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Health consequences associated with frequent wheezing in adolescents without asthma diagnosis

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Health consequences associated with frequent wheezing in adolescents without asthma diagnosis. K. Yeatts, K. Johnston Davis, D. Peden, C. Shy. ©ERS Journals Ltd 2003.
ABSTRACT: Using questions from the International Study of Asthma and Allergies in Childhood, this study evaluated the association between undiagnosed frequent wheezing and health consequences in adolescents.

The North Carolina School Asthma Survey provided self-reported questionnaire data on respiratory health from 122,829 children aged 12–14 yrs. The frequency of health consequences were compared among undiagnosed frequent wheezers, diagnosed asthmatics, and children with no wheezing symptoms or diagnosed asthma.

The odds of wheezing-related sleep disturbances, limited activities, and missed school were higher among undiagnosed frequent wheezers, relative to diagnosed asthmatics. The frequency of emergency room visits and hospitalisations did not differ substantially between the undiagnosed wheezing and diagnosed asthma groups, though the undiagnosed group was less likely to have visited a physician for wheezing in the past year.

Children with frequent wheezing symptoms but no asthma diagnosis experience substantial illness-related morbidity similar to that of diagnosed asthmatics. Undiagnosed frequent wheezers require more recognition from primary care physicians and need active disease management to reduce health consequences.
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Asthma is the most common chronic illness in the USA affecting ~5 million children. Annually, asthma accounts for ~15 million outpatient visits, >445,000 hospitalisations and 1.2 million emergency room visits. During 1980–1996, the number of asthma-associated school absence days increased >50% from 6.6 to 14.0 million [1]. Many of the published studies that focus on functional consequences of asthma morbidity are based on the National Health Interview Survey (NHIS) and National Health and Nutrition Examination Survey (NHANES III) data sets in which information is collected *via* parental report of physician-diagnosed asthma [2–6]. However, these estimates, by their design, will miss a large segment of the population suffering from asthma-like symptoms that have not been clinically diagnosed, resulting in a significant underestimation of the true impact of asthma in the population.

A growing body of evidence indicates that there are a substantial number of children who report asthma-like symptoms yet are not diagnosed with asthma [7–10]. However, there is a lack of information regarding functional consequences and healthcare utilisation rates in this population of children who wheeze, yet are not recognised as asthmatics.

The North Carolina School Asthma Survey (NCSAS), a large population-based study of middle schoolchildren (n=122,829), provides a unique opportunity to examine the functional consequences and healthcare utilisation of children reporting frequent asthma-like symptoms, without report of physician diagnosis of asthma. This study is distinct for several reasons compared with those previously published due to the following: 1) inclusion of large numbers of diverse groups of minority children (Native American, African-American, Latin and Central American, and Asian children); 2) use of two different referent groups to represent both the clinical and public health perspective of asthma; 3) use of the internationally validated International Survey of Asthma and Allergies in Childhood (ISAAC) questionnaire that allows for identification of wheezing without diagnosis; 4) a large population-based rather than clinic-based sample; 5) simultaneous adjustment for other associated risk factors including medication use, allergies, active and passive smoking, and urban/rural areas, and socioeconomic status; and 6) comprehensive evaluation of both functional consequences and healthcare utilisation, each with three different measures.

Methods

NCSAS was a large population-based cross-sectional study conducted in the 1999–2000 school year, designed to obtain

For editorial comments see page 719.

baseline surveillance data on asthma-like symptom prevalence in public school children aged 12–14 yrs. The UNC School of Public Health Institutional Review Board reviewed and approved the project. The target population was enumerated from 1999–2000 enrolment records kept by the North Carolina Dept of Public Instruction and included 565 public middle schools with 192,248 children.

The questionnaire used in the survey was adapted from ISAAC [11]. Both written and video symptom questions from the ISAAC survey were used [12–16]. The 12–14 yr age group was chosen to reflect the period when morbidity from asthma is common and to enable the use of self-completed questionnaires. The video symptom sequence showed five symptom scenes being experienced by adolescents: 1) wheezing at rest during the day; 2) wheezing after exercise; 3) waking at night by wheezing; 4) waking at night by cough; and 5) a severe wheezing attack with intercostal retractions. Questions were added regarding the functional health consequences of asthma and healthcare use. The questionnaire was administered in school to groups of children during class. To standardise the administration of the questionnaire, the entire questionnaire, including the ISAAC video wheezing sequence, was visually presented on a video screen and read aloud one question at a time with skip patterns emphasised [17]. Skip patterns were places in which children without symptoms or diagnosed asthma were told not to fill in specific questions related to asthma or wheezing. These children were reminded to wait and prompted to continue at the appropriate time.

Children were categorised by frequency of asthma-like symptoms with and without report of physician diagnosis of asthma. Three mutually exclusive groups were compared: 1) children with frequent wheezing symptoms and no diagnosis, whom the authors suspected might be comparable with diagnosed asthmatic children; 2) children who reported wheezing symptoms and a physician diagnosis of asthma; and 3) children with no symptoms or diagnosis ever (hereafter referred to as asymptomatics). A fourth group defined as infrequent wheezers, (children with infrequent wheezing symptoms and no physician diagnosis, n=38,424) was included for reference. This group was excluded from further statistical analyses as these children were beyond the scope and focus of this study. Frequent symptoms were defined as any of the video wheezing symptoms (at rest during the day, after exercise, waking at night, and severe wheezing attack with intercostal retractions) occurring once or more per month during the last 12 months. Episodic mild wheezing after exercise (once a month) was included in the definition "frequent" symptom. When these children were excluded from the statistical analyses, the associations were even more statistically significant.

Functional consequences were defined as the number of self-reported school absences, activity limitations, and sleep disturbance due to asthma-like symptoms (see Appendix for questions and response categories). Healthcare utilisation variables included the number of physician visits, emergency room visits and hospitalisation admissions for asthma-like symptoms. Frequencies for the functional consequences and healthcare use variables were tabulated for the four groups of children (table 1).

Outcome variables for the multiple logistic regression models compared the prevalence of the two highest response categories *versus* the lowest response category (none). The outcomes of activity limitations and school absence were categorised as $\geqslant 1$ days per week due to wheezing during the past 12 months *versus* none. For sleep disturbances, the outcome compared those with $\geqslant 1$ nights of sleep disturbances during the last 4 weeks *versus* none. For the healthcare utilisation variables, the outcome was categorised as three or more healthcare visits (physician, emergency room, or hospital) for wheezing, dry cough or breathing difficulties in the last 12 months compared with no visits.

Adjusted odds ratios (OR) of functional consequences and healthcare use for undiagnosed frequent wheezers were calculated against two different referent groups: 1) children with current diagnosed asthma; and 2) asymptomatic children. In addition, the authors calculated adjusted ORs comparing diagnosed asthmatics to asymptomatic children. Independent variables included in the model were age, sex, socioeconomic status, race, Latin and Central American ethnicity, any self-reported allergies (cat, dog, grasses, dust), current smoking, inhaler use, and regular source of healthcare for asthma or allergies.

Results

The survey response rate was 66.8% (128,568/192,248) for 7th and 8th grade children. There were no significant differences among the demographical variables of socioeconomic status (enrolment in the free/reduced school lunch programme), race, and sex for children who participated and those who did not (p-values from Chi-squared tests 0.66, 0.61, 0.58, respectively.) Of the 128,568 participating children,

Table 1.–Asthma-like symptom categorisation (as reported in response to International Survey of Asthma and Allergies in Childhood video questions)

Category	Description
Frequent wheezers[#]	Children with a positive response to any of four video wheezing symptoms[¶] one or more times a month in the last 12 months and no report of physician diagnosed asthma
Physician diagnosed asthmatics	Children with a positive response to any of four video wheezing symptoms in last 12 months and a report of physician diagnosis of asthma
Asymptomatic children	Children with no report of physician-diagnosed asthma and no positive responses to wheezing or coughing video questions
Infrequent wheezers	Children with only a positive response to video symptom of waking with cough in the last 12 months but no wheezing or physician diagnosis of asthma
	Children with a positive response to any of four video wheezing symptoms or ever waking with cough in the past, but not in last 12 months
	Children with a positive response to any of four video wheezing symptoms in the last 12 months but less frequently than once a month

[#]: frequent defined as symptoms occurring once or more per month during the past 12 months. [¶]: four video wheezing symptoms including scenes of: 1) wheezing at rest during the day; 2) wheezing after exercise; 3) waking at night by wheezing; or 4) a severe wheezing attack with intercostal retractions.

Table 2. – Demographic characteristics by disease group, North Carolina School Asthma Survey, 1999

		Undiagnosed frequent wheezers	Diagnosed current asthmatics	Asymptomatic	Infrequent wheezers
Subjects n*		7587	12174	64644	38424
Sleep disturbances at night due to wheezing in the last 4 weeks	<1 night per week	30	35	2	15
	⩾1 nights per week	17	15	0	4
Limited activities due to wheezing in the last 12 months	<1 time per week	23	33	1	10
	⩾1 times per week	10	14	0	2
	Almost daily	5	5	0	1
Any school days missed due to wheezing in the last 12 months	<1 day per month	15	24	2	38
	1–3 days per month	8	14	1	3
	⩾1 days per week	5	8	0	1
Physician visits due to wheezing in the last 12 months	1–2 visits	25	44	4	19
	3–4 visits	5	18	0	3
	5+ visits	3	9	0	1
Emergency room visits due to wheezing in the last 12 months	1–2 visits	7	22	1	4
	3–4 visits	1	5	0	0
	5+ visits	2	3	0	0
Hospitalisations due to wheezing in the last 12 months	1–2 visits	7	18	0	3
	3–4 visits	1	3	0	0
	5+ visits	2	2	0	0
Inhaled medicine use in the last 12 months	<1 per month	5	19	1	6
	1–3 days per month	3	20	0	2
	⩾1 times per week	2	16	0	1
	Almost every day	3	22	0	2

Data are presented as % unless otherwise stated. *: percentages are rounded to the nearest whole number.

5,739 children were excluded from the analysis due to incomplete questionnaire data. The study population (n=122,829) was 50% female, 27% African-American, 9% Latin and Central American, 1.91% Asian/Pacific Islander, 96% aged 12–14 yrs, and 33% of low socioeconomic status.

Factors independently associated with undiagnosed frequent wheezing *versus* asymptomatic children included female sex (OR=1.45, 95% confidence interval (95% CI): 1.35–1.54), current smoking (2.60, 2.43–2.79), exposure to household smoke (1.59, 1.50–1.70), low socioeconomic status (1.52, 1.42–1.63), and African American (1.25, 1.15–1.34), Native American (1.35, 1.11–1.62), and Mexican American (1.32, 1.17–1.48) race/ethnicity. Urban residence showed a weak negative association (0.91, 0.85–0.96) [18].

Table 2 compares the frequencies of the functional consequences and healthcare utilisation due to wheezing for children with undiagnosed frequent wheeze, children with diagnosed asthma, and asymptomatic children. Asymptomatic children reported essentially no functional consequences or healthcare use related to wheezing.

To illustrate the relative impact of undiagnosed frequent wheezing, the authors compared undiagnosed frequent wheezers first to diagnosed asthmatics and then to children with no symptoms or diagnosed asthma (table 3). The odds of reported functional consequences were higher in undiagnosed frequent wheezers compared with diagnosed asthmatics. The second comparison among children with no symptoms quantifies the degree to which children with undiagnosed wheezing are impacted by their symptoms relative to a healthy population. Finally, a third comparison was made between diagnosed asthmatics and asymptomatic children, in order to demonstrate the impact of the diagnosed disease relative to the population free of respiratory illness.

OR and 95% CI in the first two columns of table 3 indicate that undiagnosed frequent wheezers were significantly more likely to report sleep disturbances (1.9, 1.7–2.1), limited

Table 3. – Adjusted associations of functional consequences and healthcare use with asthma-like symptoms, three comparisons

	Undiagnosed frequent wheezers *versus* diagnosed asthmatics[#]	Undiagnosed frequent wheezers *versus* asymptomatics[¶]	Diagnosed asthmatics *versus* asymptomatics[¶]
Sleep disturbances ⩾1 nights a week due to wheezing in the last 4 weeks	1.9 (1.7–2.1)	20.1 (18.4–21.9)	10.8 (9.7–12.0)
Limited activities ⩾1 times a week due to wheezing	1.6 (1.4–1.9)	40.1 (33.3–48.7)	24.5 (19.7–30.5)
⩾1 school days per month missed due to wheezing in the last 12 months	1.2 (1.0–1.5)	12.7 (9.9–16.4)	10.1 (7.5–13.5)
⩾3 Physician visits due to wheezing in the last 12 months	0.6 (0.5–0.7)	12.4 (10.2–15.2)	20.7 (16.8–25.6)
⩾3 emergency room visits due to wheezing in the last 12 months	0.9 (0.6–1.1)	9.8 (6.6–14.7)	10.8 (7.1–16.7)
⩾3 hospitalisations due to wheezing in the last 12 months	0.9 (0.7–1.2)	10.0 (6.5–15.7)	9.6 (6.1–15.6)

Data are presented as odds ratio (95% confidence interval). Prevalence odds ratios adjusted for age, sex, low socioeconomic status, any allergies, current smoking, source of care for asthma, and inhaler use during the last 12 months. Undiagnosed frequent wheezers are children with current frequent wheezing symptoms and no diagnosis of asthma. Asymptomatics are defined as children reporting no asthma-like symptoms or asthma diagnosis, ever (n=64,644). [#]: referent group is children with diagnosed asthma with current wheezing symptoms; [¶]: referent group is asymptomatics.

activities (1.6, 1.4–1.9), and missed school (1.2, 1.0–1.5) related to wheezing compared with diagnosed asthmatics. Undiagnosed frequent wheezers were almost half as likely to report physician visits (0.6, 0.5–0.7) compared with asthmatics. However, the odds for both emergency room visits (0.9, 0.6–1.1) and hospitalisations (0.9, 0.7–1.2) did not differ markedly between diagnosed asthmatics and undiagnosed frequent wheezers.

The second column of OR in table 3 compared the odds of functional consequences and healthcare utilisation for undiagnosed frequent wheezers relative to asymptomatic children. Undiagnosed frequent wheezers were more likely to experience sleep disturbances (20.1, 18.4–21.9), limited activities (40.1, 33.3–48.7), and missed school (12.7, 9.9–16.4) due to wheezing compared with asymptomatic children. The OR of healthcare utilisation for wheezing was 9.9–12.4 times higher for the undiagnosed frequent wheezers, compared with asymptomatic children.

Relative to asymptomatic children, diagnosed asthmatics were 10–24 times as likely to experience limited activities, sleep disturbances, and missed school (table 3). Healthcare utilisation was also more common among children with diagnosed disease. Diagnosed asthmatics were 20 times as likely to visit a physician compared with asymptomatic children and more than nine times as likely to report three or more emergency room visits or hospitalisation for wheezing compared with asymptomatic children.

Discussion

In these population-based analyses of children aged 12–14 yrs, the authors found that the odds of reporting functional consequences (sleep disturbances, school absences, activity limitations) were higher in undiagnosed frequent wheezers compared with diagnosed asthmatics. Frequent undiagnosed wheezers were equally likely to report emergency room visits, and hospitalisations due to wheezing compared with diagnosed asthmatics. However, the odds of physician visits for undiagnosed frequent wheezers were almost half that of diagnosed asthmatics, suggesting that undiagnosed frequent wheezers are not receiving maintenance care from a physician.

In the analyses of the current study, the authors included diagnosed asthmatics as a referent group to illustrate the increased odds of functional consequences in frequent undiagnosed wheezers, compared with diagnosed asthmatics. This comparison highlights the substantial burden of illness in undiagnosed frequent wheezers, yet they were half as likely as the diagnosed group to visit a physician. Using the asymptomatic group as a referent illustrated the substantial impact that undiagnosed frequent wheezing and diagnosed asthma have in the daily lives of affected children, compared with relatively healthy children.

Published literature on the health consequences of frequent wheezing in children with no asthma diagnosis is scant. The earliest report of undiagnosed asthma by SPEIGHT [9] in 1978, found that of the 34 children suspected to have undiagnosed asthma, 50% missed >6 weeks of school, and 20% (seven children) were hospitalised for wheezing. LOWE and BURR [19], 20 yrs later reported that in a cohort of British children with a history of allergy, 15/39 with wheezing and no diagnosis of asthma reported sleep disturbances. In Denmark, SIERSTED *et al.* [7] conducted a very comprehensive evaluation of undiagnosed asthma. However, the only health consequence measured was physical activity, with undiagnosed children 0.65 times as likely as diagnosed children to have had physical activity in the last 4 weeks. HETVLIK *et al.* [20] and STRACHAN *et al.* [21] evaluated undiagnosed asthma in Norway and England, but only reported on medication use, while HILL *et al.* [22] investigated school absences in Scotland. In the USA, SILVER *et al.* [23] found that 28% of children with wheezing compared with 42% of children with diagnosed asthma reported sleep disturbances one or more times per week on average, while CRAIN *et al.* [8] found that 18.6% and 18.4% of parents with either wheezing children or children with diagnosed asthma, respectively, reported that their child experienced one or more sleep disturbances due to wheeze in the last week.

The findings from the current study are likely to have been influenced by local factors and the structure and function of the national healthcare system (such as costs of healthcare utilisation, availability and access to healthcare, and the education of the health providers) and thus may not be generalised to European countries. This research may be limited to countries similar to the USA that do not have socialised medicine and fewer citizens with access to affordable medical care.

In comparison, the impact of diagnosed asthma on children's lives has been addressed previously [2, 3, 5]. The results from the current study for diagnosed asthmatics agree with these other studies. Using the 1988 NHIS database, FOWLER *et al.* [5] found that 42% of children missed school due to asthma in the last year, while in the current study 46% missed school due to asthma. The authors estimate activity limitation (51% of children with diagnosed asthma) was higher than that of TAYLOR and NEWACHECK [2], who reported that 30% of children with asthma in the 1988 NHIS data had limitations in activities, but lower than the 71.5% reported by KAUR *et al.* [10]. Using data from the 1994–1995 NHIS study, NEWACHECK and HALFON [3] reported that children from low income households were 1.46 (95% CI 1.2–1.76) times as likely to report disability due to asthma. Similarly, the current study found that children with diagnosed asthma of low socioeconomic status were 1.9 (1.7–2.1) times as likely to report sleep disturbances due to asthma.

Data from the current study were self-reported by adolescents aged 12–14 yrs. The asthma-like symptoms were assessed with the ISAAC questionnaire, which has been extensively validated [12–16, 24, 25]. Symptom data collected by directly interviewing adolescents has been found to be a more reliable source of information than parental report, the current standard for asthma in the NHANES III and NHIS in the USA [25, 26]. The reliability and validity of the functional consequence and healthcare utilisation questions have been assessed [27]. The results from the current study for the burden of disease experienced by diagnosed asthmatic children agree with other published studies, further supporting the validity of this survey.

There are several strengths of the current study, the first being the comprehensiveness of the measures for both functional consequences (sleep disturbances, limited activities, and missed school all due to asthma-like symptoms) and healthcare use (physician and emergency room visits and hospitalisations) in three groups of children. Unlike other studies, the authors were also able to adjust for many independent risk factors associated with variations in asthma prevalence and morbidity (current smoking, socioeconomic status, sex, race, allergies, age, source of care, and medication use). Most of the research carried out to date has been clinic-based [7] and in children with diagnosed asthma [2–5, 28, 29], including only those whose parents seek care and have access to care. Clinic-based studies only measure the tip of the "iceberg" of asthmatic disease in the population.

Another strength of the current study is the use of the ISAAC questionnaire. The ISAAC [12, 13, 23, 30–32] has

been conducted in 56 different countries, in 463,801 children [11] and another global survey with the ISAAC is currently underway. Reporting of wheezing symptoms using the ISAAC video has been validated with a high sensitivity (0.87) and specificity (0.75) when compared with a physician's diagnosis of clinically active asthma as a gold standard [13]. These studies determined that the video questionnaire was a reliable method for determining asthma prevalence [14–16, 24, 25, 31]. Recent research has shown that bronchial hyperresponsiveness (BHR) tests had a low sensitivity (0.35–0.47), whereas using asthma symptoms had high specificity (>0.97) and sensitivity (>0.7) in relation to clinical asthma, which makes them a better tool for asthma epidemiology than BHR [30, 32–34].

To the authors' knowledge this study is the first to evaluate multiple aspects of both functional consequences and healthcare use in children with undiagnosed frequent wheezing from a population-based sample. This research provides evidence that undiagnosed frequent wheezers require more recognition from primary care physicians and need active disease management. The results support the conclusion that the current published estimates of the prevalence and impact of asthma in the paediatric population are considerable underestimates. Undiagnosed frequent wheezers should be considered in estimates of the prevalence and impact of asthma in the population.

Appendix: North Carolina School Asthma Survey functional consequences and healthcare use questions

27. In the past 4 weeks, how often on average has your sleep been disturbed at night due to wheezing, dry cough, or breathing difficulties not due to a cold or chest infection?
None
<1 night per week
⩾1 nights per week

28. In the last 12 months, how often did you limit your activities that you wanted to do (excluding school attendance) due to wheezing, dry cough, and/or breathing difficulties not due a cold or chest infection?
Never
<1 time per week
⩾1 times per week
Almost daily

29. In the latest 12 months, how often did you miss school due to wheezing, dry cough, and/or breathing difficulties not due to a cold or chest infection?
Never
<1 day per month
1–3 days per month
~1 day per week
>1 day per week

30. In the 12 months, how many times did you go to the doctor due to wheezing, dry cough and/or breathing difficulties?
0 (no visits)
1–2 visits
3–4 visits
5+ visits

31. In the last 12 months, how many times did you go to an emergency room due to wheezing, dry cough and/or breathing difficulties?
0 (no visits)
1–2 visits
3–4 visits
5+ visits

32. During the past 12 months, how many times were you admitted to a hospital due to wheezing, dry cough and/or breathing difficulties?
0 (no admissions)
1–2 admissions
3–4 admissions
5+ admissions

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