

Two main subtypes of wheezing illness? Evidence from the 2004 Aberdeen schools asthma survey

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To compare risk factors for wheezy bronchitis (WB) and multi-trigger wheeze (MTW) in pre-pubertal children along the spectrum of disease severity. Cross-sectional survey of children aged 7–12 yr in Aberdeen city primary schools in 2004 using parent-completed questionnaires as used in surveys in 1964, 1989, 1994, and 1999. Children were grouped into five categories: no wheeze in the past three years, non-severe wheeze triggered only by a cold (non-severe WB), non-severe wheeze triggered by other factors (non-severe MTW), severe WB, or severe MTW. Severe wheeze was defined as greater than four wheezing attacks, greater than or equal to one disturbed night per week, or speech limitation in the last 12 months. Questionnaires were returned by 3271 children (57.3%), of whom 7.4% had WB (6.1% non-severe and 1.3% severe) and 17.2% had MTW (9.4% non-severe and 7.8% severe). Severe disease was more frequent in children with MTW (31.8%) than in those with WB (5.1%). Whereas the prevalence of MTW had increased since 1964, the prevalence of WB had remained stable over this period. After adjustment for confounders, age had no influence on either wheeze type, and male sex was only associated with non-severe WB [OR 1.44, 95% confidence intervals (1.03–2.02)]. In the WB group eczema or/and hay fever in the child were more strongly associated with severe wheeze [OR 3.28(1.49–7.23) vs. OR 1.84(1.31–2.60)]. In the MTW group, this association was noticeably higher than in the WB group, but did not differ much between non-severe and severe wheeze [OR 5.46(3.70–7.20) and OR 6.01(4.1–8.75) respectively]. The presence of any allergic diseases in either parent increased the odds for non-severe and severe MTW at the same level of magnitude [OR 1.92(1.38–2.68) and OR 1.92(1.34–2.76) respectively], and statistically non-significantly for severe WB [OR 1.75(0.78–3.94)]. Living in a deprived area increased both severe WB and severe MTW, reaching statistical significance only for severe MTW [OR 1.96(1.39–2.78)]. Smoking in the house was associated with increased risk of WB and MTW of any severity. WB and MTW differ in prevalence trends and severity. Within severity levels, the influence of age, allergic diseases in children and parents also differed between these two wheezing subtypes.

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In the past, wheeze in children of school age occurring exclusively in the presence of upper respiratory tract infection was not labelled as asthma (1) but rather as wheezy bronchitis (WB)

in the UK (2) or chronic bronchitis of childhood in North America (3). The characteristic feature of WB as used in that epoch was wheeze triggered only by respiratory tract infection

rather than the multiple triggers characteristic of classical, usually atopic, asthma. However the WB diagnostic label gradually fell out of favour after it was concluded that WB was indistinguishable from asthma, and was merely a milder form of the same disease (4). Labelling most documented wheezing illness in school age children as asthma was also advocated to encourage the early use of anti-asthmatic therapy and discourage the use of antibiotics (5). This practice remained unchallenged until Wilson revisited the area and suggested that although virus provoked wheeze, non-specific bronchial hyper-responsiveness, and atopy frequently co-existed in children with classical asthma all three conditions could exist as independent features and by inference have distinct genetic and/or environmental contributors (6).

Although WB is now commonly used to describe infection-related wheeze in infancy and early childhood (6, 7, 8), there has been no return to the diagnostic labels of WB or chronic bronchitis of childhood in older children. There is, however, emerging evidence that in school age children WB may be a distinct subtype of wheezing illness with different long-term outcomes, different underlying mechanisms, and different risk factors from wheeze with a wide range of provoking factors more typical of classical asthma (9). Follow-up studies suggest that school age children with WB have a better outcome in early middle age than children labelled as asthmatic (10, 11, 12, 13), although a less benign longer term outcome has been suggested by the steeper rate of decline in baseline forced expiratory volume in 1 s (FEV₁) between the ages of 35 and 45 yr (14). Childhood atopic asthma and virus associated wheezy episodes appear to have different underlying pathophysiological mechanisms as demonstrated by the predominance of eosinophils and mast cells in bronchoalveolar lavage of the former but not in the latter (15). Further suggestions of different underlying mechanisms also come from the poor response to inhaled corticosteroids in school age children with predominant viral induced symptoms (16).

A series of cross-sectional surveys of school age children, carried out within a defined area in Aberdeen since 1964, have used the same questions about wheezing symptoms. The aim of the present study was to investigate whether WB, as previously defined, and asthma, defined as multi-trigger wheeze (MTW), could be distinguished on the basis of risk factors and time trends. In the most recent survey, we explored differences between the two syndromes allowing for differences in severity.

Methods

Protocol

All children in primary school years 3–7 (approx. aged 7–12 yr) in state schools within Aberdeen city boundaries as they existed in 1964 were approached in May 2004 using methodology and questions based on previous surveys (17). Additional questions on disease severity were adopted from the International Study of Asthma and Allergies in Childhood (ISAAC) (18). Unlike the previous studies, children's names and addresses were not made available to the researchers in accordance with the UK Data Protection Act (1998). We were obliged to distribute questionnaires by school class and rely on children to convey the questionnaire to and from their parents and were not able to identify or send reminders to non-responders. Completed questionnaires were collected from the schools. Stamped addressed envelopes for the return of late responses to the study centre were left at the schools at the time of the questionnaires collection. To ensure better response rates, telephone and fax reminders were sent to the schools two and four weeks after the study had commenced.

Wheeze in the past three years was defined by the question: *Has your child wheezed or had a whistle in the chest in the past three years? These children were divided into WB, defined as a positive answer to the question: Is a cold the only thing which brings on the wheeze?, or MTW, defined as a negative answer to the same question and positive answer to the question on any other triggers.* Children with WB or MTW were in turn divided into non-severe and severe wheezers. Severe wheeze was defined as greater than four wheezing attacks, greater than or equal to one night disturbed due to wheeze per week, or speech limitation due to wheeze in the last 12 months. Eczema or/and hay fever in children were defined by the questions: *Has your child ever had eczema/hay fever?* Parental allergy was defined by the presence of either asthma, eczema, or hay fever in either parent. Child age was used as a continuous variable. The Scottish index of multiple deprivation (SIMD) 2004 for Aberdeen city postcodes, based on 2001 census, was used to assess socio-economic status of the families of the participating children (19). SIMD score is a combination of 31 indicators in the six domains of income, employment, health, including mortality <75 yrs and emergency hospital admissions; education, skills and training deprivation, geographical access and telecommunications, and housing. SIMD score ranges between 0.88 and 63.59 for Aberdeen city postcodes. The

median SIMD score was used to define those living in areas of higher or lower deprivation. The question: *Does anyone living in the same house as your child smoke?* was used to assess exposure to environmental tobacco smoke at home (ETS). Information from the questionnaires was scanned using automated Eyes and Hands processing software (Trax UK Ltd, Rochester, England) and checked on the screen against the questionnaires before exporting to a database.

A stepwise forward model in multinomial logistic regression was used to assess the influence of sex, age, socio-economic deprivation, ETS, and allergic disorders in the child and parents on the odds of having non-severe and severe WB and MTW compared to having no wheeze. In the completed questionnaires, only six (0.2%) had missing values for the question on wheeze in the past three years. Thirty-two of the respondents (1.0%) reported negatively to the question on wheeze in the last three years, but positively on wheeze only with a cold. They were included in the analysis as having WB. Sixty-one questionnaires (1.9%) had a negative answer to the question on wheeze in the last three years, but positive answer to the questions on wheeze triggers other than a cold alone. In the analysis, these were considered as having MTW. Thirty-nine (1.2%) of the respondents reported wheeze in the last three years, but did not report on wheeze triggers or severity. These were excluded from the analysis. Information on the child's sex and age was available in 99.8% and 99.7% of the respondents respectively. The data on child eczema or hay fever were provided in 85.3% of the returned questionnaires. Postcode data required for deprivation coding were available in 97.6%, data on smoking at home in 99.0%, and data on family history of allergic diseases in 99.7% of the respondents. Non-responses were treated as missing values. The data were analysed in the Statistical Package for the Social Sciences (SPSS, Windows version 12.0). The study protocol was approved by the Grampian Research Ethics Committee, ref: 04/0097, and the Director of Education for Aberdeen city.

Results

Questionnaires were completed and returned by parents of 3271 of 5712 (57.3%) eligible children with a mean age of 9.8 yr. Boys and girls were equally represented in the study population (49.7% boys and 50.3% girls). Wheeze in the past three years was reported by 24.6% children ($n = 806$, 26.0% boys, 24.1% girls) and severe

wheeze by 9.1% ($n = 297$, 9.3% boys and 9.1% girls). WB was reported by 7.4% (6.1% non-severe and 1.3% severe) and MTW by 17.2% (9.4% non-severe and 7.8% severe).

Among symptomatic children, 29.9% ($n = 241$) had WB (30.7% boys, 29.0% girls) and 70.1% ($n = 565$) had MTW (69.2% boys, 71.0% girls). Severe symptoms were more commonly reported in the children with MTW (31.8%) than in those with WB (5.1%). Trends over 40 years in the prevalence of WB and MTW were examined in children in school years 5–7 only (approx. aged 9–12 yr) as data on children in years 3–4 were not collected in the 1964, 1989 and 1994 surveys (17). There was no significant change in the prevalence of WB, whereas the prevalence of MTW increased from 1964 to 1999, then decreased slightly from 1999 to 2004 (Fig. 1).

Eczema or hay fever in the child was reported in 43.2% ($n = 1190$), parental allergy in 54.7% ($n = 1758$), and exposure to tobacco smoke at home in 42.7% ($n = 1363$) of all responders.

Risk factors for non-severe and severe WB and MTW

Age had no influence on any type of wheeze (Table 1). Sex had no influence on severe wheeze. However among children with non-severe wheeze, being a boy increased the risk of having WB, but not MTW. The presence of eczema or hay fever in the children was associated with all wheeze types. However in both the non-severe and severe groups, this association was much stronger in children with MTW. In the non-severe group, the 95% confidence intervals (CI) were narrower compared to severe group. The magnitude of the association was larger for severe WB when compared to non-severe WB,

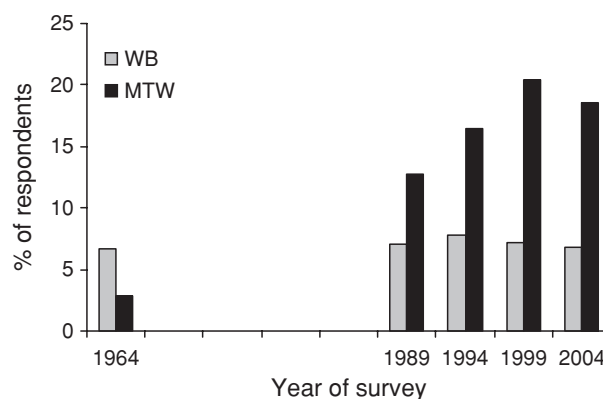


Fig. 1. Trends in wheezy bronchitis (WB) and multi-trigger wheeze (MTW) in Aberdeen schoolchildren aged 9–12 yr, 1964–2004. Gray bars represent WB, black bars represent MTW.

Table 1. Risk factors for non-severe and severe wheezy bronchitis (WB) and multi-trigger wheeze (MTW) vs. no wheeze in the past three years

Variable	Total N	Non-severe WB			Non-severe MTW			Severe WB			Severe MTW		
		n (%)	OR†	95% CI	p-value	n (%)	OR†	95% CI	p-value	n (%)	OR†	95% CI	p-value
Age (years)	3215	200 (NA‡)	0.91	0.82–1.02	0.116	308 (NA‡)	1.03	0.99–1.06	0.136	41 (NA‡)	0.98	0.80–1.21	0.854
Sex (boys)	3218	200 (55.0)	1.44	1.03–2.02	0.033	309 (50.8)	1.02	0.77–1.36	0.879	41 (43.9)	0.73	0.35–1.53	0.408
Child eczema or/and hay fever	2753	160 (51.9)	1.84	1.31–2.60	<0.001	226 (76.5)	5.46	3.70–7.20	<0.001	31 (67.7)	3.28	1.49–7.23	0.003
Parental allergy	3216	199 (57.8)	1.28	0.89–1.81	0.174	308 (69.2)	1.92	1.38–2.68	<0.001	41 (70.7)	1.75	0.78–3.94	0.177
Deprived	3147	194 (58.8)	1.38	0.96–1.97	0.083	306 (52.9)	1.10	0.81–1.50	0.528	40 (65.0)	1.81	0.81–4.03	0.150
Exposed to tobacco smoke	3194	197 (54.3)	1.80	1.26–2.58	0.001	307 (48.2)	1.53	1.12–2.08	0.008	40 (55.0)	1.68	0.77–3.67	0.191

*Number of cases and%of those with the risk factor.

†Adjusted for sex, age, eczema/hay fever in the child, deprivation, ETS, and parental atopy.

‡Continuous variable available in 99.7% of all responses.

with little difference between severe and non-severe MTW.

When children were separated into those with eczema only, hay fever only, and both eczema and hay fever, increasing strength of association for hay fever alone and both conditions in combination was observed in non-severe MTW (ORs 4.20, 5.16 and 10.10 $p < 0.001$, for eczema only, hay fever only and both conditions respectively), severe MTW (ORs 4.47, 6.85 and 10.26 $p < 0.001$) and severe WB (ORs 2.58 $p = 0.045$, 3.37 $p = 0.048$ and 6.95 $p < 0.001$), but not in non-severe WB (ORs 1.80 $p = 0.004$, 2.00 $p = 0.005$ and 1.64 $p = 0.171$ respectively).

The presence of any allergic diseases in either parent was strongly and equally associated with both non-severe and severe MTW, but not with WB. When parental atopy was examined separately in mothers and fathers, no difference in magnitude of association was found between allergic diseases in mothers and fathers alone and either non-severe (OR 1.97, $p < 0.001$ and OR 1.79, $p = 0.009$ respectively) or severe MTW (OR 1.86, $p = 0.003$ and OR 1.88, $p = 0.010$ respectively).

Socio-economic deprivation had no influence on non-severe wheeze. Among severe wheezers deprivation was associated with both WB and MTW, but statistical significance (hereafter the term 'significance' applies to a statistical probability < 0.05) was observed for MTW only. Exposure to tobacco smoke had a strong effect of a similar magnitude on both conditions regardless of the severity, but the association was not significant for the severe WB group.

Discussion

Fewer children with WB had severe disease than those with MTW, and consequently the apparent differences in associations between WB and MTW could be interpreted as reflecting different associations with, and contributors to, mild vs. severe disease. However, when severity was accounted for, male sex was found to be associated exclusively with mild WB (Table 1). Although eczema or/and hay fever in the child increased risk for all wheeze types, in both non-severe and severe groups, the association was stronger with MTW. Within each wheeze type, the association was stronger for severe symptoms compared to non-severe, which has been also reported by others (20). However, in the MTW group severity was less influenced by the presence of allergic diseases in the child. In the non-severe wheeze group, the presence of any allergic diseases in either

parent was strongly associated with MTW, but not with WB. In the severe wheeze group, the influence of parental allergy on MTW remained the same. The small number of children with severe WB is likely to be responsible for a lack of significance in the positive association with parental allergy (Table 1). For either wheeze type the study did not confirm previously published findings that the association with maternal allergic diseases was stronger than with paternal (21, 22). Socio-economic deprivation was associated only with disease severity and was significant for MTW only. Again, the small number of subjects could explain the failure in the severe WB group to reach significance for association with socio-economic deprivation and exposure to tobacco smoke. When maternal smoking was assessed separately from others smoking, the pattern remained similar (data are not shown).

In an attempt to overcome the problem of having few children in the severe WB group, we ran the same analysis in the merged database of 9507 children in primary years 5–7 (approx. aged 9–12 yr) from this survey, the 1999 survey and from the 1994 survey, which were collected using similar methodology, but available for this age group only (17). Disease severity was defined on the basis of the only question on severity common for all three studies as greater than one wheezing episode every three months in the past three years. Socio-economic deprivation was assessed using the Carstairs deprivation index based on the 1991 census for the 1994 data and based on the 2001 Census for the 1999 and 2004 data (23). Although the total number of children increased considerably after the databases had been merged, the percentages of children in each wheeze category remained similar and the percentage of children in severe WB group appeared slightly decreased due to the difference in the severe wheeze definitions used in the analysis (0.5% as opposed to 1.3% in 2004). The analysis of the combined database confirmed that no associations existed between age and any wheeze type, which was expected as the combined data included children within a narrower age spectrum. It was also confirmed that within both non-severe and severe groups, MTW was more strongly associated with allergic diseases in the child and parents than WB, and exposure to tobacco smoke influenced all categories of wheeze. In contrast to the 2004 data analysis, the combined database did not demonstrate any association between deprivation and severe wheeze.

One limitation of the study is that the definition of WB is based on 'wheeze only with a cold'.

This could exclude other respiratory infections, such as chest infection or otitis media and weaken the observed associations. Although the low response rate (57.3%) raises the possibility that allergic parents or parents of asthmatic children might have been more likely to complete and return the questionnaire, it is unlikely that this would have influenced responses from families with children with the two different types of wheezing, namely episodes associated only with respiratory infections (WB) and episodes associated with this and other provoking factors (MTW). The maintenance of the stable prevalence of WB in all five surveys from 1964 to 2004 and the similar, if slightly lower, prevalence of MTW from the previous 1999 survey also argue against any substantial reporting bias, although this cannot be excluded. The lower response rates, compared with the greater than 85% responses in previous surveys in the same schools was most likely a consequence of the conditions imposed by our local ethics committee and education authority concerning anonymity and data protection.

Previous studies lend support to the presence of WB as a major subtype of wheezing illness in school age children that can be identified at a population level (4, 24, 25). The present study found that wheeze predominantly triggered by infection is generally mild and less likely to be accompanied by eczema and hay fever in the child and parents, however, some observed differences reflect differences in disease severity. Over the past 40 years, the prevalence of WB has remained stable, whereas the prevalence of MTW and other allergic disorders has increased, suggesting that the environmental factors that have led to the increase in allergy and MTW have not affected WB. It is therefore important that future studies of wheezing disorders in schoolchildren should distinguish WB from other subtypes of wheeze.

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Conflict of interest notification

NTM, GMcN, and GR have nothing to declare; PJH has been paid by Merck Sharp and Dohme in 2003 and 2004 for chairing an advisory board, and by Boots Medical in 2005 for consultancy.

References

1. DAWSON B, ILLSLEY R, HOROBIN G, MITCHELL R. A survey of childhood asthma in Aberdeen. *Lancet* 1969; 1: 827–30.
2. HORN ME, BRAIN EA, GREGG I, INGLIS JM, YEALLAND SJ, TAYLOR P. Respiratory viral infection and wheezy bronchitis in childhood. *Thorax* 1979; 34: 23–8.
3. TAUSSIG LM, SMITH SM, BLUMENFELD R. Chronic bronchitis in childhood: what is it? *Pediatrics* 1981; 67: 1–5.
4. WILLIAMS H, MCNICOL KN. Prevalence, natural history, and relationship of wheezy bronchitis and asthma in children. An epidemiological study. *BMJ* 1969; 4: 321–5.
5. SPEIGHT AN, LEE DA, HEY EN. Underdiagnosis and undertreatment of asthma in childhood. *Br Med J (Clin Res Ed)* 1983; 286: 1253–6.
6. WILSON NM. Wheezy bronchitis revisited. *Arch Dis Child* 1989; 64: 1194–9.
7. SILVERMAN M. Out of the mouths of babes and sucklings: lessons from early childhood asthma. *Thorax* 1993; 48: 1200–4.
8. RYLANDER E, ERIKSSON M, PERSHAGEN G, NORDVALL L, EHRLST A, ZIEGLER T. Wheezing bronchitis in children. Incidence, viral infections, and other risk factors in a defined population. *Pediatric Allergy Immunol* 1996; 7: 6–11.
9. NYSTAD W, STENSRUD T, RIJCKEN B, HAGEN J, MAGNUS P, CARLSEN KH. Wheezing in school children is not always asthma. *Pediatric Allergy Immunol* 1999; 10: 58–65.
10. GODDEN DJ, ROSS S, ABDALLA M, et al. Outcome of wheeze in childhood. Symptoms and pulmonary function 25 years later. *Am J Respir Crit Care Med* 1994; 149: 106–12.
11. OSWALD H, PHELAN PD, LANIGAN A, et al. Childhood asthma and lung function in mid-adult life. *Pediatr Pulmonol* 1997; 23: 14–20.
12. ROSS S, GODDEN DJ, ABDALLA M, et al. Outcome of wheeze in childhood: the influence of atopy. *Eur Respir J* 1995; 8: 2081–7.
13. WOLFE R, CARLIN JB, OSWALD H, OLINSKY A, PHELAN PD, ROBERTSON CF. Association between allergy and asthma from childhood to middle adulthood in an Australian cohort study. *Am J Respir Crit Care Med* 2000; 162: 2177–81.
14. EDWARDS CA, OSMAN LM, GODDEN DJ, DOUGLAS JG. Wheezy bronchitis in childhood: a distinct clinical entity with lifelong significance? *Chest* 2003; 124: 18–24.
15. STEVENSON EC, TURNER G, HEANEY LG, et al. Bronchoalveolar lavage findings suggest two different forms of childhood asthma. *Clin Exp Allergy* 1997; 27: 1027–35.
16. DOULL IJ, LAMPE FC, SMITH S, SCHREIBER J, FREEZER NJ, HOLGATE ST. Effect of inhaled corticosteroids on episodes of wheezing associated with viral infection in school age children: randomised double blind placebo controlled trial. *BMJ* 1997; 315: 858–62.
17. DEVENNY A, WASSALL H, NINAN T, OMRAN M, KHAN SD, RUSSELL G. Respiratory symptoms and atopy in children in Aberdeen: questionnaire studies of a defined school population repeated over 35 years. *BMJ* 2004; 329: 489–90.
18. ASHER MI, KEIL U, ANDERSON HR, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J* 1995; 8: 483–91.
19. Scottish Executive. Statistics. Scottish Index of Multiple Deprivation. Available at <<http://www.scotland.gov.uk/topics/statistics/SIMD/overview/>>. Last update: 21/03/2007. Accessed on 30/5/2004.
20. SOLE D, CAMELO-NUNES IC, WANDALSEN GF, MELO KC, NASPITZ CK. Is rhinitis alone or associated with atopic eczema a risk factor for severe asthma in children? *Pediatr Allergy Immunol* 2005; 16: 121–5.
21. SARAFINO EP. Connections among parent and child atopic illnesses. *Pediatr Allergy Immunol* 2000; 11: 80–6.
22. WARNER JA, WARNER JO. Early life events in allergic sensitisation. *Br Med Bull* 2000; 56: 883–93.
23. CARSTAIRS V, MORRIS R. Deprivation and Health in Scotland. Aberdeen: Aberdeen University Press, 1991.
24. WASSALL HJ, DEVENNY AM, KHAN SD, NINAN TK, RUSSELL G. A comparison of virus-associated and multi-trigger wheeze in school children. *J Asthma* 2005; 42: 737–44.
25. KAPLAN BA, MASCIE-TAYLOR CG. Asthma and wheezy bronchitis in a British national sample. *J Asthma* 1987; 24: 289–96.