

Age-related changes in childhood wheezing characteristics: a whole population study

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Abbreviations:

ISAAC– The International Study of Asthma and Allergies in Childhood; EVW– Episodic Viral Wheeze; MTW– Multiple Trigger Wheeze

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Contributor's Statement:

Maja Jurca: Ms. Jurca performed the final statistical analyses, wrote and finalised the manuscript, approved the final manuscript as submitted;

Anina M. Pescatore: Dr. Pescatore conceptualised and designed the study, performed the initial statistical analyses, drafted initial manuscript, approved the final manuscript as submitted;

Myrofora Goutaki: Dr. Goutaki supported with input for interpretation of data, reviewed and revised the manuscript, approved the final manuscript as submitted;

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Caroline S. Beardsmore: Dr. Beardsmore supervised data collection, reviewed the manuscript, approved the final manuscript as submitted;

Claudia E. Kuehni: Prof. Kuehni conceptualised and designed the study, collected data, contributed to analysis and interpretation of results, critically reviewed and revised the manuscript, approved the final manuscript as submitted.

All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

ABSTRACT

BACKGROUND: Wheezing illnesses are characterised by phenotypic variability, which changes with age, but few studies report on a wide age range of children. We studied how prevalence, severity, and triggers of wheeze vary throughout childhood.

METHODS: We analysed data from a large population-based cohort of children from Leicestershire, UK, who were followed from infancy through late adolescence using postal questionnaires. We used generalised estimating equations to describe age-related changes in prevalence of any wheeze: episodic viral and multiple trigger wheeze; wheeze triggered by exercise, aeroallergens, food/drinks, laughing/crying; and of severe wheeze (frequent attacks, shortness of breath, sleep disturbance, disturbance of daily activities) from age 1 to 18 years. We analysed this in the entire cohort (absolute prevalence) and separately among children with wheeze (relative prevalence).

RESULTS: This study included 7,670 children. Current wheeze was most common in 1-year-olds (36%) and then decreased in prevalence to reach 17% in children aged 14-17 years. Absolute prevalence of episodic viral wheeze (EVW) decreased with age (from 24% to 7%), while multiple trigger wheeze (MTW) remained relatively constant throughout childhood (8-12%). Among children with wheeze, the proportion with EVW decreased, and the proportion with MTW increased with age. In older children, wheeze triggered by exercise or aeroallergens, and wheeze accompanied by shortness of breath became more frequent, while wheeze triggered by food or laughter, and sleep disturbance decreased in prevalence.

CONCLUSION: Knowledge of these age-related changes in wheezing illness is informative for health care planning and the design of future research projects and questionnaires.

INTRODUCTION

The clinical characteristics of wheezing illness in children are variable and change with age.¹⁻⁴ Some children wheeze only during respiratory infections, a phenotype called episodic viral wheeze (EVW).⁵ Other children wheeze without having infections and their episodes can be triggered by different factors. The wheezing in these children is commonly called multiple trigger wheeze (MTW).^{5, 6} Trigger factors for MTW include physical exercise,^{3, 7-9} other activities associated with increased breathing effort (laughing or crying), contact with aeroallergens^{7, 10, 11} (such as pollen, house dust, or pets), and ingestion of certain food or drink items,⁷ which lead to wheeze through varying mechanisms (including but not restricted to allergies). Severity of wheezing illness has been described in terms of frequency of episodes,^{3, 7, 8, 12} and of severity of episodes measured as sleep disturbance,^{3, 9} limitation of daily activities, or association with shortness of breath.^{9, 12}

From clinical experience, we know that absolute and relative frequency of phenotypes of wheeze, severity indicators, and trigger factors vary depending on the age of children. However, this has not been well quantified. Most studies have focused on one or two age groups, typically on schoolchildren who are 6-7 and 13-14 years old, as in the International Study on Asthma and Allergies in Childhood (ISAAC),^{3, 13} or, less often, preschool children.^{12, 14-16} No study to our knowledge has shown the change in the clinical picture of wheezing illness from the first years of life throughout childhood. This paper describes prevalence of wheezing illness during the entirety of childhood, from age 1 to 18 years, in a population-based cohort. We assessed the absolute prevalence (as a proportion of all children) and the relative prevalence (as a proportion of children with current wheeze) of a) the phenotypes EVW and MTW, b) wheeze induced by individual triggers, and c) severity indicators. Absolute prevalence reflects the public health perspective (how many children in

the general population have this type of disease), and relative prevalence describes the perspective of a physician (what proportion of the children visiting for wheeze has this type of disease).

METHODS

Study population and study design

We used data from a population-based childhood cohort study from the UK, the second Leicestershire respiratory cohort. The study was approved by the Leicestershire Health Authority Research Ethics Committee. Details are published elsewhere.¹⁷ In short, a random sample of children born from May 1993 to April 1997, stratified by year of birth, sex, and ethnic group (South Asian or White) was selected from the Leicestershire Health Authority Child Health Database, which is comprised of perinatal, demographic, and health-related information for all children resident in the area of Leicestershire. Perinatal data came from birth records and growth data from prospective health-visitor records. We assessed respiratory symptoms through postal questionnaires mailed to parents in 1998, 1999, 2001, 2003, 2006, and 2010. In the first survey (1998), 78% of the families (6,808/8,700) participated. In the following surveys, response rates were 74%, 63%, 51%, 37% and 33%, respectively (Table E1).¹⁷ In 1998 most children were 1 year old, 52% were boys, and 20% were of South Asian ethnic origin (Table 1).

Questionnaires and questions on wheezing illness

The questionnaire defined wheeze as “breathing that makes a high-pitched whistling or squeaking sound from the chest, not the throat.” We assessed current wheeze (wheeze occurring in the last 12 months) with the question from the ISAAC.¹³ In case of reported wheeze, we asked whether children wheezed only during or after a cold or flu, or also at times unassociated with these conditions, and we assessed trigger factors and aspects of severity (Table 2).¹⁸ Repeatability for questions on wheeze was very good (κ 0.61–0.80).¹⁹ We grouped phenotypes into episodic viral wheeze if parents reported that children wheezed only with colds and multiple trigger wheeze if children also wheezed apart from colds.^{6, 20} We

assessed these trigger factors: exercise (running or playing), aeroallergens (house dust, pollen, pets), food or drinks, laughing or crying or excitement. To describe severity of wheezing illness, we asked how many attacks the child had had in the past 12 months (defining frequent as ≥ 4 episodes),¹ and we inquired whether wheezing was accompanied by shortness of breath, led to sleep disturbance (one or more nights per week considered severe), or interfered with daily activities. The questionnaires were addressed to parents until the child reached 13 years (surveys in 1998, 1999, 2001, 2003, 2006), and directly to children from age 14 onwards (survey in 2010).

Statistical analyses

We included all children who participated in at least one survey (7,670 children, 88%). Due to the range in birth years (1993-7), children were age 1-4 years at the first survey in 1998 and 13-17 in 2010. For this analysis, we grouped children by age, rather than by survey, into the following age groups: 1 year, 2 years, 3-4, 5-6, 7-9, 10-13 and 14-17 years (Fig. E1). We formed narrower age groups in early childhood when physiological and environmental changes occur faster. Children were included only once in each age group (using the survey when children were closest to the midpoint of that age group) but could contribute information to several age groups if they had participated in more than one survey. For the analysis we thus used information on 4,102 children aged 1 year, 3,163 children aged 2, 4,071 aged 3-4, 4,031 aged 5-6, 3,244 aged 7-9, 2,204 aged 10-13, and 2,025 aged 14-17 years.

We calculated prevalence and 95% confidence intervals (CI) of current wheeze and of features of wheeze (wheeze induced by different triggers, wheeze severity markers). We did this for each age group in the entire cohort (absolute prevalence) and in children with current wheeze (relative prevalence). We assessed changes in prevalence with age using logistic generalised estimating equation (GEE) models with an exchangeable working correlation

structure. These models estimate population-averaged changes in prevalence, accounting for repeated measurements of wheeze for children who participated in several surveys.²¹ We calculated odds ratios (ORs) and 95% CI for wheeze in younger and older children compared to the baseline group of children aged 5-6 years.

In a sensitivity analysis, we assessed the potential effect of attrition bias on our results. Attrition bias, caused by decreasing response rates, is common in cohort studies. Since nonresponders might comprise a different population than responders, attrition could distort the results so that they are no longer representative for the entire cohort. We explored whether attrition bias might have affected our results by using inverse probability weight and comparing weighted prevalence of outcomes to unweighted prevalence. To do this, we modelled the probability of participation at each survey with logistic regression models by assessing which baseline factors were associated with participation. We used the following factors: age, sex, ethnicity (White, South Asian), low birth weight (<2,500 g), gestational age (<37 weeks), maternal age, Townsend deprivation index,²² living in an urban area (Leicester postcodes LE1-LE5), and participation in previous surveys. From these models we predicted individual response probabilities for different surveys and inverted them to obtain individual weights.²³ In a further sensitivity analysis for those who were 14 to 17 years old, an age group in which we had both parent-reported and self-reported questionnaires (from the 2010 survey), we assessed whether results differed by type of respondent. We prepared and analysed the data using Stata 14.0 (Stata Corporation, Austin, Texas), and R version 3.3.0.

RESULTS

Absolute prevalence of current wheeze, phenotypes, trigger factors, and severe wheeze in the entire cohort

Prevalence and features of wheeze varied significantly with age (Table 3 Panel a, Figs. 1 and 2). Current wheeze decreased in prevalence during preschool years from 36% in 1-year-olds to 24% in 2-year-olds, 20% in 3-4-year-olds, and 15-17% in schoolchildren irrespective of age (Table 3). This differed by wheeze phenotype. Absolute prevalence of EVW decreased steeply with age from 24% in 1-year-olds to 5% in 7-9-year-olds with no significant changes thereafter (Table E2). In contrast, MTW changed little with age. It was reported for 8-12% of children throughout childhood, with slightly higher prevalence in 1-year-olds and 10 to 17-year-olds compared to 5-6-year-olds (Table E2).

Furthermore, the presence of trigger factors also was age-dependent. Wheeze with exercise was reported for 8-9% of children until age 9, then became more frequent, reaching 13% in adolescents (Table 3, Fig. 1; Table E3). Wheeze induced by aeroallergens was rare in 1-2-year-olds (2-3%), reported more often from age 3 onwards (5-7%), and reached 10% in adolescents. Wheeze triggered by food or drinks remained rare (1-3%) throughout childhood. Laughing or crying was reported to trigger wheeze in 10% of 1-year-olds and 6% of 2-year-olds, decreased in prevalence to 3% at age 3-4, and again became slightly more common in adolescence (6% at age 14-17).

Severe wheeze was rare in the entire cohort and changed little with age (Table 3, Fig. 1; Table E4). Frequent attacks (≥ 4 /year) were reported most often for 1-year-olds (13%); this decreased slowly to 5% at age 10-13. Shortness of breath together with wheeze was rare and reported for only 2-5% of children throughout childhood. Sleep disturbance due to wheeze was most frequent in infants (9%), became gradually less common, and was reported for 2%

of children aged 14-17. Interference of wheeze with daily activities was reported for 5% of infants and decreased slowly to 2% in adolescents.

Relative prevalence of wheeze phenotypes, trigger factors, and severe wheeze among children with current wheeze

Results looked different when viewed from a physician's perspective as a proportion of all children with current wheeze (Table 3 Panel b, Figs. 2-3 and Tables E5-7). At age 1, two-thirds of children were reported to have the phenotype EVW and one-third MTW; this reversed to 60% with MTW and 40% with EVW in adolescents (Fig. 2).

The proportion of wheezing children with exercise-induced wheeze increased greatly, from 26% in infants to 78% in adolescents; this increase in relative prevalence (Fig. 3) was much steeper than the increase in absolute prevalence (Fig. 1). Similarly, aeroallergens were reported to trigger attacks in 6% of infants and around 60% of children age 10 or older. The proportion of children with wheeze reporting that attacks were triggered by food or drinks (8 to 13%) or by laughter or crying (30 to 37%) differed little between age groups.

About one-third of children with wheeze in all age groups (37%) were reported to have frequent attacks (≥ 4 /year) throughout childhood. In contrast, the proportion of current wheezers for whom parents reported shortness of breath increased with age from 7% at age 1 to 26% at age 14-17 (Fig. 3). Sleep disturbance on the other hand became less important in older children: it was reported for 24% of 1-year-old wheezing children, but for only 11% of 14-17-year-olds with current wheeze. Interference with daily activities was reported most often (20%) for 3-9-year-olds.

Sensitivity analyses

The weighted results from the sensitivity analyses that adjusted for potential attrition bias were very similar to those from the unweighted analysis, suggesting that the results were not

biased by the lower response rates (Tables E8, E9). The sensitivity analysis in 14-17-year-olds that compared parent-reported questions (N=749) with self-reported questions (N=1,072) from the 2010 survey found a mainly nonsignificant trend to lower prevalence when symptoms were reported by parents (Table E10).

DISCUSSION

Wheezing illness presents with significant, age-related changes throughout entire childhood. While it is well known that wheezing illness changes with age, this is the first study to give a detailed picture from both a population perspective (absolute prevalence) and the perspective of a physician seeing children with current wheeze (relative prevalence). With the decline in episodic viral wheeze, current wheeze becomes less common with age. Multiple trigger wheeze remains stable across the entire cohort, but its proportion among wheezing children increases with increasing age. Laughing frequently triggers wheeze in younger children, whereas exercise and aeroallergens are more common triggers in adolescents.

Strengths and limitations

The main strengths of the study include (i) its large and representative sample from a population-based cohort, (ii) detailed age resolution from infancy through adolescence, (iii) standardised methodology, and (iv) the broad array of features studied, which include phenotypes, triggers, and severity. Because of attrition in later surveys, we also performed a weighted analysis, which showed results similar to the unweighted analysis suggesting that nonresponse bias did not affect our findings. A potential limitation is that symptoms were parent-reported. However, this reflects the reality of epidemiological surveys and clinical practice in which parents describe the symptoms of their children. As in other studies such as the ISAAC, we addressed questions to parents of younger children and directly to older children (from age 14 onwards). A sensitivity analysis in those aged 14-17 suggests that this did not affect the results much. As in most other studies,^{3,4} we assessed symptom prevalence retrospectively over the last 12 months; but our questions on wheeze had a good repeatability when asked again 3 months later.¹⁹ Finally, it could be argued that age-related changes might

have been overlaid by temporal trends in prevalence of wheeze from 1998 to 2010. However, prevalence of wheezing illness in the Western world has levelled off in the last two decades.²

Prevalence and phenotypes of wheeze

Changes of prevalence with age have been documented rarely and only over limited age ranges, none covering the entire age range. However, the prevalence of wheeze we observed in children 6-7 and 13-14 years old appears comparable to that in reports on the same geographic region during the same period.^{3, 4} Current wheeze decreased from 16% in 2-year-olds to 7% in 7-9-year-olds, in 3,963 children from the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort.¹² In 370 Australian children in the Childhood Asthma Prevention Study (CAPS) cohort, wheeze decreased from 46% of 1-year-olds to 25% in 11-year-olds.²⁴ Two yet earlier studies suggested a slight decrease in prevalence in schoolchildren from age 7 to 15.^{25, 26}

Regarding wheeze phenotypes, we know that the proportion of children with EVW decreases with age, while the proportion with MTW increases.²⁷⁻³⁰ What is new in this study is that we showed a considerable proportion of children reporting EVW throughout childhood to the ages of 14 to 17 years, which may indicate that EVW is not restricted to preschoolers as is often suggested.^{6, 29, 31} Furthermore, we found that the prevalence of MTV—although increasing relatively as a proportion of all children with wheeze—does not change much in absolute prevalence throughout childhood, affecting between 8 and 12% of children at all ages. It has been questioned whether these phenotypes are stable over time and thus independent disorders.^{32, 33} However, recent data from the Leicester Respiratory Cohorts and the Avon Longitudinal Study of Parents and Children cohort (ALSPAC) suggest that MTW and, to a lesser extent, EVW track throughout childhood, independent of severity, and thus seem to be separate disorders.³⁴ Although allergic triggers (aeroallergens) become important

only in late preschool years, wheeze was reported apart from colds for many infants and toddlers. Their symptoms in infection-free periods were not triggered by allergens, but mostly by activities associated with increased breathing effort (exercise, laughing, crying).

Triggers and severity of wheeze

Exercise was relevant for all age groups and was the most common trigger reported. While absolute prevalence of exercise-induced wheeze changed little with age (8 to 13%), its importance among children with wheeze increased. It affected only one-quarter of 1-year-olds, but three-quarters of adolescents. In line with our results, an Australian study reported that at ages 7, 12, and 15 years, respectively 57%, 78%, and 80% of Melbourne children with current wheeze reported exercise as a trigger.²⁶ This study also reported an age-related increase of aeroallergen-triggered symptoms comparable to our results, from 6% at age 7 to 12% at age 15.²⁶ This mirrors the age-related increase in sensitization to inhaled allergens and atopic rhinitis described in other cohorts.^{35, 36} Also, a US study in asthmatic children aged 2-20 years showed that the impact of allergy problems and physical activity in triggering asthma episodes increased with increasing age.³⁷ Wheeze triggered by food or drinks, which can be mediated via different mechanisms, has been described with a comparable prevalence (1% in 1-5-year-olds) in the first Leicester cohort for 1,422 children born 1985-90.⁷

Severity of wheeze (frequency of attacks, shortness of breath, sleep disturbance, and activity restriction) has been assessed in other studies,^{3, 9, 12, 38} but has rarely been compared between age groups. We found that the proportion of wheezing children with frequent attacks—about one-third—remains the same throughout childhood. The proportion of children with wheeze whose sleep is disturbed decreases from 24% in infants to 11% in adolescents. Shortness of breath increases in prevalence from 7% in infants to 26% in adolescents. This might partly be due to a better ability of older children to describe this symptom. Shortness of breath was

more frequent in some German,³⁸ Dutch,¹² and Eastern European studies^{39, 40} compared to ours, but their questions were not all worded exactly the same, and interpretation might differ between languages.

Interpretation of findings

Our results are likely influenced by several factors that all change with age, including physiological, developmental, and environmental factors. Physiological changes, for instance an increase in the absolute diameter of the airways, and also the development of the immune system might explain the decreasing prevalence of virus-induced wheeze during the first years of life, while the increasing proportion of children sensitised to aeroallergens explains the rising relevance of aeroallergens as triggers. With increasing cognitive abilities, children are better able to express subjective symptoms such as shortness of breath. Disturbed sleep might seem less important in older children, whose sleep is monitored less closely by parents than it is in early childhood. Finally, exercise becomes more competitive in later school years so that limitations can no longer be avoided by an adapted lifestyle, but become obvious in comparison to peers. Nearly 80% of adolescents with wheeze reported exercise-induced symptoms in our study.

This study demonstrates in detail how prevalence and clinical presentation of wheeze vary with age and reflect fundamental immunological, physiological, and environmental changes. The results give a detailed picture of the burden of wheezing illness throughout childhood and are thus useful from a public health perspective for health-care planning. Future research projects can make use of the information on the trigger factors and severity indicators that are important for specific age groups to design their questionnaires.

A clear understanding of age-related patterns, including trigger factors and markers of severity, is essential for providing clinical care and conducting and interpreting research studies.

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Competing interests

None

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Fig. 1. Absolute prevalence of wheeze, triggered by different factors, and of different indicators of wheeze severity in entire cohort of children from age 1 to 17 years. Prevalence presented as proportion (in %) with 95% confidence intervals.

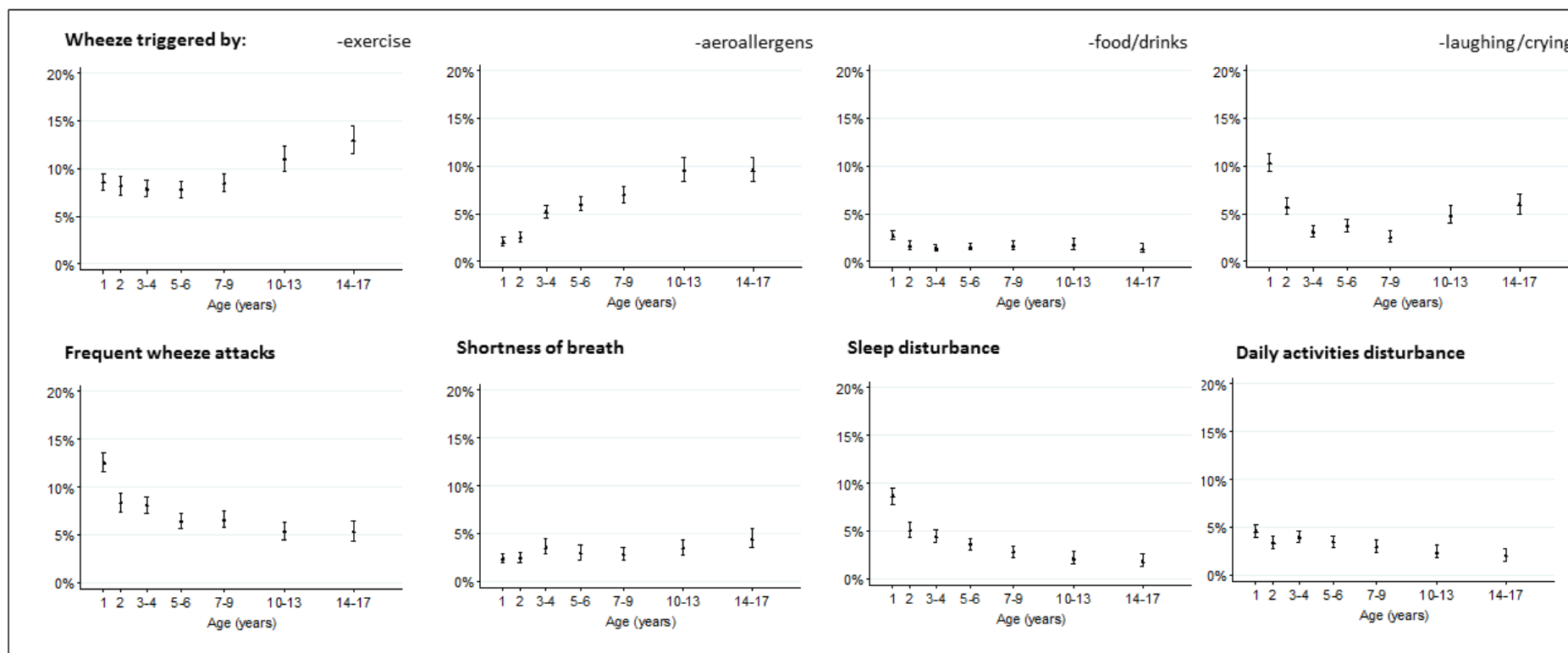


Fig. 2. Prevalence of episodic viral wheeze and of multiple trigger wheeze in the entire cohort (absolute prevalence) and among children with current wheeze (relative prevalence), from age 1 to 17 years. Prevalence is presented as proportion (in %) with 95% confidence intervals.

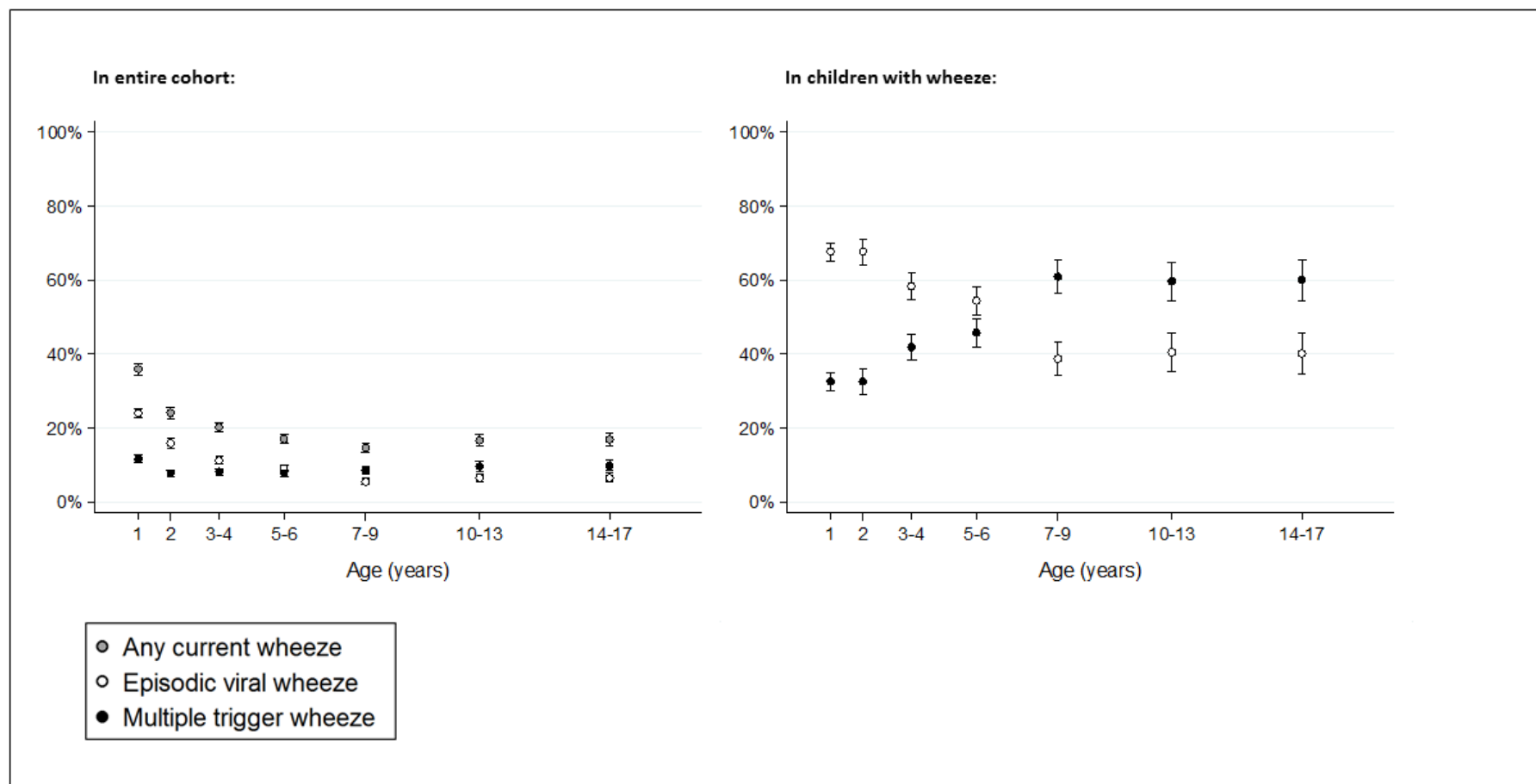


Fig. 3. Relative prevalence of wheeze, triggered by different factors, and of different indicators of wheeze severity among children with current wheeze from age 1 to 17 years. Prevalence presented as proportion (in %) with 95% confidence intervals.

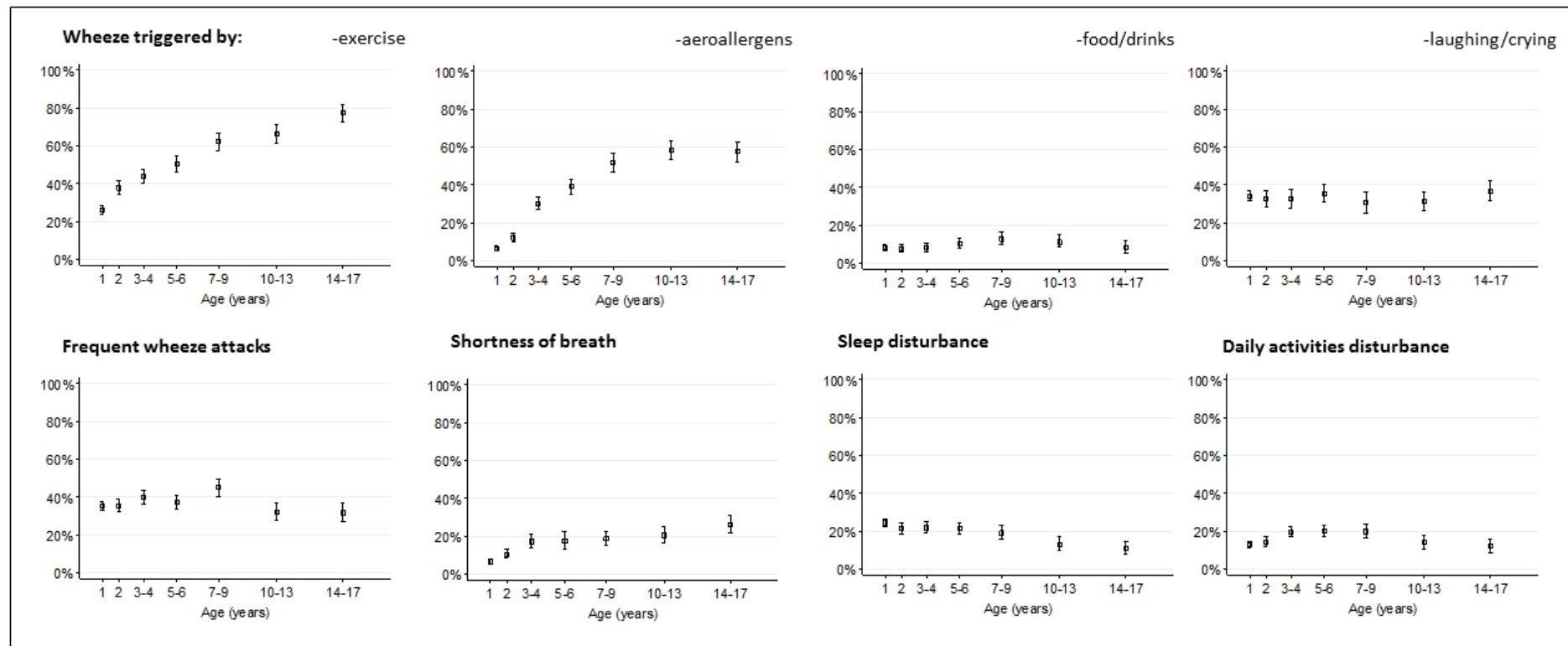


TABLE 1—Characteristics of the study population aged 1 year (N=4,102)

		n	(%)
Demographic factors			
Age (years, mean[SD])		1.5	[0.3]
Male		2,136	(52)
Ethnicity	White	3,301	(80)
	South Asian	801	(20)
Perinatal and early life factors			
Low birth weight (<2500g)		279	(7)
Gestational age <37 weeks		277	(7)
Breastfed		2,400	(58)
Symptoms of the child			
Current wheeze		1,447	(36)
Cough without colds		1,403	(34)
Number of colds (in the last 12 months)	0-3	1,862	(45)
	4-6	1,457	(36)
	≥7	772	(19)
Environmental exposures			
Nursery care		1,040	(25)
Number of older siblings	0	1,292	(32)
	1 or 2	2,228	(54)
	≥3	381	(9)
Pet ownership		1,662	(41)
Mother smoking during pregnancy		688	(17)
Mother smoking (postnatal)		889	(22)
Father smoking		1,029	(25)
Socioeconomic factors			
Higher parental education ^a		2,350	(57)
More deprived Townsend deprivation index ^b		610	(15)
Parental history of atopic diseases			
Hay fever (mother or father)		1,846	(45)
Wheeze or asthma (mother or father)		1,354	(33)

^a Age at the end of education is >16 years

^b The categories cover the following Townsend Deprivation Index intervals: more affluent [-6.222, -2.635], affluent [-2.615, -0.707], average [-0.705, 1.859], deprived [1.861, 5.147], more deprived [5.160, 11.072]

TABLE 2—Original questions about wheezing characteristics analysed in this study

Question	Source of the question
<p><i>Current wheeze</i></p> <p>Has your child had wheezing or whistling in the chest in the last 12 months?</p> <p><input type="checkbox"/> yes</p> <p><input type="checkbox"/> no</p>	International Study of Asthma and Allergy in Childhood (ISAAC) ¹
<i>If yes:</i>	
<p>In the last 12 months, has your child had wheezing or whistling in the chest during or soon after a cold or flu?</p> <p><input type="checkbox"/> yes</p> <p><input type="checkbox"/> no</p>	Adapted from American Thoracic Society questionnaires ²
<p>In the last 12 months, has your child had wheezing or whistling in the chest even without having a cold or flu?</p> <p><input type="checkbox"/> yes</p> <p><input type="checkbox"/> no</p>	Adapted from American Thoracic Society questionnaires ²
<p>In the last 12 months did the following things cause wheezing in your child?</p> <p><input type="checkbox"/> Exercise (playing, running)</p> <p><input type="checkbox"/> House dust</p> <p><input type="checkbox"/> Pollen (grass, hay, trees, flowers)</p> <p><input type="checkbox"/> Contact with pets or other animals</p> <p><input type="checkbox"/> Food or drinks</p> <p><input type="checkbox"/> Laughing, crying or excitement</p>	Adapted from the earlier questionnaire used in Leicestershire (Leicester Respiratory Cohort 1990) ³
<p>How many attacks of wheezing has your child had during the last 12 months?</p> <p><input type="checkbox"/> None</p> <p><input type="checkbox"/> 1 to 3</p> <p><input type="checkbox"/> 4 to 12</p> <p><input type="checkbox"/> More than 12</p>	ISAAC ¹
<p>Do these attacks cause him/her to be short of breath?</p> <p><input type="checkbox"/> Yes, always</p> <p><input type="checkbox"/> Yes, occasionally</p> <p><input type="checkbox"/> No, never</p>	Verbatim earlier questionnaire used in Leicestershire (Leicester Respiratory Cohort 1990) ³
<p>In the last 12 months, how often, on average, has your child's sleep been disturbed due to wheezing?</p> <p><input type="checkbox"/> Never woken with wheezing</p> <p><input type="checkbox"/> Less than one night per week</p> <p><input type="checkbox"/> One or more nights per week</p>	ISAAC ¹
<p>In the last 12 months, how much did wheezing interfere with your child's daily activities?</p> <p><input type="checkbox"/> Not at all</p> <p><input type="checkbox"/> A little</p> <p><input type="checkbox"/> A moderate amount</p> <p><input type="checkbox"/> A lot</p>	ISAAC ¹

TABLE 3—Prevalence of current wheeze, wheeze with triggers, and indicators of severe wheeze in children from age 1 to 17

3a) Absolute prevalence: proportion of children with wheeze in entire cohort

3b) Relative prevalence: proportion of children with certain features of wheeze among wheezers

Age (years):	1 (N=4,102)		2 (N=3,163)		3-4 (N=4,071)		5-6 (N=4,031)		7-9 (N=3,244)		10-13 (N=2,204)		14-17 (N=2,025)	
3a) Absolute prevalence (in entire cohort)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Wheeze	1,447	36 (34-37)	744	24 (23-26)	810	20 (19-21)	675	17 (16-18)	465	15 (13-16)	362	17 (15-18)	336	17 (15-18)
Episodic viral wheeze	955	24 (23-25)	486	16 (15-17)	445	11 (10-12)	356	9 (8-10)	173	5 (5-6)	139	6 (5-8)	122	7 (5-8)
Multiple trigger wheeze	459	12 (11-12)	233	8 (7-9)	319	8 (7-9)	299	8 (7-8)	272	9 (8-10)	208	10 (8-11)	183	10 (8-11)
Triggers of wheeze														
Exercise	331	9 (8-9)	246	8 (7-9)	306	8 (7-9)	305	8 (7-9)	266	9 (8-9)	236	11 (10-12)	255	13 (12-14)
Aeroallergens	77	2 (2-3)	74	3 (2-3)	200	5 (5-6)	236	6 (5-7)	218	7 (6-8)	205	10 (8-11)	188	10 (8-11)
Food/drinks	103	3 (2-3)	48	2 (1-2)	52	1 (1-2)	59	2 (1-2)	50	2 (1-2)	37	2 (1-2)	26	1 (1-2)
Laughing/crying	383	10 (9-11)	164	6 (5-7)	112	3 (3-4)	137	4 (3-4)	76	3 (2-3)	102	5 (4-6)	118	6 (5-7)
Indicators of severe wheeze														
≥4 wheezing attacks	504	13 (12-14)	258	8 (7-9)	318	8 (7-9)	249	6 (6-7)	208	7 (6-7)	116	5 (4-6)	104	5 (4-6)
Shortness of breath due to wheeze	95	2 (2-3)	76	3 (2-3)	76	4 (3-4)	47	3 (2-4)	84	3 (2-3)	72	4 (3-4)	85	5 (4-5)
Sleep disturbed >1/week due to wheeze	345	9 (8-10)	155	5 (4-6)	172	4 (4-5)	140	4 (3-4)	88	3 (2-3)	46	2 (2-3)	36	2 (1-3)
Wheeze interfering moderately or a lot with daily activities	185	5 (4-5)	105	3 (3-4)	155	4 (3-5)	134	4 (3-4)	92	3 (2-4)	49	2 (2-3)	39	2 (1-3)
Age (years):	1 (N=1,447)		2 (N=744)		3-4 (N=810)		5-6 (N=675)		7-9 (N=465)		10-13 (N=362)		14-17 (N=336)	
3b) Relative prevalence (among wheezers)	N	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Episodic viral wheeze	955	68 (65-70)	486	68 (64-71)	445	58 (55-62)	356	54 (51-58)	173	39 (34-43)	139	40 (35-45)	122	40 (35-46)
Multiple trigger wheeze	459	33 (30-35)	233	32 (29-36)	319	42 (38-45)	299	46 (42-50)	272	61 (56-65)	208	60 (55-65)	183	60 (55-66)
Triggers of wheeze														
Exercise	331	26 (24-28)	246	38 (34-41)	306	44 (40-48)	305	50 (46-54)	266	62 (58-67)	236	67 (62-71)	255	78 (73-82)
Aeroallergens	77	6 (5-8)	74	12 (9-14)	200	30 (27-34)	236	39 (35-43)	218	52 (49-59)	205	58 (53-64)	188	58 (52-63)
Food/drinks	103	8 (7-10)	48	8 (6-10)	52	8 (6-10)	59	10 (8-13)	50	13 (9-16)	37	11 (8-15)	26	8 (5-11)
Laughing/crying	383	34 (31-37)	164	33 (28-37)	112	33 (28-38)	137	35 (31-40)	76	30 (25-36)	102	31 (26-36)	118	37 (31-42)
Indicators of severe wheeze														
≥4 wheezing attacks	504	35 (33-38)	258	35 (32-39)	318	40 (36-43)	249	37 (34-41)	208	45 (41-50)	116	32 (27-37)	104	32 (27-37)
Shortness of breath due to wheeze	95	7 (5-8)	76	10 (8-13)	76	17 (14-21)	47	17 (13-22)	84	19 (15-22)	72	21 (16-25)	85	26 (21-31)
Sleep disturbed >1/week due to wheeze	345	24 (22-27)	155	21 (18-26)	172	22 (19-25)	140	21 (18-24)	88	19 (15-23)	46	13 (10-17)	36	11 (8-14)
Wheeze interfering moderately or a lot with daily activities	185	13 (11-15)	105	14 (12-17)	155	20 (17-22)	134	20 (17-23)	92	20 (16-23)	49	14 (10-18)	39	12 (8-16)

N, number of children who returned the questionnaire at the respective age

Percentages are calculated based on those who responded to the respective questions

All wheeze features refer to the past 12 months

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