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Cough During Infancy and Subsequent Childhood Asthma

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Abstract

OBJECTIVES—Wheezing in infancy has been associated with subsequent asthma, but whether cough similarly influences asthma risk has been little studied. We sought to determine whether prolonged cough and cough without cold in the first year of life are associated with childhood asthma.

METHODS—Participants in the Infant Immune Study, a non-selected birth cohort, were surveyed 7 times in the first 9 months of life regarding presence of wheeze and cough. Cough for more than 28 days was defined as prolonged. Parents were asked at 1 year if the child ever coughed without a cold. Asthma was defined as parental report of physician diagnosis of asthma, with symptoms or medication use between 2–9 years. Logistic regression was used to assess adjusted odds for asthma associated with cough characteristics.

RESULTS—24% (97) of children experienced prolonged cough and 23% (95) cough without cold in the first 9 months, respectively. Prolonged cough was associated with increased risk of asthma relative to brief cough (OR 3.57, CI: 1.88, 6.76), with the risk being particularly high

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Eyal Oren: Dr. Oren conceptualized and designed the study, drafted and edited the manuscript, carried out analyses, and approved the final manuscript as submitted.

Janet Rothers: Dr. Rothers conceptualized the study, carried out initial analyses, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Debra A. Stern: Ms. Stern conceptualized the study, carried out analyses as well as all aspect of data management, reviewed and revised the manuscript, and approved the final manuscript as submitted.

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among children of asthmatic mothers. Cough without cold (OR 3.13, 95% CI: 1.76, 5.57) was also independently associated with risk of childhood asthma. Both relations persisted after adjustment for wheeze and total IgE at age 1.

CONCLUSIONS AND CLINICAL RELEVANCE—Prolonged cough in infancy and cough without cold are associated with childhood asthma, independent of infant wheeze. These findings suggest that characteristics of cough in infancy are early markers of asthma susceptibility, particularly among children with maternal asthma.

Keywords

Cough; childhood asthma; allergy; parental asthma; LRIs

INTRODUCTION

Viral respiratory infections, which are common in early childhood, have been associated with persistent asthma at later ages.(1, 2) Although *upper* respiratory tract infections are associated with 40–85% of acute asthma episodes in older children and adults,(3, 4) the highest risk for development of subsequent asthma is observed among children experiencing recurrent *lower* respiratory tract illnesses (LRIs).(5) Both presence and frequency of respiratory symptoms among infants and young children are thought to significantly increase risk of developing asthma.(6–8) Risk for asthma associated with LRIs is also enhanced for children who have a familial, particularly maternal, history of asthma, and for those who develop high IgE levels.(9–11)

However, most of this work has focused on wheeze. Much less is known about the characteristics of cough in the first years of life that may confer risk for subsequent childhood asthma. Cough is extremely common in children, and typically resolves within ten days, although it can last more than 4 weeks.(12) We and others have observed that cough without cold is associated with concurrent allergic rhinitis.(13–15) However, to our knowledge, cough in infancy has not been assessed in relation to development of asthma.

We asked whether prolonged cough or cough without cold in infancy were associated with asthma development during childhood, and whether any relations observed are independent of infant wheeze, infant IgE levels and maternal asthma. Results of these analyses could identify novel cough phenotypes in early life which could help clinicians determine if a child is at risk for asthma.

MATERIALS AND METHODS

Study design and population

The Infant Immune Study (IIS) is a prospective birth cohort study of immune system maturation and its relation to the development of asthma and allergic disease in childhood. Participating mothers (N = 482), not selected for asthma status, were recruited during prenatal visits at 5 sites in Tucson between 1997 and 2003, as previously described.(16)

Cough and wheeze in Infancy

Parents were interviewed regarding presence and duration of respiratory and other symptoms in their infants at seven time-points in the first 9 months of life: 2 weeks (mean age $\pm$ SD, 16.5 ± 5.3 days; $n = 404$), 1 month (35.8 ± 6.7 days; $n = 316$), 2 months (65.5 ± 6.2 days; $n = 347$), 3 months (94.3 ± 6.4 days; $n = 236$), 4 months (128.1 ± 10.2 days; $n = 381$), 6 months (192.0 ± 12.5 days; $n = 379$), and 9 months of age (284.4 ± 15.9 days; $n = 359$). Specifically, parents were asked by the study nurse if the child had experienced any cough since the previous interview (or since birth at the first interview), and if so, for how many days. The questionnaire read: "Thinking only of the past 2 weeks/month, has (NAME) had cough? How many days did he/she have cough?" Cough duration in the first 9 months was calculated as the cumulative (sequential or non-sequential) number of days of cough reported on all surveys. To minimize under-reporting of cough, a minimum of 4 completed interviews was required for inclusion in this analysis, with at least one interview occurring at 6 or 9 months. Parents were asked about presence of wheeze in the same interview. In a questionnaire completed at 12 months (1.02 year ± 0.11), and subsequently during annual questionnaires, parents were also asked whether children had ever coughed without colds in the past year.

Asthma in the Child

Parents completed questionnaires on asthma symptoms and physician diagnosis when children were 2 (2.1 ± 0.2 years; $n=362$), 3 (3.2 ± 0.3 years; $n=371$), 5 (5.1 ± 0.4 years; $n=373$), and 9 years old (9.2 ± 1.1 years; $n=353$). Asthma in the child was defined as report of physician diagnosed asthma with symptoms (asthma attacks or episodes, and/or wheezing) and/or medication use in the last 12 months on at least one questionnaire as previously published.⁽¹⁷⁾ Children were considered to have "no asthma" if physician diagnosed asthma was never reported.

Covariates

At study enrollment, maternal asthma was defined as report of ever having been diagnosed with asthma by a doctor ($n=90$). Mothers who reported never having had asthma or having had asthma but no doctor diagnosis were designated "no maternal asthma" ($n=377$). Questionnaire-assessed demographic factors were also considered in the analysis including maternal age and ethnicity, sex of the child, daycare attendance in the first year, and whether anyone in the household smoked. Total IgE was measured from blood specimens obtained at approximately 1 year (1.1 ± 0.1 years; $n=364$) using the Pharmacia AutoCAP assay (Pharmacia/Upjohn, Kalamazoo, Mich) before its discontinuation in 2006 and subsequently using Immulite 2000 (Siemens Medical Solutions, Los Angeles, Calif). Samples analyzed on both instruments ($n=25$) yielded a correlation coefficient of 0.995. Total IgE values were log transformed for all statistical analyses. Allergen-specific IgE responses included detectable responses to any of five inhalant allergens: *Alternaria* species, Bermuda grass, careless weed, olive and mulberry trees, and *Dermatophagoides farina*. IgE was categorized as detectable based on a cutoff of 0.25 IU/ml.

Statistical analysis

Duration of cough was examined as both a discrete variable and aggregated into three categories: 0–14 (brief) days, 15–28 (intermediate) days and ≥29 (prolonged) total days. Potential demographic confounders were identified by assessing relations with either cough variable and asthma, using Fisher's exact test for categorical variables and one-way ANOVA for continuous variables. All factors that were at least marginally related to either cough variable or asthma ($P<0.10$) were included in multivariable models.

Multivariate logistic regression was used to assess the relation between cough duration and asthma after adjustment for potential demographic confounders. Cough without cold was similarly assessed for relation with childhood asthma. Regression coefficients were estimated, representing the predicted change in odds of asthma per seven additional days of cough duration. In addition, models which assessed the odds of asthma in the prolonged cough group compared to the referent (0–14 day duration) group were sequentially adjusted for total IgE, maternal asthma, and wheeze in infancy to determine if relations were independent of these characteristics. A final fully adjusted model assessed the contribution of both cough characteristics to asthma. The analyses were repeated for asthma at age 5. All analyses were conducted using Stata version 12.0. This research was approved by the Institutional Review Board of the University of Arizona and informed consent was obtained for all subjects.

RESULTS

Description of Included Sample

Of the original 482 enrolled children in the IIS, 410 (85.1%) had complete data available for cough in infancy and asthma. Online Table E1 summarizes characteristics of children included and excluded from our study. The 410 children included were more likely to be non-Hispanic white, reside in non-smoking households, have older mothers and higher levels of maternal education.

Prevalence of Childhood Asthma

Prevalence of asthma between two to nine years of age was 17.8% ($n=73$). Children with a maternal history of asthma and who resided in households with smoking were more likely to have asthma. This was also true for children who wheezed in infancy, or who had higher IgE levels at age 1 (Online table E-2). Virtually all children (96%) who developed asthma also wheezed at some point by age 9.

Cough in Infancy and Factors Associated with Cough

During the first 9 months of life, 91.0% of children (373/410) experienced at least one day of cough, with the mean cumulative duration being 21.1 days (median: 14.5 days, Interquartile range: 7–28 days) and a range from zero to 190 total days (Figure 1). 23.7% (97) of subjects had prolonged cough and 23.2% ($n=95$) of children were reported to have coughed without a cold.

Cough duration was associated with household smoking, daycare use, fewer years of maternal education as well as wheeze in infancy (Table 1). However, IgE levels at 1 year did not vary across cough duration categories, and there was no significant association between presence of maternal asthma and cough duration in the first nine months. Cough without a cold was associated with wheeze and having IgE levels above the median (Table 1), but not with maternal asthma. Mean cough duration for subjects who coughed without colds was longer than that for subjects who coughed only with colds (30.1 vs 17.1 days, $P<0.001$).

Relationship between Cough Characteristics and Asthma

A significant trend was observed between cough duration in infancy and prevalence of asthma (P-non-parametric trend <0.001). Thirty-one percent of subjects with prolonged cough in infancy developed childhood asthma, vs. 12% of subjects with brief cough. For every seven additional days of cough, odds of asthma increased by 17% (OR 1.17, 95% CI: 1.09, 1.26). Similarly, 29.5% of subjects who coughed without a cold by age one developed asthma, compared to 13.4% among children who coughed only with colds ($P=0.001$). More than half (53.3%) of subjects who both coughed without a cold and who had prolonged cough ($n=16$) developed asthma. Given that wheezing can be transient, the analysis was repeated excluding subjects who had an asthma diagnosis and active symptoms only before age 5 (data not shown). The relation of either cough characteristic to asthma was unchanged. After adjusting for demographic covariates, both prolonged cough and cough without a cold remained significantly associated with increased odds of childhood asthma (Figure 2). These associations with childhood asthma were similar when analyses were limited to children who did not wheeze in infancy, with odds being 2.47 (95% CI: 1.00, 6.09) for prolonged cough or 2.40 for cough without a cold (95% CI: 1.07, 5.39).

The odds ratio for the association between wheeze in infancy and subsequent asthma was comparable to that observed among prolonged coughers in a model adjusted for the same demographic factors (OR 2.72, 95% CI: 1.58, 4.69).

Infant Wheeze and IgE, Cough Characteristics and Childhood Asthma

As noted above, infant wheeze was associated with both cough characteristics and childhood asthma (Online Table E-2). Prevalence of asthma was 40.8% ($n=20/49$) among subjects in the prolonged cough group who wheezed and 20.8% ($n=10/48$) of children in the prolonged group who did not wheeze. The unadjusted odds for asthma associated with prolonged cough (vs. brief cough) were elevated both for children with wheeze (OR 2.84, 95% CI: 1.09, 7.43), and, of borderline significance, for those without wheeze (OR 2.26, 95% CI: 0.96, 5.33). Including wheeze in the multivariate model for prolonged cough only reduced the observed relation slightly (adjOR 2.76, 95% CI: 1.43, 5.32). Odds for asthma among subjects who coughed without a cold also remained elevated after adjusting for wheeze (adjOR 2.85, 95% CI: 1.58, 5.15). The relations of these cough characteristics to asthma were independent of total IgE, with adjusted odds for asthma associated with prolonged cough being 4.07 (95% CI: 2.00, 8.26, $n=325$) and for cough without cold being 3.55 (95% CI: 1.87, 6.77), after adjusting for IgE at one year. Relations were similar when adjusted for allergen-specific IgE at age 5: odds of 4.02 (95% CI: 1.79, 9.07, $n=259$) for prolonged cough, and 4.39 (95% CI: 2.06, 9.34, $n=250$) for cough without cold.

Maternal Asthma, Prolonged Cough and Childhood Asthma

There was no relation between either cough characteristic and maternal asthma (Table 1), although maternal asthma was strongly associated with childhood asthma (Online Table E-2). Odds for childhood asthma associated with prolonged cough were elevated both among children with and, of borderline significance, without maternal asthma (Figure 3). However, asthma prevalence was 3-fold higher in children who had prolonged cough and a history of maternal asthma (OR 9.44, 95% CI: 2.16, 41.2), compared to children with prolonged cough who lacked a history of maternal asthma (OR 2.60, 95% CI: 1.20, 5.65). This association remained robust when limited to children with a history of maternal asthma who did not wheeze in infancy (OR 6.67, 95% CI: 1.37, 35.0). Small cell sizes precluded a similar analysis for cough without cold.

Cough duration, cough without cold, and childhood asthma

To untangle whether cough duration or cough without a cold was the stronger predictor of childhood asthma, both variables were simultaneously included in a multivariate model which adjusted for demographic factors. Both prolonged cough (adjOR 2.89, 95% CI: 1.48, 5.66) and cough without a cold (adjOR 2.81, 95% CI: 1.56, 5.08) were independently associated with risk of childhood asthma. After also adjusting for wheeze in infancy, total IgE and maternal asthma, a cumulative increase in risk for childhood asthma was observed for both prolonged cough and cough without cold, with odds for asthma remaining almost 3 times higher both for children with either cough characteristic (Table 2).

DISCUSSION

This study documents a robust relation between two characteristics of cough in infancy and the development of childhood asthma. Children with prolonged cough in the 9 months of life were three times more likely to develop asthma in the first decade of life as those with little or no cough, and this association remained significant after adjustment for potential demographic confounders. Similarly, cough without cold was predictive of later asthma, particularly among subjects with prolonged cough, more than half of whom developed asthma. Both relationships persisted after adjustment for wheeze in the first year of life, total IgE at 1 year and maternal asthma. Among subjects with maternal asthma, odds for childhood asthma were almost 10 times higher if the child had prolonged cough. After adjusting for all covariates as well as each other, each of these cough characteristics was independently associated with almost a 3-fold increase in childhood asthma. These associations remained robust when analyses were limited to children without wheeze in infancy.

Cough is common among children(18). The prevalence of recurrent cough in the absence of colds in preschool children is estimated to be about 20%,(19) with a mean duration from one to 25 days.(12) Chronic or recurrent cough is often a sequelae of respiratory infection,(20, 21) with 26% of children who have acute viral respiratory infections still coughing a week after the initial consultation. (22, 23) Chronic cough may also result from bacterial infection (24) and/or colonization. (25, 26) Cough without a cold, although less well studied, shows an association with allergic rhinitis.(13, 14) While one-third of *school-age* children with

prolonged or recurrent lower airway symptoms either have mild asthma or will develop asthma in the near future,(27) to our knowledge, this is the first report which shows that cough characteristics in the first year of life may predict subsequent asthma.

While cough is considered to be part of the asthma complex, it is usually only in association with wheeze.(28) This raises the question of whether our observations simply reflect the strong association of wheeze with both cough characteristics and with subsequent asthma. However, the relation of both prolonged cough and cough without cold to asthma persisted after adjusting for wheeze. This is consistent with a previous prospective study suggesting that a quantitative measure of troublesome lung symptoms in the first 3 years of life is associated with later asthma, even in children without objective wheeze.(29) We similarly considered whether allergic propensity, as reflected in IgE levels, may be the real culprit, (30) but multivariate models reveal that the relationship of both cough characteristics to asthma is independent of IgE level and of specific IgE to aeroallergens. This suggests that certain patterns of cough in infancy may be associated with childhood asthma through pathways not associated with regulation of IgE, and not explained by wheeze. As previously reported, total IgE and active asthma through age 5 may be associated with adaptive cytokine production in the first year of life, but the relative importance of individual cytokines varied depending on the outcome, reflecting possible non-IgE-dependent pathways to asthma.(17)

Maternal asthma is one of the strongest predictors of asthma in the child.(11, 30) Subjects with maternal asthma who have prolonged cough are almost 10 times more likely to develop childhood asthma than subjects who have a maternal history of asthma but cough only briefly. This association cannot be attributed to ascertainment bias because there was no relation of maternal asthma to cough duration. Further, while there may be a bias toward a diagnosis of asthma among subjects with maternal asthma, the relation of prolonged cough to childhood asthma persisted even when adjusted for maternal asthma. Unfortunately, small sample sizes preclude a similar assessment of how the relation of cough without cold to childhood asthma is altered by maternal asthma.

We have previously shown that wheeze in early life may be either transient or persistent.(30) This analysis suggests that cough in infancy may be similarly differentiated. Children who cough without cold appear to be unable to clear symptoms as quickly as other children, possibly due to increased bronchial responsiveness or exaggerated immune response to a virus relative to those children whose cough clears up soon after an infection. Prolonged cough, similarly, may exacerbate risk through an afferent neural pathway that might be activated by viral illness, (31) be a marker of susceptibility to asthma particularly among children of asthmatic mothers, or be associated with some other factor which confers asthma risk. The fact that the relations with asthma are independent of IgE, maternal asthma and wheeze also suggests that these characteristics of cough may reflect novel components of the pathophysiology of asthma. The potential predictive value of prolonged cough and cough without cold deserves further exploration as it may help clinicians identify children who are likely to develop asthma.

This study has several strengths. A prospective, non-selected cohort was enrolled with a high proportion of eligible children recruited and followed to age 9. Frequent interviews obtained detailed information on the timing and duration of symptoms in infancy, providing more robust measures of illness and symptom history than a single retrospective assessment. Our prospective approach also reduces recall bias and the possibility of reverse causation. The outcome includes children who were diagnosed with active asthma both early in life and in later childhood, but the results are unchanged when limited to children who were diagnosed and symptomatic at age 5 or 9. Our definition of prolonged cough differs somewhat from the more commonly used chronic cough (>3–4 weeks), (32) in that cough-days did not need to be sequential. Nevertheless, the median duration of cough in this population is consistent with that reported previously.(12, 33) The number of days of child cough was collected through retrospective self-report, but the time-frame between interviews and thus the length of recall was short. Recall bias is more likely for “cough without a cold,” assessed at age 1 year. However, others have shown that parents are more likely to forget a child’s cough than to erroneously claim a cough, which would bias our results towards the null.(34) Thus, we believe our results are valid, and if anything, underestimate the true association between cough characteristics in infancy and subsequent asthma. Our definition of asthma was based on parental report of a physician’s diagnosis, rather than clinical examination. While physicians may over diagnose asthma in the context of wheeze, it is less likely in the case of recurrent cough, which is not generally linked with asthma.

The observed associations raise the question of whether prolonged cough or cough without cold should be treated, if they are indeed early manifestations of asthma. Both guidelines and published trials have recommended the use of controller medications for chronic wet coughs,(35, 36) and recommended treatment of cough-variant asthma includes inhaled bronchodilators and corticosteroids, as well as a possible trial of leukotriene antagonists.(36, 37) However, as others have pointed out, when anti-asthma therapy is used, care must be taken not to mistake natural resolution of a cough, as in the case of a viral infection, for response to the therapy.(38, 39) Although trials of the long term impact of controller medications on asthma prognosis have been disappointing,(37) additional research is required to determine if treatment of prolonged cough and cough without colds in the first year of life may reduce subsequent risk for, or exacerbation of, asthma.

CONCLUSION

This paper demonstrates for the first time that prolonged cough and cough without cold in the first year of life precede and predict the development of asthma to age 9. These relations cannot be attributed to confounding with wheeze, and are independent of maternal asthma and both total and allergen-specific specific IgE. Clinically, these findings demonstrate the value of observing the characteristics of cough in the first year of life as easily ascertained symptoms which may identify children at risk for asthma, and suggest that focus on wheeze alone may result in under-diagnosis of asthma. Further study is required to better define the phenotypes of cough considered here, and to determine if they can be combined with other indicators to better predict asthma along the lines of the Asthma Predictive Index(40).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CI	Confidence Interval
LRI	Lower Respiratory Illness
OR	Odds Ratio
SPT	Skin Prick Test

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Figure 1.
Cumulative cough duration among the IIS cohort

Figure 2.
Adjusted odds ratios for asthma for prolonged cough and cough without a cold

Figure 3.
Prevalence of asthma by cough duration, stratified by presence of maternal asthma

Table 1

Demographic characteristics and covariates, by cough characteristics

	0–14 days			14–28 days			29+ days			Cough with cold			Cough no cold		
	N	% (n)		N	% (n)		N	% (n)		N	% (n)		N	% (n)	
Total	410	49.8 (204)		26.6 (109)	23.7 (97)		393	75.8 (295)		24.2 (95)					
Gender															
Male	200	46.5 (93)		26.5 (53)	27.0 (54)		189	72.5 (137)		27.5 (52)					
Female	210	52.9 (111)		26.7 (56)	20.5 (43)		204	78.9 (161)		21.1 (43)					
Maternal ethnicity															
Non-Hispanic White	303	51.2 (144)		25.1 (76)	23.8 (72)		295	75.9 (224)		24.1 (71)					
Hispanic	76	43.4 (33)		31.6 (24)	25.0 (19)		69	75.4 (52)		24.6 (17)					
Other/Unknown	31	51.6 (16)		29.0 (9)	19.4 (6)		29	75.9 (22)		24.1 (7)					
Maternal asthma															
No	324	51.9 (168)		25.9 (84)	22.2 (72)		310	76.1 (236)		23.9 (74)					
Yes	82	42.7 (35)		29.3 (24)	28.1 (23)		80	75.0 (60)		25.0 (20)					
Total IgE (IU/ml) in year 1	325	9.1 (7.4, 11.2)		8.9 (6.7, 11.8)	8.5 (6.3, 11.6)		318	8.2 (7.0, 9.7)		12.3 (8.9, 16.8)					
Geometric mean (95% CI)															
Wheeze in first 9 months															
No	286	57.0 (163)		26.2 (75)	16.8 (48)		273	81.0 (229)		19.1 (52)					
Yes	124	33.1 (41)		27.4 (34)	39.5 (49)		120	64.2 (77)		35.8 (43)					
Household smoking															
No	333	51.4 (171)		27.6 (92)	21.0 (70)		324	75.6 (245)		24.4 (79)					
Yes	66	39.4 (26)		21.2 (14)	39.4 (26)		59	78.0 (46)		22.0 (13)					
Daycare															
No	172	62.2 (107)		22.1 (38)	15.7 (27)		165	82.4 (136)		17.6 (29)					
Yes	238	40.8 (97)		29.8 (71)	29.4 (70)			71.1 (162)		29.0 (66)					
Maternal age (years)															
mean (sd)	410	30.2 (5.9)		28.9 (5.9)	28.9 (6.0)		298	29.7 (5.9)		29.6 (5.8)					
Maternal education (years)															

	Cough with cold				Cough no cold			
	0-14 days	14-28 days	29+ days		0-14 days	14-28 days	29+ days	
	N	% (n)	% (n)	P- value [*]	N	% (n)	% (n)	P- value [*]
mean (sd)	410	15.7 (2.4)	15.6 (3.3)	15.1 (2.8)	298	15.6 (2.8)	15.8 (2.6)	0.357

* P-values from Fisher's exact tests or Chi-squared and one-way ANOVA (for total IgE, maternal age and education).

** Chi squared test for trend across cough categories, P = <0.005

Table 2

Multivariate odds ratios (OR) for childhood asthma associated with cough characteristics

	Model 1 [*] n=393		Model 2 Fully Adjusted n=390	
	OR	P-val	OR	P-val
Cough Intervals				
0–14 days	REF		REF	
15–28 days	1.14	0.729	1.14	0.714
29+ days	2.89	0.002	2.35	0.017
Cough no cold	2.81	0.001	2.49	0.003

* Adjusted for maternal age, household smoking, maternal education and daycare attendance. Model 2 adjusts for the above as well as wheeze, IgE and maternal asthma.

Bold indicates P<0.10.