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Agreement of parent- and child-reported wheeze and its association with measurable asthma traits

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Abstract

Objectives: In epidemiological studies, childhood asthma is usually assessed with questionnaires directed at parents or children, and these may give different answers. We studied how well parents and children agreed when asked to report symptoms of wheeze and investigated whose answers were closer to measurable traits of asthma.

Methods: LuftiBus in the school is a cross-sectional survey of respiratory health among Swiss schoolchildren aged 6–17 years. We applied questionnaires to parents and children asking about wheeze and exertional wheeze in the past year. We assessed agreement between parent–child answers with Cohen's kappa (k), and associations of answers from children and parents with fractional exhaled nitric oxide (FeNO) and forced expiratory volume in 1 s over forced vital capacity (FEV₁/FVC), using quantile regression.

Results: We received questionnaires from 3079 children and their parents. Agreement was poor for reported wheeze (k = 0.37) and exertional wheeze (k = 0.36). Median FeNO varied when wheeze was reported by children (19 ppb, interquartile range [IQR]: 9–44), parents (22 ppb, IQR: 12–46), both (31 ppb, IQR: 16–55), or neither (11 ppb, IQR: 7–19). Median absolute FEV₁/FVC was the same when wheeze was reported by children (84%, IQR: 78–89) and by parents (84%, IQR: 78–89), lower when reported by both (82%, IQR: 78–87), and higher when reported by neither (87%, IQR: 82–91). For exertional wheeze findings were similar. Results did not differ by age or sex.

Conclusion: Our findings suggest that surveying both parents and children and combining their responses can help us to better identify children with measurable asthma traits.

Abbreviations: CI, confidence interval; FEF₂₅₋₇₅, forced expiratory flow at 25–75% of forced vital capacity; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; IQR, interquartile range; LUIS, LuftiBus in the school; ppb, parts per billion; RRR, relative risk ratio.

Claudia E. Kuehni and Alexander Moeller contributed equally as co-senior authors.

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3814

KEYWORDS

agreement, child, fractional exhaled nitric oxide, parent, spirometry

1 | INTRODUCTION

Asthma is a complex lung disease and physicians use a combination of symptoms, lung function, and airway inflammation tests to diagnose it.¹⁻³ In large epidemiological surveys; however, researchers usually rely on reported wheeze to assess prevalence, risk factors, and prognosis of asthma.⁴⁻⁶

Reports of wheeze differ between parents and children and it is unclear whose reports are a more accurate indication of asthma measured by physiological traits, such as airflow limitation or airway inflammation.^{3,7} Knowledge of this would help to decide whether researchers should question parents or children, or both. The latter approach might be more informative but does increase complexity and costs of the study. Three previous studies compared answers from parents and children to measurable asthma traits.⁸⁻¹⁰ Two were done in asthma outpatient clinics and used composite symptom scores.^{8,9} One was a population-based study.¹⁰ All three studies used spirometry to assess airflow limitation and compared spirometry results to reported wheeze, but none combined answers from parents and children to consider their agreement. We compared wheeze reported by children, by parents, and by both, to two asthma traits that measure different aspects of this complex disease: airflow limitation assessed by spirometry and eosinophilic airway inflammation assessed by Fractional exhaled Nitric Oxide, FeNO. We measured agreement between parents' and children's reports of wheeze and exertional wheeze, identified determinants of agreement, and examined the association with lung function and FeNO.

2 | METHODS

2.1 | Study design and setting

LuftiBus in the school (LUIS) is a cross-sectional study performed between 2013 and 2016 in schools of the canton of Zurich, Switzerland. Recruitment methods and procedures have been described.¹¹ In short, all schools in the canton were invited to participate. If the headteacher agreed, trained lung function technicians visited the school with a mobile lung function lab on a bus.¹² Parents completed a detailed questionnaire at home. Children were interviewed and underwent lung function tests at school. Technicians were not aware of the answers to the parental questionnaire. For this analysis, we included all children with consent to participate for whom we had both a child's questionnaire and a parent completed questionnaire. The ethics committee of the Canton of Zurich approved the study (KEK-ZH-Nr: 2014-0491) and informed consent was obtained from parents and children.

2.2 | Questionnaire design and definitions

The parental questionnaire was printed and completed at home. It asked about respiratory diagnoses, symptoms and their trigger factors, medication, parental history of atopic diseases, family, and household characteristics, child's country of birth, and parents' countries of origin. Questions came from the International Study of Asthma and Allergies in Childhood (ISAAC) and the Leicester Respiratory Cohort studies questionnaires.^{13,14} We asked who completed the parental questionnaire (mother or father) and whether the child helped to complete it. The questionnaire for children was short and completed online by study technicians who interviewed the children at school.¹⁵ Children were asked key questions on respiratory symptoms and triggers of wheeze. Questionnaires to both children and parents included a written explanation of the term wheeze. The wording in the child and parental questionnaires was almost identical with slight simplifications in the child's version (Table S1).¹⁶

2.3 | FeNO and spirometry

FeNO was measured before spirometry with a fast response chemiluminescence analyzer CLD 88, Eco Medics AG, Duernten, Switzerland, and expressed as parts per billion (ppb). For spirometry we used Masterlab, Jaeger, Würzburg, Germany, according to ERS/ ATS standards.¹⁷ Our main outcomes were the ratio of forced expiratory volume in one second and forced vital capacity (FEV₁/FVC) in absolute percent, z-scores of FEV₁, z-scores of FEV₁/FVC, and zscores of forced expiratory flow between 25% and 75% of the FVC (FEF₂₅₋₇₅) using Global Lung Initiative (GLI) references.¹⁸ Quality criteria of flow-volume curves were assessed post hoc and only valid tests were included in the analysis.¹¹

2.4 | Statistical analysis

We assessed agreement between answers from parents and children to questions on wheeze and on exertional wheeze by crosstabulation and calculated unweighted Cohen's kappa to adjust for agreement by chance.^{19,20} We interpreted kappa as: 0–0.20=none, 0.21–0.39=poor, 0.40–0.59=weak, 0.60–0.79=moderate, 0.80– 0.89=strong, 0.90–1=almost perfect agreement.¹⁹ Questions about triggers of wheeze had also a "don't know" answer category, which we recoded as "no" to simplify the analysis.

We then studied the determinants of agreement between answers from parents and children using multinomial logistic regression. The models had three possible outcomes: parents and children both answered "yes" (agreed for yes), parents and children both answered "no" (agreed for no), and parents and children disagreed (reference). We chose possible determinants a priori based on the literature^{16,21-23}: age, sex, ethnicity, parents' countries of origin, number of children in the household, neighborhood socioeconomic position index (Swiss SEP),^{11,24,25} parental history of asthma, and the person completing the parental questionnaire. We included also body mass index (BMI) as possible determinant of agreement because a previous study showed that adolescents with obesity had poorer asthma symptom perception, that is, more often expected their lung function to be lower than it actually was, than nonobese peers.²⁶ We calculated BMI z-scores using the WHO references and categorized children as overweight or with obesity when their z-score was greater than one.²⁷ As a proxy for ethnicity, we classified children as "nonwhite" when their families came from countries where the majority of the population is nonwhite. We assessed collinearity between determinants of agreement using a correlation matrix, the variance inflation factor (VIF), and the condition number. VIF larger than 5 to 10 and condition numbers greater than 10 to 30 indicate the presence of multicollinearity.²⁸

Lastly, we studied the associations of parent-child reported wheeze and exertional wheeze with FeNO and lung function. For the analysis, we used three scenarios, which reflect hypothetical studies where questionnaires were sent only to children (scenario A), only to parents (scenario B), or to both (scenario C). Main outcomes were FeNO as a measure of airway inflammation and FEV₁/FVC as a sensitive measure of airflow limitation. We reported median values for FeNO and FEV₁/FVC, as they were not normally distributed. We calculated median differences in FeNO and FEV₁/FVC between children with wheeze and children without wheeze for each of the three scenarios using quantile regressions. Additional lung function outcomes were z-scores of FEV₁, FEF₂₅₋₇₅, and FEV₁/FVC. There, we used linear regression to calculate mean differences between children with and without wheeze in all three scenarios. Age and sex were included as confounders in all models. In a sensitivity analysis, we also adjusted for whether the child had helped the parents in completing their questionnaire. We did not include in our models other socioeconomic or clinical factors that may influence objective measurement results because we considered these as effect modifiers, rather than confounders and because their effect would not alter the comparison between the three scenarios, which relate to the same sample of children.

We assessed differences between the scenarios by calculating the difference in median FeNO and FEV₁/FVC and in mean z-scores of FEV₁, FEF₂₅₋₇₅ and FEV₁/FVC, in children with wheeze between scenario A (child-reported) and B (parent-reported), scenario A and C (parent- and child-reported), and scenario B and C. We calculated 95% confidence intervals using the bootstrap method with 500 repetitions and considered there was a statistically significant difference between scenarios when the 95% confidence intervals excluded 0. We reported these results also stratified by age, in children aged less than 10 years and 10 years or more, to compare our findings with the literature.^{8–10} We used the software STATA (Version 16.1, StataCorp) for statistical analysis, and followed STROBE reporting guidelines.²⁹

3 | RESULTS

3.1 | Study population

A total of 490 schools from the canton of Zurich were invited and 37 participated. 3870 children aged 6–17 years took part. For 3079, we had questionnaires with information on wheeze and exertional wheeze from both parents and children (Table 1). FeNO results were available for 2762 children (median 12 ppb, interquartile range [IQR]: 7–21) and FVC measurements for 2217 (median 87%, IQR: 82–91). Most questionnaires were completed by the mothers (n = 1765, 57%). 667 children (22%) helped their parents to complete the questionnaire. Parents of 425 children (14%) had a history of asthma.

3.2 | Prevalence of wheeze and agreement between parents and children

The prevalence of wheeze was comparable, independent of whether information arose from parents or from children (Figure 1, left). However, the group of children who reported wheeze was not the same as the group whose parents reported wheeze, although there was an overlap (Figure 1, right). The occurrence of wheeze in the past 12 months was reported by 273 (9%) children and 236 (8%) parents (*p* value for difference in proportions .090). Only in 108 (4%), wheeze was reported by both parents and children. Exertional wheeze in the past 12 months was reported by 12% of children (*n* = 369) and 8% of parents (*n* = 234; *p* value <.001), and by both in only 4% (*n* = 127). Using kappa (k) statistics, we found poor agreement between parents' and children's reports for wheeze (*k* = 0.37) and exertional wheeze (*k* = 0.36; Figure 1). Agreement was poor for reported triggers of wheeze, lowest for colds or infections (*k* = 0.12), and highest for pets (*k* = 0.40).

3.3 | Determinants of agreement

Children's age, parental history of asthma, and whether the child helped to complete the parental questionnaire determined the agreement between parents' and children's reported wheeze, after adjustment for sex, BMI, socioeconomic, and family characteristics (Figure S1). Older children agreed less with their parents when answering "no" to exertional wheeze (age 10-13 vs. 6-9 years: relative risk ratio [RRR]: 0.5, 95% confidence interval [CI]: 0.4-0.7; age 14-17 versus 6-9 years: RRR: 0.6, 95% CI: 0.4-0.8; Figure S1, right panel). We found weak evidence that boys agreed less often than girls with their parents when reporting wheeze (RRR: 0.8, 95% CI: 0.5-1.2) and exertional wheeze (RRR: 0.7, 95% CI: 0.5-1.1). Families with more than two siblings agreed more on wheeze (RRR: 1.6, 95%CI 1.0-2.5) and exertional wheeze (RRR: 1.4, 95% CI: 0.9-2.1). Children with overweight or obesity agreed less with their parents when answering "no" to wheeze (RRR: 0.6, 95% CI: 0.4-0.8) than children without. Children whose ethnicity was other than white were also less likely to

TABLE 1 Sociodemographic characteristics of schoolchildren in the LUIS study (*N* = 3079)

	n	(%)
Men	1519	(49)
Age in years, median (range)	12.3	(6.0–17.2)
Overweight or obesity (BMI > 1 z-score)	609	(20)
Who answered the parental questionnaire		
Mother alone	1765	(57)
Father alone	406	(13)
Mother and father	202	(7)
One or both parents and the child	667	(22)
Other	28	(1)
Child born in Switzerland	2726	(89)
Mother born in Switzerland	1764	(58)
Father born in Switzerland	1859	(60)
Ethnicity		
White	2879	(93)
Other	200	(7)
Number of children per household		
One or two	2073	(67)
More than two	926	(30)
Swiss socioeconomic position index, median (range)	70.5	(28.0, 98.5)
Parental history of asthma		
None	2599	(84)
Yes, the mother	246	(8)
Yes, the father	179	(6)
Both parents	19	(1)

Note: All the information on this table was obtained from the parental questionnaire, except for the socioeconomic position index and the body mass index (BMI). BMI z-scores were calculated using WHO references. The Swiss socioeconomic position index can range from 0 to 100 and is a neighborhood measure of socioeconomic status based on data about rent per square meter, education and occupation of households' heads, and household crowding that was developed as part of the Swiss National Cohort Study. The proportion of missing values was <3% for all these questions.

agree with their parents when answering "no" to wheeze (RRR: 0.6, 95% CI 0.4–0.9) but more likely to agree reporting exertional wheeze (RRR: 2.1, 95% CI: 1.0–4.3) than their white peers. We found no strong influence on agreement of country of birth of the mother and socioeconomic position. If parents had a history of asthma, parents and children were more likely to agree on wheeze (RRR: 1.5, 95% CI: 0.9–2.5) or exertional wheeze (RRR: 1.9, 95% CI: 1.2–3.1), but less likely to agree on answering "no" to wheeze (RRR: 0.4, 95% CI: 0.3–0.5) or exertional wheeze (RRR: 0.5, 95% CI: 0.4–0.7). When the child helped to complete the parental questionnaire, parents and

children were more likely to agree on reporting wheeze (RRR: 2.6, 95% CI: 1.6-4.4) or exertional wheeze (RRR: 1.9, 95% CI: 1.2-3.0). There was no indication of multicollinearity (mean VIF: 1.04; condition number: 8.88).

3.4 | Association between reported wheeze and FeNO and lung function

FeNO was higher in children who reported wheeze (19 ppb, IQR: 9-44) than in those who did not (12 ppb, IQR: 7-20) (Figure 2A; Table S3). When considering parental reports (Figure 2B), median FeNO was 22 ppb (IQR: 12-46) for children with wheeze compared to 12 ppb (IQR: 7-20) for those without. When we used both sources of information (Figure 2C), FeNO was highest when parents and children both reported wheeze (31 ppb, IQR: 16-55), intermediate when only one of them reported wheeze (17 ppb, IQR: 8-34) and lowest when neither parents nor children reported wheeze (11 ppb, IQR: 7-19). For exertional wheeze findings were similar (Figure 2, right panel). We estimated the difference in median FeNO between children with and without wheeze as reported by children or parents or both, adjusted for age and sex in a regression model. The difference was largest when both reported wheeze (21 ppb, 95% Cl: 18-23) or exertional wheeze (13 ppb, 95% CI: 11-16; Table S3). We also compared differences in FeNO between scenarios (Table S4). FeNO was similar between children with child-reported wheeze and children with parent-reported wheeze (scenarios A-B, p value .236), but was higher when wheeze was reported by both than by children (scenarios A-C, p value 0.003) or parents (scenarios B-C, p value .020). When we stratified by age, older children had higher FeNO when wheeze was reported by parents than by children (scenarios A-B), with no differences among younger children (Table S5).

Lung function was lower in children with wheeze than in those without wheeze when reported by both children and parents. Results followed the same pattern as for FeNO. There was a difference in FEV₁/FVC between groups of children with and without wheeze (Figure 3). When children reported wheeze, median FEV₁/FVC was 84% (IQR 78-89) compared to 87% (IQR: 82-91) when they did not (scenario A). We found the same when using answers from parents (scenario B). When we combined answers from parents and children (scenario C), median FEV₁/FVC was lowest when both parents and children reported wheeze (82%, IQR: 78-87), compared to when only one of them reported wheeze (85%, IQR: 79-89), and when neither reported wheeze (87%, IQR: 82-91). Findings for exertional wheeze were similar. We obtained similar results when we adjusted for age and sex in regression analyses, and when we used FEV₁, FEF₂₅₋₇₅, or FEV₁/FVC z-scores as outcomes instead of FEV₁/FVC in absolute percentage (Table S3). When we compared results between scenarios, we found similar lung function results in children with wheeze between scenarios A and B (p value for FEV₁/FVC: .964), but lung function was lower in scenario C than A (p value .045) or B (p value .030; Table S4). The associations with lung function did not vary by age (Table S5).



FIGURE 1 Parent and child reported prevalence of wheeze in the past 12 months, and proportion of agreement between their answers (N = 3079). ^ap values next to the bars test for a difference between the two proportions (parent vs. child reported symptoms). ^bKappa = 1 means perfect agreement, Kappa = 0 means agreement due to chance. Differences in total percentages between the left and right columns are due to rounding. The online supplement includes information on exact numbers and prevalence confidence intervals for this figure. CI, confidence interval



FIGURE 2 Distribution of FeNO in schoolchildren with and without wheeze as reported by (A) children, (B) parents, (C) either parents or children, and both parents and children (N = 2762). The left vertical lines of the boxes represent 25th percentiles, middle lines and data labels show the median, and right lines show the 75th percentiles of FeNO values. Outliers not displayed. FeNO, fractional exhaled nitric oxide, measured in parts per billion (ppb)

Exertional wheeze

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Additional adjustment for the child's help in completing questionnaires did not change the results for any model (data not shown).

4 | DISCUSSION

Wheeze

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This study found that parents and children agree poorly when reporting wheeze. When comparing parents' and children's reporting of wheeze with measurable traits of asthma, we found that lung function and FeNO differed depending on who reported wheeze. Children seemed to show highest FeNO levels and more limited airflow when both children and parents reported wheeze.

4.1 | Comparison with other studies

Few studies compared parent and child reported wheeze. Some found the same prevalence of wheeze when they questioned parents

or children,^{30,31} while others observed a higher prevalence when questioning adolescents rather than their parents (Table 2).^{21,32,33} Hedman et al. described that exertional wheeze was reported by 14% of teenagers and 8% of their parents.³¹ Children may be more aware of mild symptoms during exercise than their parents, which may also explain why in our study child-reported exertional wheeze was less strongly associated with measurable asthma traits than parent-reported.

In our study, the agreement between answers from parents and children was poor both for current wheeze (kappa 0.37) and exertional wheeze (kappa 0.36). Other studies found similarly weak agreement rates with kappa estimates for parent-child agreement in the range of 0.18–0.61 for current wheeze and 0.21–0.44 for exertional wheeze (Table 2).^{21,30–32,34} A reason could be that the understanding of the term wheeze by parents and children is limited.^{16,35} Definitions of wheeze from parents attending respiratory clinics often differ from definitions given in surveys.³⁵ Also a population-based study found that parental understanding of wheeze was moderate, but better for children with severe asthma, and those whose mothers had asthma, and worse for



Exertional wheeze

FIGURE 3 Distribution of FEV1/FVC in schoolchildren with and without wheeze as reported by (A) children, (B) parents, (C) either parents or children, and both parents and children (N = 2217). The left vertical lines of the boxes represent 25th percentiles, middle lines, and data labels show the median, and right lines the 75th percentiles of FEV1/FVC. FEV1/FVC, forced expiratory volume in one second over forced vital capacity, measured in percentage

Study	LUIS	Braun-Fahländer ²¹	Hedman ³¹	Renzoni ³²	Mallol ³⁰	Decker ³³
Country of the study	СН	СН	SE	IT	CL	US
Study sample size (N)	3113	1374	294	21068	3178	230
Age of study population (years)	5-17	13-15	13-14	13-14	13-14	10-12
Respiratory symptoms						
Wheeze						
Child-reported prevalence	9%	11%	8%	10%	11%	11%
Parent-reported prevalence	8%	7%	7%	5%	10%	6%
Карра	0.37	0.48	0.61	0.44	0.29	0.18
Exertional wheeze						
Child-reported prevalence	12%	20%	14%	-	26%	25%
Parent-reported prevalence	8%	8%	8%	-	13%	12%
Карра	0.36	0.39	0.44	-	0.21	0.38

TABLE 2 Prevalence of parent- and child-reported wheeze, and kappa estimates for chance-adjusted agreement between parents and children in different studies

Note: Wheeze and exertional wheeze refer to the past 12 months.

Abbreviations: CH, Switzerland; SE, Sweden; IT, Italy; CL, Chile; US, United States.

children of ethnic minorities and those living in deprived areas.¹⁶ Other studies showed that belonging to ethnic minorities was associated with poorer perception but also to higher severity of asthma.^{22,23} We found poorer agreement between children with overweight and obesity and their parents when reporting no wheeze, which might be explained by differences in symptom perception, as shown by Kopel et al. who found higher asthma symptom magnification scores in obese white 12–17 years old than in nonobese peers.²⁶ In line with our findings, Braun-Fahrländer et al. described better parent-child agreement for girls, when children helped to complete questionnaires, and when parents had a history of asthma.²¹ The latter could be due to better recognition of wheeze by parents, increased awareness in children, or higher prevalence of wheeze when parents had asthma.

Few studies have compared parent- and child-reported symptoms with measurable traits of asthma, and those done in clinical populations are not directly comparable to ours.^{8,9} Only one study was done on children from the general population.¹⁰ Yu compared lung function in 1963 schoolchildren aged 8-12 years with reports from parents and children.¹⁰ Children aged less than 10 years were more likely to have low FEV1/FVC if wheeze was reported by parents (OR: 3.1) compared to children (OR: 1.5), but no difference was found when children were older than 10 years. We found that the association between lung function and wheeze was similar for parent- and child-reported wheeze. FeNO was higher when wheeze was reported by parents than by children for children aged 10 or more, but not for younger children. Previous studies did not investigate the usefulness of combining answers from parents and children to assess agreement. In our study, when parents and children both reported wheeze or exertional wheeze, children had the highest FeNO and worst lung function, indicative traits of asthma.

5 | STRENGTHS AND LIMITATIONS

This is the first study that investigated the association of parent and child reported wheeze with two different traits related to asthma. FeNO, and lung function in the general population. In contrast to others, we did not only assess answers from parents and children separately (scenarios A and B) but also combined (scenario C). Further strengths are our large sample size and comprehensive evaluation of lung function. The LUIS did not include a random sample of schoolchildren and we do not have information on non-participants. However, participating schools were proportionally distributed in urban and rural areas and the socioeconomic status of participating families was roughly comparable to that of households with school-aged children in the whole canton of Zurich.¹¹ One limitation of the present study is that parents completed the guestionnaire at home while children were interviewed on the bus at school by a study technician. This may have helped children to understand the term "wheeze" so we cannot extrapolate our results to a situation where children answer printed questionnaires. Questionnaires to parents and children contained explanations of what we mean by wheeze. Understanding of wheeze and agreement between parents and children varies between countries and regions, so our results may not be generalizable to populations with different socioeconomic, linguistic, and cultural backgrounds. We compared the responses for wheezing and exertional wheezing with the two most widely recommended measurable traits for asthma: airflow limitation and airway inflammation. We acknowledge the fact that children with current asthma may have normal lung function and atopic children may show elevated FeNO without asthma. However, we believe that this should not have significantly biased the comparison between the three scenarios since all scenarios include the same children.

6 | IMPLICATIONS AND CONCLUSION

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Our results apply to population-based settings. Epidemiological studies commonly rely on reported wheeze as a proxy measure for asthma. Results of objective measurements are valuable data in epidemiological studies, though also time-consuming and costly. In clinical settings, a complete clinical assessment must include a detailed clinical history and physiological measurements.³⁶ Our study raises awareness of the fact that parents and children do not report wheeze consistently. Our findings suggest that using reports from both parents and children may bring us closer to measurable traits of asthma. This highlights the importance of asking both children and parents about wheeze in epidemiological studies. The advantage of asking both may also be valid in clinical practice, our clinical experience supports this, but the population-based study that we present here cannot prove this. The use of online questionnaires that can be completed via mobile phones may reduce the costs of asking both, and future studies should assess parent-child agreement when using these resources. Researchers may be able to distinguish schoolchildren with a greater likelihood or severity of airflow limitation and elevated airway inflammation when both, parents and children, report wheeze. Similarly, lung function and FeNO results are likely to be normal when both independently do not report wheeze. Our results suggest that future epidemiological studies on childhood asthma should whenever possible address both, parents and children.^{21,30-33}

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CONFLICT OF INTERESTS

Alexander Moeller reports personal fees from Vertex and OM Pharma, outside the submitted work. Philipp Latzin reports personal fees from Gilead, Novartis, OM pharma, Polyphor, Roche, Santhera, Schwabe, Vertex, Vifor, Zambon, and grants from Vertex, all outside the submitted work. Florian Singer reports personal fees from Vertex and Novartis, outside the submitted work. Jakob Usemann reports personal fees from Vertex and Aha, Allergy Center Switzerland, all outside the submitted work. The remaining authors declare no conflict of interests.

DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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