

# Outcome of a Randomized Multifaceted Intervention With Low-Income Families of Wheezing Infants

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**Objective:** To evaluate the outcome of a secondary intervention conducted with infants at risk for asthma.

**Design:** Families of wheezing infants were randomized to a 1-year intervention or control group; outcome evaluation occurred from April 1, 2000, through September 30, 2003, when children reached 4 years of age.

**Setting:** Home intervention and clinic evaluation.

**Participants:** A total of 149 children from low-income urban families with multiple wheezing episodes before the age of 2 years.

**Intervention:** Nurse home visitors provided a multifaceted intervention (environmental allergen and tobacco smoke reduction as well as illness management) that lasted 12 months, with the goal of decreasing asthma onset and/or severity when children reached 4 years of age.

**Main Outcome Measures:** Asthma status (parent-reported symptoms, impulse oscillometry, and documented asthma diagnosis), caregiver quality of life, medication use, and emergency department visits.

**Results:** A total of 46.0% of children from the intervention group and 54.9% from the control group met criteria for asthma at the age of 4 years ( $P=.33$ ). Caregiver quality of life was better for the intervention group ( $P=.01$ ). Children in the intervention group were less likely to have reactive airways (prebronchodilator-postbronchodilator decrease in impulse oscillometry resistance at 10 Hz of  $\geq 15\%$ ;  $P=.07$ ). Outcome was modified by baseline illness severity; among children with low severity, odds of developing asthma by the age of 4 years were 3 times lower for intervention children than controls ( $P=.04$ ), and symptom severity was lower for intervention children ( $P=.03$ ).

**Conclusions:** Multifaceted intervention did not decrease asthma among children with early wheezing illness as a whole, but only for children with low illness severity in infancy. Despite having an impact on only less severely ill children, results demonstrate the possibility of ameliorating illness burden for some inner-city families with children at high risk for poor asthma outcomes.

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**A**STHMA PREVALENCE AND morbidity are disproportionately high among economically disadvantaged children from urban communities in the United States.<sup>1-5</sup> Asthma results from gene-environment interactions, and increased prevalence levels among the impoverished are believed to be related to exposure to environmental factors, including aspects of the psychosocial environment.<sup>6,7</sup> Increased asthma severity and morbidity among poor children have also been attributed to environmental exposures, inadequate medical care, and poor psychosocial functioning and illness management among caregivers.<sup>8,9</sup>

Most childhood asthma onset, manifested as wheezing illness, occurs during the first 2 or 3 years of life.<sup>10,11</sup> In an unselected cohort, persistent childhood asthma developed in approximately a third

of children with early wheezing,<sup>12</sup> suggesting that children with early wheezing may be at high risk for persistent asthma. This risk group contrasts with offspring of parents with allergy wheeze typically targeted in primary prevention studies,<sup>13-17</sup> who constitute only a small proportion of those who develop asthma.<sup>18,19</sup> Intervention studies are needed that cover a broader spectrum of the population of children at risk.<sup>20</sup> Secondary prevention efforts are required to determine whether asthma prevalence, severity, or morbidity can be decreased among young children with symptoms that may develop into asthma. With this group it is reasonable to institute interventions aimed at a broad range of factors, such as exposure to environmental allergens and tobacco smoke and also the psychosocial and medical aspects of caregiving that may influence the course of early asthma.

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We report on the Childhood Asthma Prevention Study (CAPS), which targeted low-income families of children with wheezing early in life and provided a multifaceted intervention that included psychosocial and environmental factors. Our primary objective was to evaluate the impact of the early intervention that occurred for the year after study enrollment at the age of 9 to 24 months on the children's asthma status at the age of 4 years. We previously reported modest impact on the targeted environmental variables, with some reduction of indoor allergen levels and environmental tobacco smoke exposure and increases in caregiver asthma knowledge and collaboration with health care professionals but no impact on illness severity or morbidity at the end of the intervention.<sup>21</sup> However, the primary outcome evaluation was planned to occur with children at the age of 4 years, with assessments of asthma status, asthma symptom severity, and morbidity due to asthma. Although the rate of morbidity attributable to wheezing illness at study entry was high on average in this sample, considerable variability was seen in the severity of the children's symptoms,<sup>22</sup> and we planned to take into account baseline illness severity in assessing study outcome. We also expected that caregiver psychological resources would modify the impact of the intervention such that caregivers with lower psychological resources, and their children, would show greater response to the intervention.

## METHODS

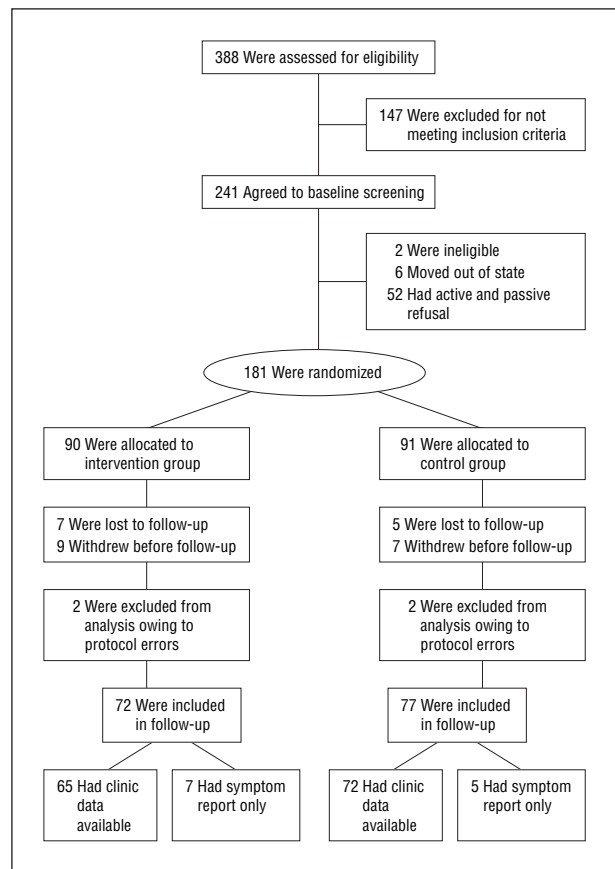
### PARTICIPANTS

Eligible infant participants were 9 to 24 months old, had medical record documentation of 3 or more wheezing episodes, and were from low-income (Medicaid-eligible) families. Infants were excluded if they were born at less than 34 weeks' gestation, had a postnatal oxygen requirement of more than 48 hours, or had complicating medical conditions. Families were recruited from pediatric departments of local hospitals and clinics from January 1, 1998, through March 31, 2000 (**Figure 1**).

During enrollment in families' homes, caregivers signed consent forms approved by the institutional review boards of participating institutions. Following baseline evaluations, families were randomly assigned to the intervention or control group. Randomization was based on a computer-generated random dichotomous table, stratified by race and language status and accessed by the project coordinator, who assigned families to intervention vs control groups.

### BASELINE EVALUATION

Interviews were conducted with the infants' primary caregivers in their homes to obtain baseline medical, environmental, and psychosocial information. Also obtained were infant urine specimens for analysis of cotinine and household dust samples for determination of allergen content (cockroaches, dust mites, cat dander, and dog dander). Interview-embedded questions queried medications prescribed for infants, classified as daily (bronchodilators or controllers) vs as needed, and caregiver behavior for ratings of illness management practices.<sup>23</sup> Infants' wheezing illness severity was assessed with a checklist that was originally validated for school-age children<sup>24</sup> and modified for infants with wheezing illness.<sup>22,25</sup> Consistent with the symptom report dimension of the National Heart, Lung, and Blood Institute asthma



**Figure 1.** Study participant flowchart.

severity classification,<sup>26</sup> symptom frequency was assessed for daytime and nighttime and after physical activity; an additional item queried the occurrence of severe breathing difficulty. Caregivers rated frequency of their children's respiratory symptoms for the past 6 months for 4 symptom domains: (1) wheezing, coughing, or tightness in the chest, (2) nights awakened by breathing problems, (3) slowed or stopped play due to breathing problems, and (4) breathing problems on awakening, using a 5-point scale: daily (4 points), weekly (3 points), monthly (2 points), less than monthly (1 point), or never (0 points). A fifth question asked, "Has your child had breathing problems so severe he/she couldn't talk/vocalize?" Yes (4 points)/No (0 points). Total scores ranged from 0 to 20; mean scores (range, 0-4) were calculated and are reported. Caregiver psychosocial measures assessed mental health,<sup>27</sup> cognitive functioning,<sup>28,29</sup> and sense of mastery,<sup>30</sup> combined to indicate caregivers' psychological resources.<sup>31</sup> During a clinic visit after enrollment, infants underwent venipuncture for determination of total serum IgE levels and skin prick testing for common indoor inhalant allergens and food allergens.

### INTERVENTION

After the baseline assessment and randomization, the nurse home visitor intervention occurred throughout 12 months. Intervention goals included decreasing allergens and environmental tobacco smoke (ETS) exposure and improving quality of maternal caregiving and illness management. Details of the intervention have been previously described.<sup>21</sup> Briefly, nurses used baseline exposure levels and psychosocial information to guide individualized plans for behavior change. For infants with elevated cotinine levels, ETS reduction and smoking cessation techniques

were used, whereas for families with elevated home allergen levels, reduction techniques specific to the allergen were used.<sup>21</sup> Caregivers were helped to assess and manage infant wheezing illness in collaboration with their medical professional and to address life stresses, family difficulties, and mental health problems.

## EVALUATION AND OUTCOME AT THE AGE OF 4 YEARS

Evaluations of children at the age of 4 years took place from April 1, 2000, through September 30, 2003. Caregivers were contacted before the children's fourth birthday and scheduled for a clinic visit that included a physical examination, venipuncture, pulmonary function testing, skin prick testing, and a caregiver interview (n=137) with health care professionals, technicians, and interviewers who were unaware of treatment group status. Caregivers who declined full participation were administered consent forms and brief asthma symptom questionnaires by telephone (n=12).

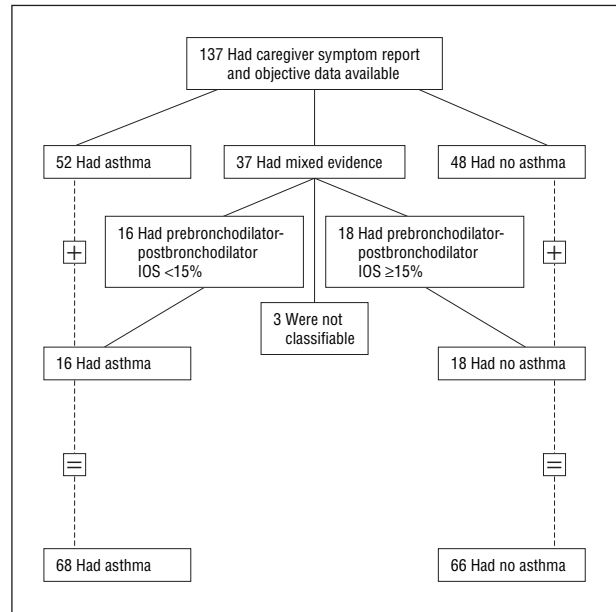
Classification of asthma at the age of 4 years used caregiver report of symptoms together with objective evidence derived from impulse oscillometry (IOS) and medical records. Caregiver reports of asthma symptoms were assessed for the past 12 months using the modified ATS-B (American Thoracic Society-B) 5-symptom list<sup>32</sup> and the symptom severity scale described herein.<sup>24</sup> **Figure 2** shows the 2-step algorithm used for asthma classification.

Impulse oscillometry was measured using a Jaeger MasterScreen Impulse Oscillometry system (Jaeger Co, Wurzburg, Germany). Procedural details and reproducibility data have been reported for this sample.<sup>33</sup> After a baseline assessment, albuterol (2.5 mg) was administered, and lung function measurements were repeated 15 minutes later. We previously reported prebronchodilator to postbronchodilator changes in resistance at 10 Hz as an index of bronchial reactivity.<sup>33</sup> Spirometry was measured after IOS, before and after bronchodilator administration (Jaeger MasterScreen Spirometry system). Given developmental limitations of spirometry measurements, modified criteria were applied<sup>34</sup> and forced expiratory volume was evaluated at 0.5 second,<sup>35</sup> resulting in forced expiratory volume at 0.5 second and forced vital capacity data for 113 children.

Caregivers responded to the Pediatric Asthma Caregiver's Quality of Life scale.<sup>36</sup> The children's medical records for the period from the age of 3 to 4 years were obtained and coded for asthma diagnoses, medication prescribed, and health care contact type.<sup>37</sup>

## STATISTICAL ANALYSES

Unadjusted comparisons of outcome variables between control and intervention groups were based on 2-sample *t* tests or 2-sample proportion tests. Adjusted estimates for intervention effects were determined by fitting regression models. Multiple logistic regression was used for binary outcome variables, and multiple linear regression was used for continuous outcomes. Covariates in the regression models included sex, foreign-born caregiver status, caregiver psychological resources, baseline illness severity (continuous), baseline medication level, and mother's educational level. Baseline illness severity and caregiver psychological resources were tested as intervention effect modifiers based on a priori hypotheses; associated interaction terms were included in models when *P* < .10. For descriptive (unadjusted) results, high- and low-severity groups were formed by cutting baseline symptom severity scores at the mean. For model-based (adjusted) results, estimates for high- and low-severity groups were determined by evaluating the continuous baseline severity variable at the 75th and 25th percentiles, respectively. The in-



**Figure 2.** Algorithm for classifying children as having asthma vs no asthma at the age of 4 years. "Asthma" indicates a positive caregiver report ( $\geq 3$  ATS-B [American Thoracic Society-B] symptoms or total symptom severity score of  $\geq 6$ ) and positive objective data (medical record documentation of current asthma diagnosis or current asthma medications prescribed). "Mixed evidence" indicates a positive caregiver report but negative medical record data (n=17) or a negative caregiver report but a positive medical record report (n=17). "Not classifiable" indicates good-quality impulse oscillometry (IOS) data unavailable for use in asthma classification.

clusion of the intervention group  $\times$  baseline severity interaction term in models for certain outcomes allowed for separate estimates for the high- and low-severity groups. The symptom severity outcome variable was analyzed on the natural log scale ( $y' = \ln[y + 1]$ ), because the original scores were right skewed. Estimates and associated confidence intervals were then derived on the original scale using asymptotic methods.<sup>38</sup>

Intention-to-treat analyses were performed in all cases. A 2-sided *P* < .05 was considered statistically significant. SAS statistical software (version 9.1; SAS Institute Inc, Cary, North Carolina) was used for all statistical analysis.

## RESULTS

### STUDY PARTICIPANTS

Outcome data reported by caregivers were available for 149 children (84.2% of those randomized); for 137 children (77.4% of those randomized) this included a clinic evaluation with lung function measures (Figure 1). Families lost to follow-up and dropouts were not significantly different from those followed up on any baseline measure (*P* > .10 for all). **Table 1** gives the baseline characteristics of caregivers and children who participated in the follow-up at the age of 4 years. Caregivers were primarily of minority background and were highly impoverished. Infants' mean scores for wheezing illness severity fell in the less-than-monthly range (0-1.0) for 53 children (35.6%), monthly for 56 (37.6%), weekly for 29 (19.5%), and daily for 11 (7.4%). Rates of maternal asthma, child atopy, and baseline illness severity were similar across the intervention and control groups.

**Table 1. Baseline Caregiver and Child Characteristics for Families Followed Up When Children Were 4 Years of Age**

Characteristic	Intervention (n = 72) <sup>a</sup>	Control (n = 77) <sup>a</sup>	P Value
Ethnic group <sup>b</sup>			.34
European American	15 (20.8)	16 (20.8)	
African American	16 (22.2)	19 (24.7)	
US-born Hispanic	25 (34.7)	22 (28.6)	
Foreign-born Hispanic	16 (22.2)	17 (22.1)	
Other (Native American or Asian)	0	3 (3.9)	
Income ≤ \$12 000/y	38 (52.8)	38 (49.4)	.60
Maternal educational level < high school	41 (56.9)	31 (40.3)	.04 <sup>c</sup>
Marital status, single	38 (52.8)	37 (48.1)	.56
Maternal age < 20 y	17 (23.6)	19 (24.7)	.88
Maternal asthma	19 <sup>d</sup> (26.8)	23 <sup>d</sup> (31.1)	.87
Male	44 (61.1)	60 (77.9)	.03 <sup>e</sup>
Child age at study enrollment, mean (SD), mo	16.8 (4.7)	17.0 (4.8)	.76
Prenatal smoke exposure	20 (27.8)	25 <sup>d</sup> (32.9)	.50
Infant eczema	25 (34.7)	24 (31.2)	.64
≥ 1 Positive baseline skin test result	12 <sup>f</sup> (17.4)	13 <sup>f</sup> (17.6)	.98
Total serum IgE, geometric mean (95% CI), µg/L	36.9 (29.1-50.3)	36.3 (26.4-49.9)	.73
Symptom severity, mean (SD)	1.50 (0.88)	1.60 (0.90)	.52
Daily medications	32 (44.4)	37 (48.1)	.66
Caregiver psychological resources, mean (SD)	99.3 (9.9)	99.5 (10.4)	.90

Abbreviation: CI, confidence interval.

SI conversion factor: To convert IgE to milligrams per liter, multiply by 0.001.

<sup>a</sup>Data are given as number (percentage) of study participants unless otherwise indicated.

<sup>b</sup>Caregiver self-reported race, ethnic group, primary language, and country of origin; foreign-born Hispanic caregivers were born in Mexico.

<sup>c</sup>Maternal educational level was not different for the intervention and control groups at baseline; there was differential loss at follow-up at the age of 4 years, leaving fewer women with a high school education in the intervention group.

<sup>d</sup>Denominator for maternal asthma: intervention: n = 71; control: n = 74; for prenatal smoke exposure: control: n = 76; missing data due to primary caregiver/respondent not being the biological mother.

<sup>e</sup>Child sex distribution was unequal after randomization and was included as a covariate in all statistical analyses.

<sup>f</sup>Denominator for baseline skin test: intervention: n = 69; control: n = 74; missing data owing to skin testing not completed at study entry.

## ASTHMA AND ATOPY AT THE AGE OF 4 YEARS

Among 134 children with complete data from clinical evaluations, 68 (50.7%) had asthma at the age of 4 years (Figure 2). For 15 children with partial data, 8 (53.3%) had probable asthma based on caregiver report of 3 or more ATS-B symptoms. Boys and girls were equally likely to have asthma (48.0% of boys and 58.3% of girls;  $P = .39$ ). Fewer children of foreign-born Hispanic mothers had asthma at the age of 4 years (30.3%) compared with European American (70.4%), African American (48.4%), or US-born Hispanic mothers (60.0%) ( $P = .003$ ). No significant difference was found in asthma rates for children whose mothers had asthma ( $P = .26$ ), and no significant differences were found in asthma rates for children with 1 or more positive skin test results at baseline (asthma, 16.4%; no asthma, 15.6%;  $P = .90$ ) or at the age of 4 years

(asthma, 33.8%; no asthma, 29.0%;  $P = .56$ ). Children prescribed daily medication before study entry had higher rates of asthma at the age of 4 years (64.5%) compared with those taking medication as needed (38.9%) ( $P = .003$ ). At the age of 4 years, mean scores for wheezing illness symptom severity for the past 12 months fell in the never range (0) for 28 children (20.0%), less-than-monthly range (0.2-1.0) for 64 (45.7%), monthly for 31 (22.1%), weekly for 14 (10.0%), and daily for 3 (2.1%). Higher symptom severity scores at baseline were related to higher symptom severity scores at the age of 4 years ( $r = 0.30$ ;  $P < .001$ ), and they were strongly related to the probability of having asthma at the age of 4 years ( $P < .002$ ); the modifying effect of this continuous variable was evaluated for intervention outcomes. Caregivers' psychological resources were unrelated to active asthma at the age of 4 years.

## INTERVENTION OUTCOME AT THE AGE OF 4 YEARS

The percentage of children with asthma at the age of 4 years was not significantly different by intervention group (Table 2). No significant differences were found between groups for specific ATS-B symptoms or for symptom severity for the past year.

More caregivers from the intervention group reported better quality of life in relation to their children's asthma at the age of 4 years ( $P = .01$ ). Of the children, 18.6% from the intervention group and 24.3% from the control group had had a course of oral corticosteroids during the previous year (adjusted  $P = .44$ ). No significant difference was seen between groups for emergency department visits between the ages of 3 and 4 years. Hospitalizations for asthma were rare, so they were not analyzed statistically.

A greater proportion of children from the control group had a prebronchodilator-to-postbronchodilator decrease of 15% in IOS pulmonary resistance at 10 Hz, indicating more bronchial reactivity in the control group at a marginally significant level ( $P = .07$ ). No significant differences were seen between groups for the spirometry measures.

## MODIFIED EFFECTS

Intervention effects were modified by symptom severity at study entry, indicated by significant interactions between group and baseline illness severity (Table 2, far right column) for several outcome variables: number of children with asthma at the age of 4 years ( $P = .05$ ), wheezing with colds during the past year ( $P = .02$ ), symptom severity at the age of 4 years ( $P = .07$ ), and oral corticosteroid use ( $P = .05$ ). Table 3 gives the unadjusted percentages and means stratified for high and low baseline severity. Table 3 also gives the model-based adjusted estimates, indicating that the probability of developing asthma at the age of 4 years was significantly different for the intervention and control groups at the 25th percentile for baseline severity ( $P = .04$ ; Figure 3) but not at the 75th percentile ( $P = .68$ ). Among children with lower baseline severity, those in the intervention group were less likely to have had wheezing with colds ( $P = .01$ ) and mean symptom severity scores were significantly lower ( $P = .03$ ), whereas for children with high baseline severity, no significant difference was found be-

**Table 2. Comparisons of Outcomes Between Groups: Unadjusted Percentages or Means and Adjusted Estimates Based on Multiple Regression**

Response Variable	Intervention/ Control	Unadjusted % or Mean (SD)		Adjusted Estimates <sup>a</sup>		
		Intervention Group	Control Group	Group Effect <sup>b</sup>	P Value	Group × Baseline Severity P Value
Asthma <sup>c</sup>	63/71	46.0	54.9	0.67 (0.30 to 1.49)	.33	.05
ATS-B symptoms						
Wheezing with colds	71/77	66.2	77.9	0.63 (0.27 to 1.48)	.29	.02
Wheezing without colds	71/77	39.4	37.7	1.12 (0.55 to 2.29)	.76	
Shortness of breath with wheezing	71/77	42.3	48.1	0.79 (0.39 to 1.60)	.51	
Wheezing with exercise	71/77	59.2	64.9	0.75 (0.36 to 1.58)	.45	
Persistent cough	71/77	29.6	40.3	0.60 (0.29 to 1.22)	.16	
Symptom severity, mean	67/73	0.86 (0.85)	1.04 (0.89)	-0.15 (-0.38 to 0.09) <sup>d</sup>	.20	.07
Quality of life, high	63/68	54.0	30.9	2.97 (1.37 to 6.46)	.01	
Medical utilization, yes/no						
Inhaled corticosteroids	67/74	25.4	23.0	1.55 (0.62 to 3.87)	.35	
Oral corticosteroids	70/74	18.6	24.3	0.69 (0.27 to 1.76)	.44	.05
Emergency department visits	70/74	18.6	24.3	0.85 (0.35 to 2.07)	.72	
IOS						
Prebronchodilator-postbronchodilator R10 decrease ≥ 15%	60/65	48.3	60.0	0.49 (0.23 to 1.07)	.07	
Spirometry						
Prebronchodilator FEV <sub>0.5</sub> <sup>e</sup>	53/60	0.62 (0.14)	0.63 (0.15)	-0.01 (-0.06 to 0.04) <sup>d</sup>	.59	
Prebronchodilator FVC <sup>e</sup>	53/60	0.74 (0.19)	0.79 (0.20)	-0.04 (-0.11 to 0.02) <sup>d</sup>	.15	
Prebronchodilator FEV <sub>0.5</sub> /FVC	53/60	0.85 (0.12)	0.81 (0.15)	0.02 (-0.03 to 0.07) <sup>d</sup>	.52	
Postbronchodilator FEV <sub>inf,0.5</sub> /FVC	53/58	0.91 (0.10)	0.88 (0.11)	0.02 (-0.02 to 0.07) <sup>d</sup>	.29	

Abbreviations: ATS-B, American Thoracic Society-B; FEV<sub>0.5</sub>, forced expiratory volume at 0.5 second; FVC, forced vital capacity; IOS, impulse oscillometry, R10, resistance at 10 Hz.

<sup>a</sup>Multiple regression analyses adjusted for sex, caregiver foreign-born status, caregiver psychological resources (continuous), baseline illness severity, baseline medication, and caregiver's educational level. The group × baseline severity interaction was added to an outcome model if  $P < .10$ , indicated in the far right column.

<sup>b</sup>Data are given as odds ratios and 95% confidence intervals unless otherwise indicated. The control group is the reference group for all odds ratios.

<sup>c</sup> $n = 134$ ; see Figure 2 for algorithm used to classify asthma vs no asthma.

<sup>d</sup>Data are given as mean differences (95% confidence interval); mean differences are intervention minus control group estimates.

<sup>e</sup>FEV<sub>0.5</sub> and FVC were measured in liters; analyses included additional covariates of child height and race.

tween groups for wheezing with colds ( $P = .59$ ) or symptom severity ( $P = .96$ ). Unadjusted results show that among children with low baseline severity, 8.3% of children from the intervention group compared with 23.5% from the control group had 1 or more courses of oral corticosteroids during the follow-up year compared with 29.4% and 25.0% for the control group; however, these differences were not statistically significant in model-based analyses ( $P = .11$  and  $P = .58$ , respectively). Level of caregiver psychological resources did not modify effects for any outcome variable.

## COMMENT

We report the outcome of the first secondary intervention study at the age of 4 years among high-risk inner-city families for whom the goal was to prevent early asthma and reduce asthma severity and morbidity. The multifaceted intervention targeted infants from low-income families who had 3 or more wheezing episodes documented by a medical care professional. Caregivers assigned to the intervention group reported higher quality of life in children at the age of 4 years, but no difference was found between groups for asthma prevalence or severity. However, the children's baseline illness severity modified the outcome effects; children with lower illness severity at study entry were less likely to have asthma at the age of 4 years.

The primary outcome assessed was persistent asthma at the age of 4 years. Defining asthma in the preschool period is challenging<sup>39</sup> because of difficulty in obtaining pulmonary function testing and reliance on caregiver report for symptoms and history. Furthermore, 4-year-old children with asthma symptoms represent several different phenotypes, each with a different prognosis.<sup>40</sup> Since 4-year-old children with asthma have high morbidity regardless of phenotype,<sup>1</sup> we did not make this differentiation in assessing outcome at the age of 4 years; rather, we focused on caregiver reports of asthma symptoms that were above a moderately high threshold. We also required objective corroboration in the form of documented physician diagnosis of asthma or laboratory evidence of airway responsiveness to bronchodilators. Thus, we are confident that the children identified had active asthma at the age of 4 years.

Our failure to find a difference between the intervention and control groups for the number of children classified as having asthma at the age of 4 years indicated that the intervention did not alter the progression from infant wheezing illness to persistent asthma at the age of 4 years. In contrast, the intervention had a significant positive effect on caregivers' asthma-related quality of life compared with the control group. Increases in caregivers' coping skills and self-efficacy may have led to better quality of life regardless of the children's symptom levels. At the end of the intervention year, caregivers' asthma knowl-

**Table 3. Unadjusted Percentages or Means Stratified for Low and High Baseline Severity Levels and Adjusted Estimates Based on Interaction Term (Group × Continuous Baseline Severity Score) From Multiple Regression Equation<sup>a</sup>**

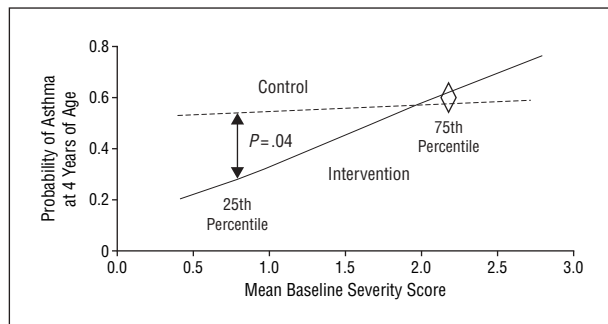
Response Variable	Intervention/ Control	Unadjusted % or Mean (SD)		Adjusted Estimates	
		Intervention Group	Control Group	Group Effect <sup>b</sup>	P Value
Low baseline severity					
Asthma	33/33	27.3	45.5	0.33 (0.12 to 0.96)	.04
ATS-B symptoms					
Wheezing with colds	37/34	51.4	76.5	0.26 (0.10 to 0.72)	.01
Wheezing without colds	37/34	24.3	29.4		
Shortness of breath with wheezing	37/34	32.4	44.1		
Wheezing with exercise	37/34	45.9	47.1		
Persistent cough	37/34	27.0	44.1		
Symptom severity, mean	36/33	0.57 (0.75)	0.99 (0.93)	-0.30 (-0.58 to -0.03) <sup>c</sup>	.03
Medical utilization, yes/no					
Inhaled corticosteroids	34/34	14.7	11.8		
Oral corticosteroids	36/34	8.3	23.5	0.34 (0.09 to 1.26)	.11
Emergency department visits	36/34	11.1	23.5		
High baseline severity					
Asthma	30/38	66.6	63.2	1.25 (0.44 to 3.59)	.68
ATS-B symptoms					
Wheezing with colds	34/43	82.4	79.1	1.39 (0.42 to 4.68)	.59
Wheezing without colds	34/43	55.9	44.2		
Shortness of breath with wheezing	34/43	52.9	51.1		
Wheezing with exercise	34/43	73.5	79.1		
Persistent cough	34/43	32.4	37.2		
Symptom severity, mean	31/40	1.19 (0.84)	1.09 (0.86)	0.01 (-0.32 to 0.33) <sup>c</sup>	.96
Medical utilization, yes/no					
Inhaled corticosteroids	33/40	36.4	32.5		
Oral corticosteroids	34/40	29.4	25.0	1.32 (0.49 to 3.60)	.58
Emergency department visits	34/40	26.5	25.0		

Abbreviations: ATS-B, American Thoracic Society-B.

<sup>a</sup>Multiple regression analyses adjusted for sex, caregiver foreign-born status, caregiver psychological resources (continuous), baseline illness severity (continuous), baseline medication, and caregiver's educational level. Estimates for low and high baseline severity were modeled using the 25th and 75th percentiles, not by stratifying the data (see "Statistical Analyses" subsection of the "Methods" section).

<sup>b</sup>Data are given as odds ratios (95% confidence interval) unless otherwise indicated. The control group is the reference group for all odds ratios.

<sup>c</sup>Data are given as mean differences (95% confidence interval); mean differences are intervention minus control group estimates.



**Figure 3.** Relationship between baseline symptom severity and probability of asthma at the age of 4 years. Probability estimates were derived from the logistic regression model using asthma as the outcome variable (see the "Statistical Analyses" subsection and Tables 2 and 3 for model details).

edge and collaboration with their physicians had improved significantly for the intervention compared with the control group<sup>21</sup>; these improvements may have influenced quality of life reported for the child at the age of 4 years. Furthermore, the home-based intervention provided by the nurses gave considerable attention to caregivers' psychological health and well-being, and caregiver affective states have been shown to be a primary determinant of pediatric asthma caregiver quality of life.<sup>41</sup>

Despite overall negative effects of the intervention, the severity of the children's wheezing illness at baseline had a modifying role on study outcome. Among children with lower symptom severity at study entry, significantly fewer children in the intervention group had active asthma at the age of 4 years. The same pattern of modified effects was evident for wheezing with colds, symptom severity ratings, and oral corticosteroid use. These data suggest decreased asthma in the intervention group, but only for children with less serious illness before the age of 2 years. It is possible that children with lower severity at baseline were more susceptible to changes in environmental exposures or illness-related caregiving.

Children with high baseline severity from both the intervention and control groups were far more likely to have persistent asthma at the age of 4 years, when they also had equivalently high numbers of ATS-B symptoms reported, symptom severity ratings, and medical care utilization. Notably, already at baseline children with high symptom severity were more likely to be described as having regular vs episodic wheezing (data not shown) and to be prescribed daily medications. Regardless of asthma diagnosis or atopic status, for the children with more severe early symptoms, the intervention was ineffective in reducing their chances of having persistent asthma at the age of 4 years.

Early severe respiratory illness may set children on a course that cannot be changed.<sup>42</sup> In a recently reported study,<sup>43</sup> 2- and 3-year-old children with early wheezing and a positive asthma predictive index were prescribed inhaled corticosteroids for 2 years and then followed up for a 1-year period. Although asthma symptoms were controlled during the treatment period, neither symptoms nor lung functions were different from a control group during the third, treatment-free year, suggesting that for infants with regular wheezing, even consistent anti-inflammatory treatment may not influence disease progression from wheezing in infancy to persistent asthma.

Specific strategies used in asthma prevention studies have varied, depending on definition of risk status and timing in relation to disease development. Several primary prevention studies<sup>44-47</sup> have attempted to impede the development of allergy and asthma among children at familial risk for atopy by reducing exposure to allergens early in life, with mixed results. Of note, the Canadian primary prevention study,<sup>48</sup> which addressed both allergen and ETS exposure in a multifaceted intervention that began prenatally, found less asthma within the intervention group at the evaluation at the age of 7 years. The current secondary prevention study<sup>22</sup> was implemented with infants with early-onset wheezing illness, previously demonstrated to be associated with multiple factors and of variable severity. The intervention aimed to reduce allergen and ETS exposure and to improve caregivers' illness management, including medication administration. Although there was some reduction in allergens and ETS,<sup>21</sup> our intervention did not directly ensure that children whose illness severity required inhaled corticosteroids received the medication and instead relied on physicians to prescribe medication and on caregivers to administer it. The combination of various etiological factors in the infants' wheezing and multiple intervention strategies used in this study may explain improvements for children with only milder disease and also the lack of effectiveness in reducing symptoms for children with established asthma.

Several important limitations of this study must be considered. First, the study may have been inadequately powered to address our aims. Among the results are several instances of statistical trends, and the direction of the effects suggests that the intervention may have had significant effects had either the effect size or the sample size been larger. Second, generalizability of the study results is limited by the sample characteristics. Although representative of low-income families in the Denver area, approximately half of the families were Hispanic, of Mexican origin. Half of the Hispanic caregivers were born in Mexico and were monolingual Spanish speaking; we found this subgroup to be distinctive in terms of risk factors for asthma and utilization of the health care system.<sup>25</sup> Generalizability may also be limited because of Denver's high altitude and arid climate, which precludes the pervasive allergenic environment of dust mites and cockroaches that has been implicated in the development of asthma in more humid climates.

Intervention effects may have been mitigated by the challenges associated with low-income, urban minority families, such as high stress levels, difficulties in coping, and mental health problems. The intervention was aimed at behaviors most proximal to asthma symptoms and exac-

erbations, such as environmental exposures and symptom assessment and management, but necessarily addressed caregiver psychological and social problems that impeded the care of their infants. Nevertheless, great variability was seen in caregivers' desire and capacity to use the intervention. Given that the feasibility of changing the developmental course of asthma is itself in question, interventions to prevent asthma may be better tested on families of higher socioeconomic status and education who are more likely to be adherent to recommendations, such as those of the Canadian primary prevention study.<sup>48</sup> It may be prudent to attempt to decrease asthma among wheezing infants from families who have the resources and motivation to assess efficacy and only then adapt the intervention to families with fewer resources.

Finally, evaluating the effectiveness of the intervention based on asthma status at the age of 4 years is inherently difficult, because symptoms resolve for some children but persist for others. A follow-up at the age of 7 years is under way, when objective lung function measures will facilitate more accurate assessment of asthma status. The follow-up at the age of 7 years will also be informative regarding which of the children's early wheezing was transient vs persistent and whether the intervention effects on asthma at 4 years of age prove to have a continued effect at 7 years of age.

This is the first study, to our knowledge, to provide a nonmedical intervention for infants with early wheezing illness to determine whether the developmental course of asthma can be altered. The intervention was multifaceted, addressing environmental exposures, illness management behavior, and social and psychological challenges experienced by these caregivers. Although the intervention had minimal benefit overall among these at-risk children, it is possible that the intervention succeeded for those with lower baseline severity. However, it is clear that this intervention did not appreciably affect the children who had more severe early disease. Nevertheless, this study demonstrates the possibility of ameliorating illness burden for selected inner-city families with children at high risk for poor asthma outcomes.

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