−0.74 (0.97)	−0.71 (0.98)	.011[c]
Mean (SD) FVC z-score (*N* = 2394)	−0.42 (1.03)	−0.44 (1.04)	−0.28 (0.98)	−0.48 (1.06)	−0.23 (1.03)	.051[c]
Mean (SD) FEV_1/FVC z-score (*N* = 2394)	−0.21 (1.07)	−0.16 (1.06)	−0.27 (1.07)	−0.52 (1.03)	−0.68 (1.32)	<.001[c]
Mean (SD) FEF_{25-75} z-score (*N* = 2394)	−0.59 (1.01)	−0.56 (1.00)	−0.58 (1.01)	−0.92 (1.02)	−1.06 (1.24)	<.001[c]
Healthcare pattern use						
Number of primary care visit ≥2	260 (8)	128 (4)	39 (13)	48 (27)	45 (45)	<.001[d]
Emergency visit to primary care	160 (5)	79 (3)	22 (7)	36 (20)	23 (23)	<.001[d]
Emergency visit to hospital	31 (1)	14 (0)	1 (0)	10 (6)	6 (6)	<.001[e]
Visit to pulmonary/allergy specialist	85 (2)	29 (1)	7 (2)	27 (15)	22 (22)	<.001[e]
Hospitalization	11 (0)	6 (0)	1 (0)	4 (2)	0 (0)	.006[e]
Asthma diagnosis and treatment						
Asthma diagnosis	293 (8)	132 (5)	33 (11)	78 (43)	50 (50)	<.001[d]
Asthma inhalers use						
SABA	257 (7)	86 (3)	31 (11)	82 (45)	58 (58)	<.001[d]
Any ICS	179 (5)	53 (2)	24 (8)	59 (33)	43 (43)	<.001[d]
ICS-LABA	137 (4)	37 (1)	16 (5)	49 (27)	35 (35)	<.001[d]
ICS-LABA and OCS	25 (1)	6 (0)	1 (0)	6 (3)	12 (12)	<.001[e]

Abbreviations: ICS, inhaled corticosteroids; FeNO, fractional exhaled nitric oxide; FEF_{25-75}, forced expiratory flow at 25–75% of the vital capacity; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; IQR, interquartile range; LABA, long-acting bronchodilator; ppb, parts per billion; OCS, oral corticosteroid; SABA, short-acting bronchodilator; SD, standard deviation.

[a]For simplicity, we refer to "dry night cough" as "cough" and to "asymptomatic" for children who report neither dry night cough nor wheeze, but these children could report other types of cough.

[b]*p*-Value calculated using Kruskal–Wallis test.

[c]*p*-Value calculated using one-way analysis of variance test.

[d]*p*-Value calculated using chi-square test.

[e]*p*-Value calculated using Fisher exact test.

4.1 | Comparison with other studies

Other population-based studies found children who cough without wheeze differed from children who wheeze.[13,18–21,27] A study of 8–13-year-olds in Scotland found a personal history of eczema and parental history of asthma more common among children with night cough than asymptomatic children, but less common among children with wheeze-related symptoms.[18] We did not find the same, possibly because they asked about cough of extended duration (≥ 4 weeks). In Finland, the prevalence of parental asthma was higher among children with dry night cough alone than asymptomatic children but lower than among children with wheeze.[21] As we, this study, reported that respiratory symptoms triggered by pollen, pets, and house dust were less common in children with cough compared with children with wheeze.

FeNO has not been described in studies comparing children with cough and wheeze. Although airflow limitation was assessed in some population-based studies, it was mostly in younger children.[20,22,23]

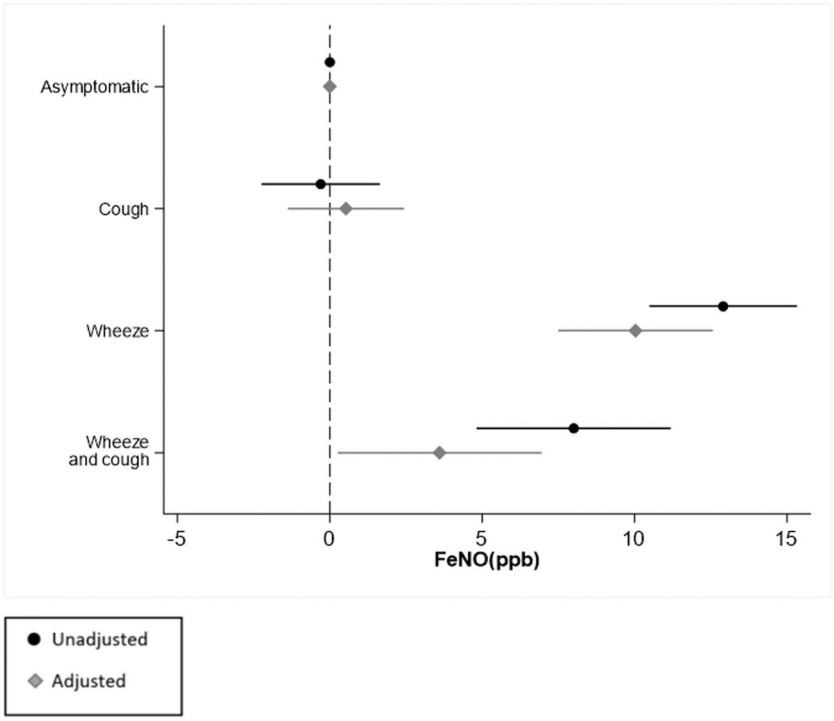

FIGURE 3 Association of fractional exhaled nitric oxide (FeNO) among children with cough ($N = 251$), wheeze ($N = 156$), and wheeze and cough ($N = 88$) compared with asymptomatic children ($N = 2535$) (reference group). For simplicity, we refer to "dry night cough" as "cough" and to "asymptomatic" for children who report neither dry night cough nor wheeze, but some of these children have reported cough at daytime after certain triggers; the adjusted quantile regression model is adjusted for age, sex, presence of hay fever, use of inhaled corticosteroid, use of leukotriene receptor antagonist, and passive and active smoking. The numeric confidence intervals are described in online Table S4. FeNO, fractional exhaled nitric oxide; ppb, parts per billion.

Only one study included 7–12-year-old schoolchildren and found the maximal mid-expiratory flow higher among children with dry night cough when compared with children with wheeze, while there were no differences in FVC and FEV_1.[21] Further studies are needed to determine whether our findings of higher FVC among children with "cough" than "asymptomatic" children was chance or a true phenomenon, perhaps via a training effect of vital capacity and full expiration among children with recurrent cough.

Since hardly any children with "cough" in our study visited the hospital emergency unit and no children were hospitalized, it means their symptoms–while bothersome–were not alarming. Similarly, in a study of children aged 6–12 years in Australia, no hospital admissions were reported among children with cough only, although they used a more stringent definition of cough (lasting more than 3 weeks without a cold or flu).[27]

The two studies, which also differentiated between children with wheeze and those with both wheeze and cough were longitudinal and children were younger than in our study.[20,24] The first study included 6-year-olds and defined the "cough" group as children reporting two or more episodes of cough without a cold in the past year. It found that physician-diagnosed asthma was almost thrice as common in those with wheeze and cough (46%) compared with those with wheeze only (17%).[20] Also, in our study, physician-diagnosed asthma was more common in children with wheeze and cough (50%) than in children with wheeze alone (43%), but the magnitude of the difference was less. The second study included children aged 1–7 years and defined the "cough" group similarly as we did, as dry night cough apart from a cough associated with a cold or chest infection in the last 12 months. It found that children reporting wheeze and dry night cough had a higher risk of asthma at age 8 compared to children with wheeze alone.[24]

4.2 | Interpretation and implication of findings

The new ERS clinical guidelines for diagnosing asthma among schoolchildren recommend wheezing as requisite symptom for asthma (i.e., not diagnosing asthma for children only reporting cough) and measuring FeNO and spirometry in the asthma diagnostic work-up,[36] which our results support. Indeed, we found most children who report dry night cough without wheeze ("cough") do not have typical features of asthma. We found no evidence of bronchial obstruction or eosinophilic airway inflammation and no association with a family history of asthma or a personal history of hay fever or eczema. Hence, our findings suggest that in children with cough without any signs of wheeze, atopy, and other typical asthma features, the probability of asthma is very low, and asthma treatment may, therefore, not be indicated. In our study, local healthcare providers diagnosed asthma and prescribed asthma inhalers for only a small proportion (7%) of children with dry night cough alone. It appears that in these cases, the physicians were right, as these children shared features with those who wheeze. We offer two explanations for this: these children may have a rare type of asthma characterized by cough without wheeze; or these children's wheeze was unrecognized and unreported by parents. Many parents incorrectly understand the word wheeze.[37]

We found "cough" was associated with lower socioeconomic status, more frequent colds, and ENT problems, such as rhinitis and snoring. Lower socioeconomic status is known to be associated with exposure to infectious agents and decreased host resistance to infection.[38] The association of cough with the report of ENT-related complaints, such as rhinitis and snoring, may be explained by several mechanisms, such as stimulating pharyngeal cough receptors by

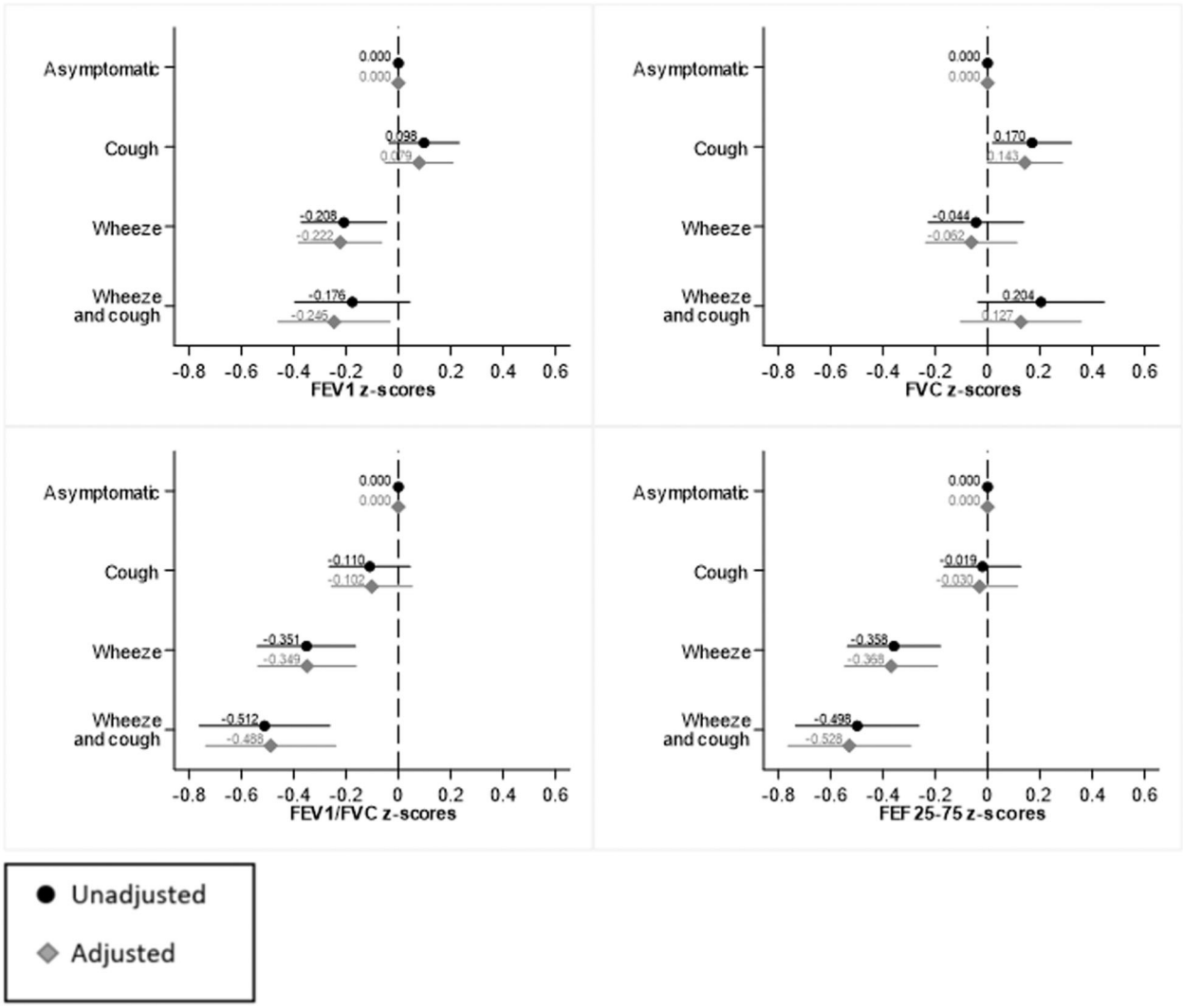

FIGURE 4 Spirometry z-scores for children with cough ($N = 230$), wheeze ($N = 150$), and wheeze and cough ($N = 80$) compared with asymptomatic children ($N = 2343$) (reference group). For simplicity, we refer to "dry night cough" as "cough" and to "asymptomatic" for children who report neither dry night cough nor wheeze, but some of these children have reported cough at daytime after certain triggers. In the adjusted linear regression model, the lung function parameters are adjusted for BMI z-scores. The numeric confidence intervals are described in online Table S4. BMI, Body Mass Index; FEF_{25-75}, forced expiratory flow at 25–75% of the vital capacity; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity.

post-nasal drip, hyperresponsive cough receptors, or mouth breathing due to nasal obstructions, leading to reduced filtration, humidification, and warming of inhaled air.[39] In a study of 103 children with upper airway cough syndrome suffering from chronic cough, adenoidal hypertrophy was the main cause for pre-school children, whereas, allergic or nonallergic rhinitis caused chronic cough for the majority of school-aged children.[40] Our findings suggest investigating children with isolated cough for differential diagnoses, particularly upper respiratory problems.

As a novel aspect, our study compared children reporting "wheeze and cough" with children reporting only "wheeze." Surprisingly, maternal smoking was negatively associated with wheezing but since our study is cross-sectional, this could be due to reverse causation whereby mothers with a known family history of asthma or with asthmatic children might have avoided or quit smoking. We found higher FeNO and more parental asthma among children with "wheeze," suggesting they might have an asthma phenotype linked closely to atopy. However, dust, pollen, and pets, as allergic triggers, were more frequently reported in children with "wheeze and cough" compared with children with "wheeze." One possible explanation could be that cough is easier to observe after exposure to these triggers than wheeze and it might occur earlier than wheeze. Children with "wheeze and cough" frequently reported upper respiratory symptoms (otitis media, rhinitis) and physical triggers, such as cold air and temperature changes, suggesting some of these children may have two independent problems (i.e., cough unrelated to coexisting asthma). When two diseases are common, by chance some people have both. It is also possible, that children who report both wheeze

and cough and those who report wheeze alone could represent different phenotypes of asthma. As our study is cross-sectional and we lack information on additional tests such as bronchodilator reversibility, challenge tests, or allergy tests, we cannot conclude about the existence of different phenotypes. In a study comparing epidemiological and clinical phenotypes of asthma and wheeze, Depner et al. found that (recurrent) unremitting wheeze characterized by symptoms—mostly night cough—occurring between wheezing episodes, was a sensitive alternative to asthma diagnosis in epidemiological studies.[41] Although we suspect that the additional occurrence of night cough to wheezing episodes contributes to the pathophysiology of asthma, our study did not inquire about the exact timing of night cough with respect to wheezing episodes to conclude on that.

4.3 | Strengths and limitations

Our study has several strengths. It is large, population-based, and representative of children in the community with dry night cough or wheeze. We collected details of accompanying symptoms and medical histories and measured FeNO and spirometry—two objective traits related to asthma. We also distinguished four mutually exclusive groups, which allowed for investigating differences between children with both night cough and wheeze compared with those with wheeze alone. We gathered data about healthcare utilization and treatment by local physicians. Our study also has limitations. The sample of schoolchildren included in LUIS was not selected at random among inhabitants of the canton of Zurich but whole schools were invited. The distribution of participating schools in rural and urban areas was comparable to the average distribution in the canton of Zurich, and the area-based socioeconomic index of participating families was similar to families in the rest of the canton.[26] We, therefore, believe our sample is representative of children living in the canton of Zurich. Cough and wheeze were both parent-reported and there are known discrepancies between reported and recorded respiratory symptoms.[42,43] Parents might also not, in all cases, have been able to distinguish "dry night cough" occurring "apart from colds" from postinfectious cough commonly associated with some viral infections. This study captured cross-sectional data only, and did not cover longitudinal aspects relevant for determining whether cough and wheeze persisted and whether children who reported only cough on this occasion developed wheeze later. In a longitudinal study, Jurca et al.[13] found that wheeze as a symptom persisted more than cough; and that children who coughed without wheeze were not at higher risk of developing wheeze compared to asymptomatic children. Other limitations of our study include lack of objective recordings of respiratory sounds, including wheeze and night cough and their duration and frequency. This limits the interpretation of the results. We also lacked information on signs and symptoms of gastroesophageal reflux, allergy tests, bronchial responsiveness, or cough receptor sensitivity, which we could not collect in this school-based study.

5 | CONCLUSION

Our findings align with the new ERS guidelines for diagnosing asthma among schoolchildren, which state that children with only cough as a symptom are unlikely to have asthma, and differential diagnoses, particularly upper respiratory problems, should be investigated.

AUTHOR CONTRIBUTIONS

Maria C. Mallet: Formal analysis; writing—original draft; writing—review & editing; conceptualization. **Rebeca Mozun**: Conceptualization; writing—review & editing; data curation. **Cristina Ardura-Garcia**: Conceptualization; writing—review & editing. **Eva S.L. Pedersen**: Conceptualization; writing—review & editing. **Maja Jurca**: Writing—review & editing. **Philipp Latzin**: Conceptualization; writing—review & editing. **Alexander Moeller**: Conceptualization; funding acquisition; writing—review & editing. **Claudia E. Kuehni**: Conceptualization; writing—review & editing; supervision.

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CONFLICTS OF INTEREST STATEMENT

Mallet MC, Mozun R, Ardura-Garcia C, Pedersen ESL, Jurca M, and Kuehni CE have nothing to disclose. Latzin P reports personal fees from OM Pharma, Polyphor, Santhera, Vertex, Vifor, Sanofi Aventis, and grants from Vertex—all outside the submitted work. Moeller A reports personal fees from Vertex outside the submitted work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study was approved by the ethics committee of the canton of Zurich (Kanton Zürich, Kantonale Ethikkommission (KEK-ZH) No.2014-0491). Written informed consent was obtained from participants.

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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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