

Behavior Problems Antecede the Development of Wheeze in Childhood

A Birth Cohort Study

Rachel Calam, Lynsey Gregg, Angela Simpson, Bridget Simpson, Ashley Woodcock, and Adnan Custovic

Academic Division of Clinical Psychology, Education and Research Centre, and Academic Division of Medicine and Surgery South, North West Lung Centre, University of Manchester, Wythenshawe Hospital, Manchester, United Kingdom

Rationale: It is not clear to what extent behavior problems observed in children with asthma antecede asthma development, or are a consequence of the disease. **Objectives:** We investigated psychologic factors at age 3 years and subsequent development of wheeze by age 5 in an unselected birth cohort study. Children were recruited prenatally, followed prospectively, and reviewed at age 3 and 5 years. The rate of significant behavior problems at age 3 (above the clinically relevant cut-off on the Eyberg Child Behavior Inventory) was compared between children who had never wheezed ($n = 397$) and those developing late-onset wheezing (after age 3 years; $n = 39$). Late-onset wheezers were more likely to be above cut-offs for behavior problems at 3 years (before wheeze onset), compared with children who never wheezed, on Intensity (23.1% vs. 6.0%, $p < 0.001$) and Problem scores (10.8% vs. 1.3%, $p < 0.001$). Families of late-onset wheezers had poorer scores on family functioning variables, but we found no evidence of increased anxiety or depression scores in parents. In the multivariate analysis, significant and independent associates of late-onset wheeze were as follows: maternal asthma (odds ratio [OR] 5.4, 95% confidence intervals [CI] 2.1–13.8, $p < 0.001$), maternal smoking when child was 3 years (OR 3.3, CI 1.2–8.7, $p = 0.02$), expressiveness (OR 0.71, CI 0.55–0.9, $p = 0.005$), and significant behavior problems at age 3 years (OR 3.5, CI 1.2–9.9, $p = 0.02$). **Conclusions:** Behavior problems in early life are associated with increased risk of subsequent development of wheeze.

Keywords: asthma; child; child behavior; family

There is now a substantial body of evidence indicating that children with asthma have higher levels of behavior problems compared with children without asthma (1). However, it is unclear to what extent behavior problems antecede asthma development or are a consequence of the disease. To date, the few studies examining prospectively the contribution of psychologic factors have been performed exclusively in children at high risk for the development of asthma (2–6). These studies have shown that psychosocial factors may have some predictive value in identifying children at risk for the development of symptoms. A large-scale prospective study of children with atopic dermatitis showed ratings of problem behavior predicted subsequent development of asthma symptoms (4).

In a whole population-based birth cohort study that included

children at low risk for the development of asthma (the National Asthma Campaign Manchester Asthma and Allergy Study [NACMAAS]), we recently have shown that at age 3 years the occurrence of recurrent wheeze was significantly positively correlated with elevated behavior problems ratings (7). However, we were unable to provide any evidence for the direction of causality in relationships between behavior ratings and development of wheeze. Further follow-up of the children to age 5 years enabled us to test the hypothesis that behavior problems and psychosocial factors measured at age 3 antecede the development of respiratory symptoms. Some of the results of this study were reported in the form of an abstract (8).

METHODS

The NACMAAS is an unselected, population-based birth cohort study (9–12). Ethical approval for the study was granted by the local research ethics committee. Informed consent was obtained from all parents.

Study Population

A detailed description of methods is presented in the online supplement. Participants were recruited prenatally (10), and attended reviews at age 3 and 5 years (± 4 weeks). A validated respiratory questionnaire (13) was interviewer-administered to collect the information on parentally reported symptoms, physician-diagnosed illnesses, and treatments received (10). Based on parentally reported history of wheeze at two follow-up visits, children were defined as follows (14):

No wheezing: no wheeze during the first 3 years, no wheezing by age 5

Transient early wheezing: wheezing during the first 3 years, no wheezing in the previous year at age 5

Late-onset wheezing: no wheeze during the first 3 years, wheezing in the previous year at age 5

Persistent wheezing: wheezing during the first 3 years, wheezing in the previous year at age 5

Allergic sensitization was determined by skin-prick testing (mite, cat, dog, grasses, milk, egg; sensitization defined as a wheal 3 mm or larger than the negative control).

Psychosocial Assessment

When children were 3 years old, parents completed questionnaires on child behavior, family functioning, and parental mental health (15–19). The administration of questionnaires is described in detail in the online supplement. The following four questionnaires were distributed 2 weeks before the clinical follow-up, with written information for parents asking them to return the questionnaires in a sealed envelope at the clinical follow-up appointment:

The Eyberg Child Behavior Inventory (ECBI; measure of child problem behavior) (15) is made up of a list of 36 common behavioral problems. Parents respond yes or no to each item to record whether each of these is currently a problem with their child (Problem) and rate how often the specific behavior currently occurs (Intensity; 1–7, “never” to “always,” respectively). Scores are totaled for each scale, yielding separate Problem and Intensity scores. Reliability and validity was confirmed in the pediatric population (16). Clinically relevant cut-offs of a score of 131 or more for Intensity and 15 or more for Problem

(Received in original form June 22, 2004; accepted in final form November 11, 2004)

Supported by Asthma UK grant 01/012 and the Moulton Charitable Trust.

Correspondence and requests for reprints should be addressed to Rachel Calam, Ph.D., Academic Division of Clinical Psychology, 2nd Floor, Education and Research Centre, Wythenshawe Hospital, Manchester M23 9LT, UK. E-mail: rachel.calam@man.ac.uk

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 171, pp 323–327, 2005

Originally Published in Press as DOI: 10.1164/rccm.200406-7910C on November 19, 2004
Internet address: www.atsjournals.org

(17) may indicate significant psychopathology requiring intervention and parental concerns about the child's behavior.

The Family Relationships Index (FRI; measure describing the family) (18) is derived from the Family Environment Scale and measures expressiveness, cohesion, and conflict.

The Hospital Anxiety and Depression Scale (HAD; measure of parental psychologic adjustment) (19) is a 10-item questionnaire often used to screen anxiety and depression.

The General Health Questionnaire (GHQ) (20, 21) is widely used to identify psychiatric disorder in community settings and indicates level of disturbance in the parent.

Statistical Analysis

Data were analyzed using SPSS version 11.0 (SPSS, Chicago, IL). We limited comparisons to never wheezers and late-onset wheezers. A χ^2 test was used to investigate the differences between children above and below the cut-off on the ECBI. Appropriate univariate tests for parametric (analysis of variance, t test) and nonparametric data (Kruskal-Wallis, Mann-Whitney U test) were used to assess relationships between wheeze and psychosocial variables. Other risk factors of late-onset wheeze were evaluated using logistic regression analysis. Variables found to be associated with late-onset wheeze at a significance level of $p \leq 0.1$ in the univariate analyses were included in multivariate regression analysis.

RESULTS

Figure 1 shows the study profile. Of the 963 questionnaires distributed, 771 (80.1%) were returned at the 3-year follow-up visit. Parents who returned the psychosocial questionnaires were more likely to be employed than those who did not ($p = 0.02$). There were no differences in terms of family history, parental smoking, maternal age, gestational age, birth weight, history of wheeze, and allergic sensitization between children of parents who re-

turned the psychosocial questionnaires compared with those who did not (data available on request). The parents of 37 children completed the ECBI Intensity but not the ECBI Problem scale. A total of 721 children (392 boys) attended the follow-up visit at age 5 years (93.5% follow-up rate). Of those, 397 never wheezed, 163 had transient early wheeze, 39 developed late-onset wheezing and 84 had persistent wheezing. A further 38 children could not fit into a wheeze phenotype classification (e.g., no reported wheeze, but receiving asthma medication at age 3 or 5 years).

Demographic Data

Socioeconomic status (SES) was derived using the National Statistics Socio-Economic Classification (data missing in five children). For the purpose of analysis, groups were reduced to four SES categories: managerial/professional, intermediate, routine/manual, and not working. We found significant differences between SES categories in cohesion, with nonsignificant trends for expressiveness and ECBI intensity (Table 1). There were no significant differences in SES for sex and family size.

Behavior Ratings and Wheeze

Table 2 shows the number of children above and below the clinically relevant cut-offs for ECBI Intensity and Problem scores for each of the four phenotypes of wheeze. To test the hypothesis that behavior problems precede the development of wheeze, we compared children with late-onset wheezing to those who had never wheezed, excluding transient and persistent wheezers from the analysis. We used both actual scores and clinical cut-offs for ECBI Intensity and Problem scales. There were no significant differences between children who had never wheezed and late-onset wheezers in actual scores on the ECBI Intensity (mean, 95% confidence intervals [CI] 97.4, 95.3–99.5 vs. 102.5, 92.6–112.1, respectively; $p = 0.3$) or Problem scales (median, interquartile range: 1, 0–5 vs. 2, 0–7.5, respectively; $p = 0.3$). However, late-onset wheezers were significantly more likely to have Intensity and Problem scores on the ECBI above clinically relevant cut-offs at age 3 years (both $p < 0.001$; Table 2).

To examine this finding further, we compared individual items on the ECBI between children who had never wheezed and late-onset wheezers (see Table E1 in the online supplement). Of the eight items for which a significantly higher proportion of late wheezers were reported as showing difficulties, six related to problems of inattention/concentration or overactivity. Because of the small numbers and the problem of assessing results of multiple statistical testing (36 ECBI items), these findings should be interpreted with caution.

Family Psychosocial Factors and Wheeze

We compared parental and family psychosocial variables (FRI, HAD, and GHQ) between never wheezers and children with late-onset wheezing (Table 3).

Families of children with late-onset wheeze had significantly lower scores for FRI expressiveness, and we observed a trend that failed to reach statistical significance on the FRI Cohesion and Conflict scales. However, we found no differences in parental anxiety or depression, analyzed by either actual scores or whether they were above or below the clinically relevant cut-off of 11. There was a significant correlation between all but one of the psychosocial measures (Table E2).

Other Associates of Late-Onset Wheeze

Logistic regression analysis was used to identify factors associated with late-onset wheeze, using never wheezers as a reference category. The results of the univariate analysis are presented in

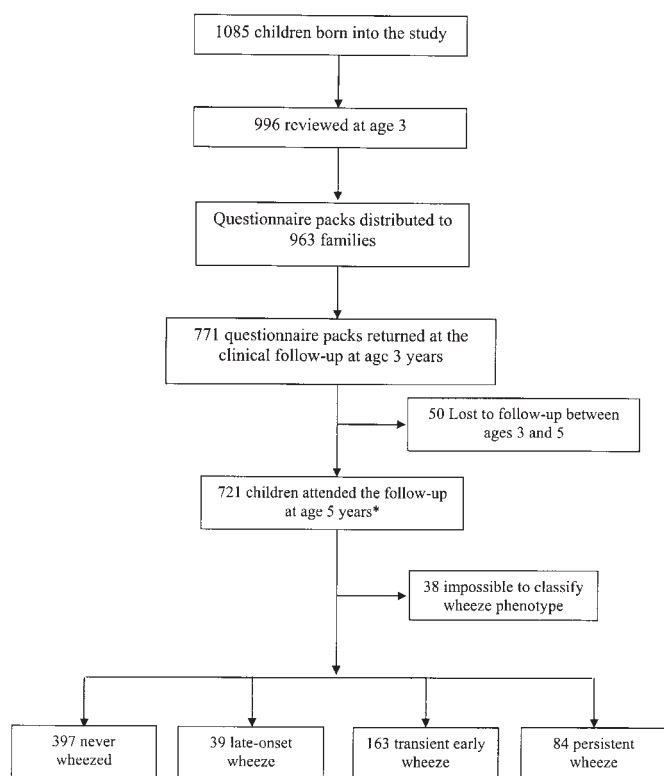


Figure 1. Schematic representation of study profile. *Thirty-seven respondents did not complete the ECBI Problem scale (23 never wheezers, 2 late-onset wheezers).

TABLE 1. SCORES ON PSYCHOSOCIAL VARIABLES AND SOCIOECONOMIC STATUS

Variable	Managerial (<i>n</i> = 464)	Intermediate (<i>n</i> = 165)	Routine (<i>n</i> = 94)	Not Working (<i>n</i> = 26)	<i>p</i> Value
ECBI Intensity, mean (SD)	98.3 (23.2)	98.4 (25.4)	99.9 (26.7)	111.4 (29.0)	0.06
ECBI Problem, median (interquartile range)	3.0 (0–5)	4.0 (0–6)	3.0 (0–3)	4.0 (0–6.25)	0.38
Cohesion, median (interquartile range)	9 (8–9)	9 (8–9)	9 (7–9)	8 (7–9)	< 0.001
Expressiveness, mean (SD)	6.9 (1.5)	6.6 (1.6)	6.4 (1.6)	6.4 (1.8)	0.06
Conflict, mean (SD)	1.9 (1.8)	1.9 (1.7)	1.8 (1.9)	2.7 (2.5)	0.22
Anxiety, mean (SD)	6.5 (3.6)	6.6 (3.5)	7.3 (3.9)	7.6 (3.9)	0.13
Depression, median (interquartile range)	3.0 (1–5)	3.0 (1–5)	3.0 (2–6)	3.5 (2.25–6)	0.12
General health, median (interquartile range)	0 (0–2)	0 (0–2)	0.5 (0–3)	1.0 (0–5)	0.14

Table 4. In addition to scores above clinically relevant cut-offs on the ECBI Intensity and Problem scales, other significant associates of the late-onset wheeze were as follows: maternal asthma ($p < 0.001$), maternal smoking ($p = 0.006$), SES status ($p = 0.007$), FRI expressiveness ($p < .003$), cohesion ($p < 0.005$), and conflict ($p < 0.02$), whereas strong trends were observed for child's gender and sensitization status at age 3 years (Table 4).

Multivariate Analysis

Multivariate logistic regression analysis included factors significant at $p \leq 0.1$ in the univariate analyses and parental atopic status, which was found to be associated with late-onset wheeze in previous studies (although no significant association was observed in the current study; $p = 0.29$). Separate models were used for Intensity and Problem scores, because these variables were highly interrelated ($r = 0.49$, $p < 0.001$, Spearman correlation; Table E2). In the analysis using ECBI Intensity, the following risk factors remained significant and independent associates of late-onset wheeze: maternal asthma (odds ratio [OR] 5.4, 95% CI 2.1–13.8, $p < 0.001$), maternal smoking when child was 3 years (OR 3.3, CI 1.2–8.7, $p = 0.02$), expressiveness (OR 0.71, CI 0.55–0.9, $p = 0.005$), and ECBI Intensity above the clinically relevant cut-off (OR 3.5, CI 1.2–9.9, $p = 0.02$).

The remaining variables were not significant associates of the late-onset wheeze (parental atopic status, $p = 0.94$; child atopic status, $p = 0.47$; child gender, $p = 0.29$; conflict, $p = 0.29$; cohesion, $p = 0.27$). A trend was observed for an overall effect for SES ($p = 0.07$). When we repeated the analysis using ECBI Problem scores, this trend was not found to be an independent predictor of late-onset wheeze ($p = 0.26$).

DISCUSSION

Our data suggest that behavior problems in early life may be associated with subsequent development of wheeze. Our finding that behavioral disturbance anteceded the development of wheeze and was not a secondary psychological reaction to dis-

ease is consistent with another recently published prospective study of a high-risk population (4). Although we must treat our analysis of ECBI individual items with caution, it appears that the specific problems that parents reported related particularly to attention problems and overactivity. With the exception of two items involving teasing or arguing with peers or siblings, the remaining six items corresponded exactly to a factor of Inattentive Behavior identified and confirmed in major factor analyses of the ECBI on large samples of children (17). This is a potentially important finding, because this specific constellation of inattentive, overactive behavior problems may have a physiologic component (22). To pursue this further, it would be necessary to undertake behavioral observation of children, because parental report is not a particularly sensitive index of hyperactivity. An adequate discussion of this issue goes beyond the scope of this article, but the consistency of our finding highlights the potential value of studying interactions between specific behavioral patterns, physiologic systems, and health variables.

Cross-sectional studies have suggested a link between oral medication for asthma and hyperactivity (23–25). The present article excluded children who had received asthma medication before behavior rating; behavioral problems thus anteceded both the development of wheeze and use of asthma medication. Behavioral problems may not be caused by or attributable to wheezing illness or asthma medication but may antecede the development of symptoms.

The scores for family relationship variables in our study indicated that the families of children who developed late-onset wheeze showed significantly lower expressiveness and trends toward lower levels of cohesion and higher levels of conflict. In multivariate analysis, however, cohesion and conflict were no longer significant, leaving maternal asthma, maternal smoking, ECBI Intensity above cut-off, and expressiveness associated with late-onset wheeze. It is important to note that we found no differences in parental mental health scores between children who had never wheezed and those with late-onset wheezing.

TABLE 2. NUMBER AND PROPORTION OF CHILDREN ABOVE THE CLINICALLY RELEVANT CUT-OFFS FOR EYBERG CHILD BEHAVIOR INVENTORY INTENSITY AND PROBLEM SCORES IN CHILDREN FOR FOUR PHENOTYPES OF WHEEZE

Variable	ECBI Intensity*		ECBI Problem*	
	Number above cut-off	Percentage above cut-off	Number above cut-off	Percentage above cut-off
Never wheezed	24/397	6.0	5/374	1.3
Late-onset wheeze	9/39	23.1	4/37	10.8
Transient early wheeze	26/163	16.0	9/154	5.8
Persistent wheeze	8/84	9.5	3/81	3.7

* Never wheezed vs. late-onset wheezing; $p < 0.001$.

TABLE 3. FAMILY RELATIONSHIP INDEX, HOSPITAL ANXIETY AND DEPRESSION SCALE, AND GENERAL HEALTH QUESTIONNAIRE SCORES FOR PARENTS OF CHILDREN WHO HAD NEVER WHEEZED AND THOSE WITH LATE-ONSET WHEEZE

Measure	Never Wheezed	Late-Onset Wheeze	p Value
Family Relationship Index			
Cohesion, median (interquartile range)	9.0 (8–9)	9.0 (8–9)	0.06
Expressiveness, mean (SD)	6.9 (1.5)	6.0 (1.8)	0.003
Conflict, mean (SD)	1.8 (1.8)	2.5 (2.3)	0.06
Hospital Anxiety and Depression Scale			
Anxiety, mean (SD)	6.4 (3.4)	7.0 (4.4)	0.30
Depression, median (interquartile range)	3.0 (1–5)	4.0 (1–7)	0.23
General Health Questionnaire, median (interquartile range)	0 (0–2)	1.0 (0–3.25)	0.18

In interpreting our findings, it is important to note that all the data were obtained from parental (usually maternal) report, which raises the possibility that some of the findings arise from common method variance and response tendencies in the parent. If this were primarily the case, however, it would be expected that anxiety and depression would also be elevated. One important methodologic point that has clear clinical relevance is that preliminary analyses did not show significant differences in mean scores for the ECBI between children who had never wheezed and those who developed late-onset wheeze. However, when we looked at the number of children with scores above the clinically relevant cut-off on the ECBI, which would represent parents who perceive their child's behavior to present a considerable challenge, the difference in distribution became striking. The implication of our finding is that it is the children with marked behavior problems who are at increased risk of subsequent wheeze, and that more modest elevations in perceived behavioral difficulty at age 3 are not so strongly associated with late-onset wheeze. This implication is consistent with findings of meta-analysis in this area (1).

We do not suggest that behavior problems *per se* cause wheeze or predict specific aspects of asthma onset. They are likely to show dynamic, reciprocal relationships with other causal factors, which are intertwined and contribute to the development of both behavior and wheeze. Parents who report behavior problems tend to have other psychosocial stressors; studies have identified several linked psychosocial and environmental factors that contribute to the development of asthma (26). For example, maternal smoking during pregnancy increases risk of attention deficit and hyperactivity disorder (27, 28) and behavior problems (29) and respiratory symptoms. Smoking is, in turn, related to a range of other variables (30). SES was related to late-onset

wheeze in the univariate analysis, but after adjusting for other risk factors, this association was no longer significant. However, behavior scores above clinically relevant cut-offs remained a substantial and significant predictor of late-onset wheeze in the multivariate analysis.

Other studies have shown links between stressors in early childhood and wheeze or asthma (26, 31, 32), although the processes of mediation of inflammatory responses in the presence of stressors require further elucidation (33). Caregiver stress is associated with the modification of infant immune functioning and cytokine production, and may lead to enhanced responses to allergens (34). In our study, family relationship dysfunction showed trends in the predicted direction, with reduced expressiveness at 3 years remaining a significant associate of late-onset wheeze in the multivariate model. Again, these variables are not independent; parental capacity to express difficulties and problem-solve will be associated with successful management of child behavior. Parental anxiety and depression, which might be expected to be proxy measures of stress, were not associated with late-onset wheeze. It is possible that our measure was not sufficiently sensitive. In addition, different environmental stressors may have different degrees of impact, or operate with different levels of intensity, at different stages in the development of the immune system. Further longitudinal exploration of relationships between physiologic factors and psychosocial variables would be valuable.

We are aware that even within this large-scale prospective cohort, the numbers are relatively small and our comments can therefore only be tentative. However, given the increasing prevalence of asthma, the prediction of onset of symptoms and strategies for prevention are important issues. Identifying pathways for the development of asthma across childhood has the potential

TABLE 4. FACTORS ASSOCIATED WITH LATE-ONSET WHEEZE IN THE UNIVARIATE LOGISTIC REGRESSION ANALYSIS

Variable	Odds Ratio	95% Confidence Intervals	p Value
Maternal asthma	4.17	2.03–8.58	< 0.001
Maternal smoking	2.93	1.37–6.26	0.006
Male gender	1.90	0.95–3.74	0.07
Child sensitization at age 3	2.01	0.96–4.22	0.06
Socioeconomic status			0.007
Managerial vs. intermediate	3.07	1.44–6.57	0.004
Managerial vs. routine/manual	3.81	1.52–9.52	0.004
Managerial vs. not working	1.90	0.23–15.96	0.55
ECBI Intensity score above cut-off	4.66	1.99–10.93	< 0.001
ECBI Problem score above cut-off	8.95	2.29–34.93	0.002
Expressiveness	0.74	0.61–0.91	0.003
Cohesion	0.78	0.66–0.93	0.005
Conflict	1.22	1.03–1.44	0.02

to enable crafting of tailored interventions addressing both biological and psychosocial factors. It is an empiric question whether interventions to enhance parenting from infancy, and to prevent the development of behavior problems in very young children (35), have the potential to reduce asthma prevalence and severity.

Conflict of Interest Statement: R.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; L.G. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; A.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; B.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; A.W. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; A.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

Acknowledgment: The authors thank all the parents and children who took part in the study, all members of NACMAAS study group, and Julie Morris, M.Sc., for statistical advice.

References

- McQuaid EL, Kopel SJ, Nassau JH. Behavioral adjustment in children with asthma: a meta-analysis. *J Dev Behav Pediatr* 2001;22:430–439.
- Klennert MD, Mrazek PJ, Mrazek DA. Early asthma onset: the interaction between family stressors and adaptive parenting. *Psychiatry* 1994;57:51–61.
- Klennert MD, Nelson HS, Price MR, Adinoff AD, Leung DY, Mrazek DA. Onset and persistence of childhood asthma: predictors from infancy. *Pediatrics* 2001;108:E69.
- Stevenson J. Relationship between behavior and asthma in children with atopic dermatitis. *Psychosom Med* 2003;65:971–975.
- Mrazek DA, Klennert M, Mrazek PJ, Brower A, McCormick D, Rubin B, Ikle D, Kastner W, Larsen G, Harbeck R, *et al.* Prediction of early-onset asthma in genetically at-risk children. *Pediatr Pulmonol* 1999;27:85–94.
- Mrazek DA, Klennert MD, Mrazek P, Macey T. Early asthma onset: consideration of parenting issues. *J Am Acad Child Adolesc Psychiatry* 1991;30:277–282.
- Calam R, Gregg L, Simpson B, Morris J, Woodcock A, Custovic A. Childhood asthma, behavior problems, and family functioning. *J Allergy Clin Immunol* 2003;112:499–504.
- Calam R, Gregg L, Simpson A, Simpson B, Woodcock A, Custovic A. Behavior problems precede the development of wheeze in early childhood [abstract]. *Am J Respir Crit Care Med* 2004;169:A260.
- Custovic A, Simpson BM, Simpson A, Kissen P, Woodcock A. Effect of environmental manipulation in pregnancy and early life on respiratory symptoms and atopy during first year of life: a randomised trial. *Lancet* 2001;358:188–193.
- Simpson BM, Custovic A, Simpson A, Hallam CL, Walsh D, II, Marolia H, Campbell J, Woodcock A. NAC Manchester Asthma and Allergy Study (NACMAAS): risk factors for asthma and allergic disorders in adults. *Clin Exp Allergy* 2001;31:391–399.
- Custovic A, Simpson BM, Simpson A, Hallam C, Craven M, Brutsche M, Woodcock A. Manchester Asthma and Allergy Study: low-allergen environment can be achieved and maintained during pregnancy and in early life. *J Allergy Clin Immunol* 2000;105:252–258.
- Lowe L, Murray CS, Custovic A, Simpson BM, Kissen PM, Woodcock A. Specific airway resistance in 3-year-old children: a prospective cohort study. *Lancet* 2002;359:1904–1908.
- Pearce N, Weiland S, Keil U, Longridge P, Anderson HR, Strachan D, Bauman A, Young L, Gluyas P, Ruffin D, *et al.* Self-reported prevalence of asthma symptoms in children in Australia, England, Germany and New Zealand: an international comparison using the ISAAC protocol. *Eur Respir J* 1993;6:1455–1461.
- Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995;332:133–138.
- Robinson EA, Eyberg SM, Ross AW. The standardization of an inventory of child conduct problem behaviors. *J Child Clin Psychol* 1980;9:22–29.
- Burns GL, Patterson DR. Normative data on the Eyberg Child Behavior Inventory and Sutter-Eyberg Student Behavior Inventory: parent and teacher rating scales of disruptive behavior problems in children and adolescents. *Child Fam Behav Ther* 2001;23:15–28.
- Eyberg SM, Pincus MA. Eyberg Child Behavior Inventory and Sutter-Eyberg Student Behavior Inventory-Revised: professional manual. Lutz, FL: Psychological Assessment Resources; 1999.
- Moos RH, Moos BS. Family Environment Scale manual. Palo Alto, CA: Consulting Psychologists Press; 1986.
- Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67:361–370.
- Goldberg D. The manual of the General Health Questionnaire. Windsor, UK: NFER-Nelson; 1978.
- Goldberg DP, Gater R, Sartorius N, Ustun TB, Piccinelli M, Gureje O, Rulter C. The validity of two versions of the GHQ in the WHO study of mental illness in general health care. *Psychol Med* 1997;27:191–197.
- Bauer AM, Quas JA, Boyce WT. Associations between physiological reactivity and children's behavior: advantages of a multisystem approach. *J Dev Behav Pediatr* 2002;23:102–113.
- Hadjikhouri I, Loader P, Bracken M, Milner AD. Bronchodilator therapy and hyperactivity in preschool children. *Arch Dis Child* 2002;86:202–203.
- Kayani S, Shannon DC. Adverse behavioral effects of treatment for acute exacerbation of asthma in children: a comparison of two doses of oral steroids. *Chest* 2002;122:624–628.
- Rachelefsky GS, Wo J, Adelson J, Mickey MR, Spector SL, Katz RM, Siegel SC, Rohr AS. Behavior abnormalities and poor school performance due to oral theophylline use. *Pediatrics* 1986;78:1133–1138.
- Klennert MD, Price MR, Liu AH, Robinson JL. Unraveling the ecology of risks for early childhood asthma among ethnically diverse families in the southwest. *Am J Public Health* 2002;92:792–798.
- Hofhuis W, Merkus PJ, de Jongste JC. Negative effects of passive smoking on the (unborn) child [in Dutch]. *Ned Tijdschr Geneesk* 2002;146:356–359.
- Linnert KM, Dalsgaard S, Obel C, Wishborg K, Henriksen TB, Rodriguez A, Kotimaa A, Moilanen I, Thomsen PH, Olsen J, *et al.* Maternal lifestyle factors in pregnancy risk of attention deficit hyperactivity disorder and associated behaviors: review of the current evidence. *Am J Psychiatry* 2003;160:1028–1040.
- Wakschlag LS, Hans SL. Maternal smoking during pregnancy and conduct problems in high-risk youth: a developmental framework. *Dev Psychopathol* 2002;14:351–369.
- Lu Y, Tong S, Oldenburg B. Determinants of smoking and cessation during and after pregnancy. *Health Promot Int* 2001;16:355–365.
- Wright RJ, Rodriguez M, Cohen S. Review of psychosocial stress and asthma: an integrated biopsychosocial approach. *Thorax* 1998;53:1066–1074.
- Shalowitz MU, Berry CA, Quinn KA, Wolf RL. The relationship of life stressors and maternal depression to pediatric asthma morbidity in a subspecialty practice. *Ambul Pediatr* 2001;1:185–193.
- Segerstrom SC, Miller GE. Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry. *Psychol Bull* 2004;130:601–630.
- Wright RJ, Finn P, Contreras JP, Cohen S, Wright RO, Staudenmayer J, Wand M, Perkins D, Weiss ST, Gold DR. Chronic caregiver stress and IgE expression, allergen-induced proliferation, and cytokine profiles in a birth cohort predisposed to atopy. *J Allergy Clin Immunol* 2004;113:1051–1057.
- Sanders MR. Parenting interventions and the prevention of serious mental health problems in children. *Med J Aust* 2002;177:S87–S92.

**BEHAVIOR PROBLEMS ANTECEDE THE DEVELOPMENT OF
WHEEZE IN CHILDHOOD: A BIRTH COHORT STUDY**

Rachel Calam PhD, Lynsey Gregg MRes, Angela Simpson MD, Bridget Simpson RN,
Ashley Woodcock MD FRCP, Adnan Custovic MD PhD

ONLINE SUPPLEMENT

METHODS

The Manchester Asthma and Allergy Study (MAAS) is a prospective study of the development of asthma and other atopic disorders in a cohort of infants. Families were recruited from the maternity catchment areas of Wythenshawe and Stepping Hill Hospitals, an area comprising 50 square miles of South Manchester and Cheshire, UK, a stable mixed urban-rural population. All aspects of the study were approved by the Local Research Ethics Committee. Informed consent was obtained from all parents, and children gave their assent.

Screening & Recruitment

All pregnant women were screened for eligibility at 'Booking' antenatal visits (8th-10th week of pregnancy). The study was explained to parents, and informed consent for initial questionnaires and skin prick testing was obtained. Both parents completed a questionnaire about their and their partner's history of asthma and allergic diseases and smoking habits.

If the pregnant woman's partner was not present at the antenatal clinic visit, an invitation was sent for him to attend an open-access evening clinic for skin prick testing and completion of a questionnaire. Once both parents had completed questionnaires and skin testing, a full explanation of the proposed future follow-up for the child was given. Of the 1499 couples who met the inclusion criteria (≤ 10 weeks of pregnancy, maternal age ≥ 18 years, questionnaire and skin test data available for both parents), 288 declined to take part in the study. Of 1211 couples who initially agreed to take part, 1085 had a successful full-term pregnancy (>36 weeks gestation; child did not need intensive care) and gave consent to a further follow-up.

Allocation to study groups

Children were assigned to risk groups according to parental sensitisation status. Nested within the cohort is a primary prevention study in which a subgroup of children at high risk (both parents atopic) without pets in home was randomised to either stringent environmental control (allergen impermeable covers for the parental and infant bed, hot washing of bedding weekly, HEPA vacuum cleaner, hard floor for the nursery) or a normal regime. We have found no differences in the psychological assessments between children in the environmental control group and non-randomized high-risk children. In addition, there was no difference between these groups in the relationship between psychological variables and clinical outcomes (respiratory symptoms, allergic sensitization) at age 3 years. Therefore, children in the environmental control group were not excluded from this analyses at age 5 years.

Psychological assessment

Psychological assessment was carried out at age 3 years. Study participants were visited at home 2 weeks prior to the clinical follow-up at age 3 and were given standardized questionnaire measures of child behavior problems, family functioning and parental mental health. The research assistant provided parents with written information asking them to complete the four questionnaires at home in their own time, and return them in a sealed envelope at the clinical follow-up appointment. Questionnaires were selected for brevity and acceptability for large-scale screen, and included the following:

Eyberg Child Behavior Inventory (ECBI)^{E1,E 2}

This inventory lists 36 common behavioral problems, for example, “Refuses to eat food presented”, “Has temper tantrums”, “Constantly seeks attention”, “Is easily distracted”.

Parents respond yes or no, recording whether each of these is currently a problem with their child (Problem score), and how often the behavior currently occurs, (1- “never” to 7- “always”; Intensity score); scores are totaled. The ECBI was originally standardised in 1980 on a sample of children attending pediatric outpatients in an urban setting in the northwest US^{E3}. Further standardisation data were reported from two additional samples. In 1999, the ECBI was re-standardised on parents of 798 children from 6 outpatient pediatric settings in the southeast US^{E1}. All age groups from 2 to 16 were equally and adequately represented. Cut-off scores for Intensity and Problem scores were established on the 1999 normative sample, based on frequency distributions. Discriminative validity of the ECBI has been described in studies where it has distinguished between conduct disorder referred and non-referred children. Convergent validity has been described with the Child Behaviour Checklist. The ECBI Intensity and Problem scales both show internal consistency of 0.98, test-retest of 0.86, Intensity and 0.88, Problem over 3 weeks, and 0.75 for both scales over 10 months.

Family Relationships Index (FRI) ^{E4}

This 27 item measure, derived from the Family Environment Scale measures: (1) expressiveness, how much family members express feelings directly; (2) cohesion, degree of help, commitment and support family members provide, and (3) conflict, including open conflict, anger and aggression within the family.

Hospital Anxiety and Depression Scale (HAD) ^{E5}

The HAD is a 10 item questionnaire frequently used in screening to provide an indication of anxiety and depression. Its subscales are considered to be a valid means of estimating severity of emotional disorder.

General Health Questionnaire (GHQ)^{E6 7}

This 12-item questionnaire is widely used to identify psychiatric disorder in community settings. It has been evaluated on large samples internationally, and shows good detection of psychological disorder. Gender, age and educational level do not appear to affect responding. The GHQ was used to indicate level of disturbance in the parent.

Follow-up

The children have been followed prospectively, and attended review clinics at age 3 and 5 years (± 4 weeks). Assessment at age 5 years was completed in April 2003. The study population for this analysis comprised 683 children whose parents returned psychological questionnaires at age 3 years, have attended the follow-ups at both age 3 or age 5 years and could be allocated into one of four phenotypes of wheeze based on the questionnaire data^{E8} (see below).

Outcomes

Symptoms

A standard respiratory questionnaire (ISAAC)^{E9} was interviewer-administered at age 3 and 5 years to collect the information on symptoms, physician-diagnosed illnesses and treatments received. Of 771 children with psychological assessment at age 3 years, 50 (6.5%) were lost to follow-up between ages 3 and 5 years.

Allocation to the phenotypes of wheeze

According to parentally-reported history of wheeze at the follow-ups at age 3 and 5 years, children were assigned to the following categories using criteria proposed by Martinez et al^{E8} :

- i) No wheezing: no recorded wheeze during the first three years of life, no wheezing at age 5 years, parents reported at age 5 that the child had never wheezed (n=397)
- ii) Transient early wheeze: at least one episode of wheezing during the first three years of life, but no subsequent wheezing reported at age 5 years (n=163)
- iii) Late-onset wheeze: no recorded wheeze during the first three years of life, but reported wheezing in the previous 12 months at age 5 years (n=39)
- iv) Persistent wheeze: at least one episode of wheezing during the first three years of life, and reported wheezing in the previous 12 months at age 5 years (n=84)

A further 38 children could not fit into this classification. For example, some children were reported as never having wheezed, but were but receiving asthma medication at age 5 years.

Statistical Analysis

Data were analyzed using SPSS version 11.0. We limited comparisons to never- and late-onset wheezers. Chi-squared test was used to investigate the differences between children above and below cut-off on the ECBI. Appropriate univariate tests for parametric (analysis of variance, t-test) and non-parametric data (Kruskal-Wallis, Mann-Whitney U-test) were used to assess relationships between wheeze and psychosocial variables.

Other risk factors of late-onset wheeze were evaluated using logistic regression analysis. Variables found to be associated with late-onset wheeze at significance level $p \leq 0.1$ in the univariate analyses were included in multivariate regression analysis.

REFERENCES

- E1. Eyberg SM, Pincus MA. *Eyberg Child Behavior Inventory and Sutter-Eyberg Student Behavior Inventory-Revised: Professional Manual*. Lutz:FL: Psychological Assessment Resources Inc., 1999.
- E2. Eyberg SM, Robinson EA. Conduct problem behavior: Standardisation of a behavior rating scale with adolescents. *Journal of Child Clinical Psychology* 1983;12:347-354.
- E3. Robinson EA, Eyberg SM, Ross AW. The standardization of an inventory of child conduct problem behaviors. *J Child Clin Psychol* 1980;9:22-9.
- E4. Moos RH, Moos BS. *Family Environment Scale Manual*. Palo Alto, CA: Consulting Psychologists Press, 1986.
- E5. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67(6):361-70.
- E6. Goldberg D. *The Manual of the General Health Questionnaire*. Windsor, UK: NFER-Nelson, 1978.
- E7. Goldberg DP, Gater R, Sartorius N, Ustun TB, Piccinelli M, Gureje O, et al. The validity of two versions of the GHQ in the WHO study of mental illness in general health care. *Psychol Med* 1997;27(1):191-7.
- E8. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995;332(3):133-8.

E9. Pearce N, Weiland S, Keil U, Langridge P, Anderson HR, Strachan D, et al. Self-reported prevalence of asthma symptoms in children in Australia, England, Germany and New Zealand: an international comparison using the ISAAC protocol. *Eur Respir J* 1993;6(10):1455-61.

Online Supplement Table E1: Parental responses to individual ECBI items, children
who never wheezed vs. children with late onset wheeze

	Never Wheezed		Late-onset Wheeze		Chi
	(N = 374)		(N = 37)		Square
ECBI Item	No	%	No	%	P
1. Slow getting dressed	33	8.8	5	13.5	0.35
2. Slow at mealtimes	67	17.9	11	29.7	0.08
3. Has poor table manners	25	6.7	5	13.5	0.13
4. Refuses to eat food presented	87	23.3	13	35.1	0.10
5. Refuses to do chores	19	5.1	3	8.1	0.43
6. Slow getting ready for bed	21	5.6	2	5.4	0.97
7. Refuses to go to bed on time	55	14.7	7	18.9	0.48
8. Does not always obey	78	20.9	12	32.4	0.10
9. Refuses to obey until threatened	72	19.3	12	32.4	0.06
10. Acts defiant	73	19.5	7	18.9	0.93
11. Argues with parents	40	10.7	6	16.2	0.30
12. Gets angry when does not get own way	63	16.8	9	24.3	0.25
13. Has temper tantrums	64	17.1	7	18.9	0.78
14. Irritates adults	18	4.8	3	8.1	0.38
15. Whines	58	15.5	6	16.2	0.91
16. Cries easily	25	6.7	3	8.1	0.73
17. Yells or screams	44	11.8	8	21.6	0.08

18. Hits parents	43	11.5	3	8.1	0.55
19. Destroys toys and other objects	10	2.7	5	13.5	0.001
20. Careless with toys and other objects	18	4.8	1	2.7	0.57
21. Steals	0	0	0	0	N/A
22. Lies	5	1.3	1	2.7	0.50
23. Teases or provokes other children	11	2.9	5	13.5	0.001
24. Argues with peers	9	2.4	3	8.1	0.05
25. Argues with siblings	36	9.6	3	8.1	0.78
26. Physically fights with peers	8	2.1	2	5.4	0.21
27. Physically fights with siblings	30	8.0	3	8.1	0.97
28. Seeks attention	24	6.4	6	16.2	0.03
29. Interrupts	32	8.6	6	16.2	0.12
30. Is easily distracted	8	2.1	3	8.1	0.03
31. Has short attention span	9	2.4	3	8.1	0.05
32. Fails to finish tasks	8	2.1	3	8.1	0.03
33. Has difficulty entertaining self	11	2.9	2	5.4	0.41
34. Has difficulty concentrating	5	1.3	3	8.1	0.004
35. Is overactive or restless	8	2.1	6	16.2	<0.0001
36. Wets the bed	4	1.1	1	2.7	0.38

Items 1, 2, 14, 24, 25 modified from US to UK English

Online Supplement Table E2: Relationship between different psychosocial measures

(Spearman correlation)

	ECBI intensity	ECBI problem	Cohesion	Expressive- ness	Conflict	Anxiety	Depression
ECBI intensity							
ECBI problem	.488*						
Cohesion	-.250*	-.167*					
Expressiveness	-.126*	-.153*	.270*				
Conflict	.342*	.288*	-.337*	-.072			
Anxiety	.248*	.257*	-.246*	-.249*	.283*		
Depression	.275*	.232*	-.330*	-.261*	.230*	.563*	
General Health	.198*	.243*	-.251*	-.268*	.198*	.549*	.503*

*P<0.01