*Original article*

# Demographic and clinical characteristics of children and adolescents with severe or difficult-to-treat asthma

**Bradley E. Chipps, MD,[a] Stanley J. Szefler, MD,[b] F. Estelle R. Simons, MD,[c] Tmirah Haselkorn, PhD,[d] David R. Mink, MS,[e] Yamo Deniz, MD,[d] and June H. Lee, MD,[d] for the TENOR Study Group*** *Sacramento and South San Francisco, Calif, Denver, Colo, and Winnipeg, Manitoba, Canada*

**Background: Young patients with severe or difficult-to-treat asthma are an understudied population.**
**Objective: To assess age-associated and gender-associated differences in children and adolescents in the observational study, The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens.**
**Methods: Cross-sectional baseline data for patients greater than or equal to 6 years and less than or equal to 17 years (n = 1261) were stratified by age group (6-8, 9-11, 12-14, and 15-17 years). The $\chi^2$ test for categorical variables and analysis of variance for continuous variables were used to identify differences among age groups, stratified by gender.**
**Results: Most patients had moderate (55%) or severe (41%) asthma by physician assessment. Of those using greater than or equal to 3 long-term controllers (62%), 53% of children (6-11 years) and 44% of adolescents (12-17 years) reported an oral corticosteroid burst and 25% and 19%, respectively, had an emergency department visit in the previous 3 months; 10% and 15%, respectively, reported past intubation. In females, weight for age ranged between the 67th and 70th percentiles; height for age was between the 42nd and 54th percentiles ($P < .01$ among age groups). Lung function was lower in adolescents than children: prebronchodilator percent predicted forced expiratory volume in 1 second ($FEV_1$)/forced vital capacity was 0.92 (6-8 years) and 0.83 (15-17 years), $P$ less than .05, in males; and 0.94 (6-8 years) and 0.87 (15-17 years), $P$ less than .05, in females.**
**Conclusions: Children and adolescents demonstrated high rates of health care use and loss of lung function, despite using multiple long-term controllers.**
**Clinical implications: Asthma treatments that prevent loss of lung function and reduce health care resource use are needed in young patients with severe or difficult-to-treat asthma. (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)**

***Key words:*** *Asthma, health care use, long-term controllers, lung function, observational, pediatric*

Asthma is one of the most common chronic childhood medical disorders in the United States, which affects more than 9 million children under 18 years of age.[1] The prevalence of asthma symptoms and asthma diagnosis in US children is among the highest in the world.[2] In children aged 5-14 years, the prevalence of self-reported asthma increased from 1.5 million cases in 1980 to 2.3 million cases in 1999.[3] Along with increasing prevalence, asthma severity seems to be on the rise in pediatric and adolescent patients, based on increases in the rates of office visits, hospital admissions, and emergency department (ED) visits. Moreover, the increasing burden of asthma is consistently focused on children and young adolescents. Asthma-attributable mortality nearly doubled between 1980 and 1999 in children aged 5 to 14 years, which was a substantially greater increase than that observed in older adolescents and adults.[3]

Children and adolescents with severe or difficult-to-treat asthma are an understudied population. Most of the economic burden of asthma is related to severe disease,[2] and severe disease is associated with more symptoms, more limitations in daily activities, greater medical resource use, and higher health care costs.[4] Additional

From [a]the Capital Allergy and Respiratory Disease Center, Sacramento; [b]National Jewish Medical and Research Center, Denver; [c]the University of Manitoba, Winnipeg; [d]Genentech, Inc., South San Francisco; and [e]the Ovation Research Group, San Francisco.

*For a complete list of TENOR Study Group members, please contact Genentech, Inc.

Supported by Genentech, Inc. and Novartis Pharmaceuticals Corp.

Disclosure of potential conflict of interest: B. E. Chipps has consulting arrangements with Aventis, Genentech, AstraZeneca, GlaxoSmithKline, MedPoint, Novartis, Schering, Sepracor, and Merck; has received grant support from Aventis, Genentech, AstraZeneca, GlaxoSmithKline, Novartis, Schering, Sepracor, and Merck; is on the speakers' bureau for Aventis, Genentech, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, MedPoint, Novartis, Pfizer, Schering, Sepracor, and Merck; and has served as an expert witness in mold litigation. S. J. Szefler has received grant support from AstraZeneca, GlaxoSmithKline, Aventis, Genentech, and Merck and has received grant support from the National Institutes of Health, the National Institute of Allergy and Infectious Diseases, the National Institutes of Health, and Ross Pharmaceuticals. T. Haselkorn has consulting arrangements with Genentech. D. R. Mink is employed by the Ovation Research Group. Y. Deniz owns stock in and is employed by Genentech. J. H. Lee owns stock in and is employed by Genentech. F. E. R. Simons has declared that she has no conflict of interest.

Received for publication December 20, 2005; revised November 22, 2006; accepted for publication December 1, 2006.

Reprint requests: Bradley E. Chipps, MD, Capital Allergy and Respiratory Disease Center, 5609 J Street, Suite C, Sacramento, CA 95819. E-mail: BChipps@capitalallergy.com.

0091-6749/$32.00



doi:10.1016/j.jaci.2006.12.668

*Abbreviations used*
BMI: Body mass index
CAMP: Childhood Asthma Management Program
ED: Emergency department
FVC: Forced vital capacity
HCU: Health care use
IRB: Institutional review board
NHANES: National Health and Nutrition Examination Survey
TENOR: The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens

information is needed about these patients and the treatment patterns and outcomes related to their asthma.

The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) is an observational study of a large cohort of patients with severe or difficult-to-treat asthma. This TENOR analysis focuses on cross-sectional baseline data from the children and adolescents enrolled in the study. It provides the opportunity to characterize and better understand the natural history of asthma in these patients in terms of disease severity, lung function, medication use, and health care use (HCU). We hypothesized that children and adolescents with severe or difficult-to-treat asthma would have high rates of HCU and loss of lung function despite being on currently accepted guideline-directed therapy.

## METHODS

### Study design and participants

The TENOR study was a prospective, observational, 3-year study (2001-2004) conducted in the United States in patients with severe or difficult-to-treat asthma who received care from either an allergist or a pulmonologist. No experimental intervention was involved; participants continued to receive medications and treatments for their asthma as directed by their asthma specialist. The design and protocol of TENOR were approved by a central institutional review board (IRB) and, when necessary, by the IRB at each site; Genentech, Inc, contracted with an independent, external IRB to review and approve the protocol for sites without an IRB. All patients or their parents/guardians supplied written informed consent.

The TENOR study included patients greater than or equal to 6 years of age with severe or difficult-to-treat asthma; patients with mild or moderate asthma were eligible for enrollment if their physician considered their asthma difficult-to-treat and if they met the additional inclusion and exclusion criteria.[5] Patients had to have evidence of either high HCU (2 or more unscheduled care visits for asthma or 2 or more oral corticosteroid bursts) or high medication use (currently requiring $\geq$3 medications to control asthma or long-term daily high doses of inhaled corticosteroids or use of 5 mg/day or more of oral prednisone), or both, in the past year.[5] Patients were excluded if they were heavy smokers ($\geq$30 pack-years) or if they had a diagnosis of cystic fibrosis. Few current or former smokers were included in this cohort; therefore, smoking data were not included in this analysis. Additional detail regarding inclusion/exclusion criteria has been described previously[5] and can be found in this article's Online Repository at www.jacionline.org.

### Demographic, clinical, and laboratory assessments

Data presented in this analysis were obtained at study entry and are cross-sectional. In addition to assessing the asthma severity of each participant, physicians reported whether their patient's asthma was considered difficult-to-treat based on specified parameters (that is, complex treatment regimen, multiple drugs required, unable to avoid triggers, frequent exacerbations, severe exacerbations, and/or unresponsive to therapy).[5]

For participants less than 12 years of age, the parent or guardian was present to help answer interview questions and complete questionnaires fully and accurately; if needed, adolescents were permitted to obtain assistance from a parent (or other adult if a parent was not available). Demographic (age, gender, race, height, and weight), clinical data (including HCU and medication use), and laboratory data (total serum IgE, spirometry) were collected by study coordinator interview and evaluation. Overweight was defined as weight-for-age greater than or equal to the 95th percentile based on the US growth charts developed by the Centers for Disease Control.[6]

### HCU

Data on asthma-related HCU were based on data collected at study entry by study coordinator interview[5] and included ED visits, overnight hospitalizations, corticosteroid bursts, and unscheduled office visits/contacts with physician during the previous 3 months. Baseline data on intubation was obtained in answer to the question "have you ever been intubated?"

### Asthma medications

Information about all current asthma medications, including long-term controller and quick-relief medications, was collected by the study coordinator during an interview in which patients and parents actually brought in their medications for review.

### IgE data

Total serum IgE levels (IU/mL) were measured at baseline by each study site using any commercially available assay. All total serum IgE assay tests used in TENOR received 510 (k) Food and Drug Administration approval and were considered substantially equivalent in accuracy and precision.[7] In addition, all total serum IgE assays were calibrated to the World Health Organization's second International Reference Preparation for Human Serum IgE, World Health Organization IRP 75/502.

### Spirometry

Spirometry measurements in TENOR were performed according to American Thoracic Society guidelines.[8] All sites were required to have a certified device that was calibrated daily for performing flow spirometry. For this analysis, predicted values for spirometry measures were race-adjusted. Formulas of Wang et al[9] were applied for the predicted values of white and black patients. Because these formulas do not address Hispanics, the formulas of Hsu et al[10] were used for Hispanic patients. About 5% of patients self-described as "other" did not have predicted spirometry values calculated but were included in the overall study.

### Data retrieval and monitoring

The TENOR study used a Web-based system for data collection (developed using Quintiles WebCollect services and PhaseForward's InForm application; Quintiles Transnational Corp, Research Triangle Park, NC). Data were entered directly on electronic case report forms and transferred in encrypted form onto a secure server at the data coordinating center. All study coordinators received website and study protocol training.

**TABLE I.** Demographic and clinical characteristics of female and male pediatric and adolescent patients at baseline*

| | Male | | | | | Female | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Age group (y) | | | | | Age group (y) | | | | |
| | 6-8 | 9-11 | 12-14 | 15-17 | *P* value | 6-8 | 9-11 | 12-14 | 15-17 | *P* value |
| All patients, n | 145 | 282 | 240 | 124 | | 88 | 120 | 171 | 91 | |
| Race/ethnicity, n (%) | | | | | | | | | | |
| White | 87 (60) | 165 (58) | 141 (59) | 76 (61) | NS† | 62 (70) | 65 (54) | 115 (67) | 73 (80) | .0008† |
| Black | 38 (26) | 70 (25) | 69 (29) | 31 (25) | | 17 (19) | 33 (27) | 39 (23) | 11 (12) | |
| Hispanic | 9 (6) | 31 (11) | 16 (7) | 11 (9) | | 7 (8) | 17 (14) | 12 (7) | 3 (3) | |
| Asian/PI | 3 (2) | 3 (1) | 3 (1) | 1 (1) | | 1 (1) | 1 (1) | 3 (2) | 0 (0) | |
| Other | 8 (5) | 13 (5) | 11 (5) | 5 (4) | | 1 (1) | 4 (3) | 2 (1) | 4 (4) | |
| Height for age, mean ± SD (percentile) | 48.8 ± 30.5 | 51.0 ± 29.3 | 47.2 ± 28.7 | 45.0 ± 31.0 | NS | 54.2 ± 30.4 | 54.3 ± 31.2 | 46.8 ± 29.0 | 41.6 ± 32.1 | <.01 |
| Weight for age, mean ± SD (percentile) | 64.8 ± 29.5 | 64.8 ± 30.7 | 67.9 ± 29.9 | 66.9 ± 34.0 | NS | 66.9 ± 30.9 | 68.8 ± 29.7 | 70.4 ± 27.7 | 68.9 ± 27.4 | NS |
| Weight for age percentile, n (%) | | | | | | | | | | |
| ≤85th | 102 (70) | 174 (62) | 138 (56) | 69 (56) | <.01 | 52 (60) | 70 (58) | 101 (59) | 54 (59) | NS |
| 85th to ≤95th | 10 (7) | 54 (19) | 41 (17) | 18 (14) | | 16 (18) | 17 (14) | 32 (19) | 15 (16) | |
| 95th+ | 33 (23) | 54 (19) | 61 (25) | 37 (30) | | 19 (22) | 33 (27) | 37 (22) | 22 (24) | |
| Body mass index, mean ± SD ($kg/m^2$) | 18.9 ± 7.4 | 20.6 ± 5.4 | 23.6 ± 6.4 | 25.6 ± 7.1 | <.0001 | 19.2 ± 5.2 | 21.9 ± 5.8 | 24.5 ± 7.1 | 26.4 ± 7.6 | <.0001 |
| Total serum IgE (IU/mL), geometric mean (95% CI) | 145.7 (106.0-200.0) | 232.9 (190.5-284.8) | 260.2 (219.5-308.4) | 253.9 (199.5-323.1) | <.01 | 112.0 (75.7-165.6) | 144.2‡ (102.3-203.2) | 215.6 (169.3-274.6) | 145.4‡ (98.7-214.2) | <.05 |
| Physician-assessed asthma severity, n (%) | | | | | | | | | | |
| Mild | 8 (5) | 17 (6) | 8 (3) | 6 (5) | <.001 | 4 (5) | 4 (3) | 9 (5) | 2 (2) | NS |
| Moderate | 88 (61) | 164 (58) | 133 (55) | 45 (36) | | 55 (63) | 71 (59) | 90 (53) | 42 (46) | |
| Severe | 49 (34) | 101 (36) | 99 (41) | 73 (59) | | 29 (33) | 45 (37) | 72 (42) | 47 (52) | |
| Treating physician specialty, n (%) | | | | | | | | | | |
| Pulmonology | 82 (57) | 158 (58) | 134 (57) | 58 (47) | NS | 51 (60) | 80 (68) | 109 (64) | 45 (51) | NS |
| Allergy | 58 (41) | 115 (42) | 100 (44) | 65 (53) | | 34 (40) | 37 (32) | 60 (35) | 44 (49) | |

*NS*, Not significant; *PI*, Pacific Islander.
*All data are from baseline visit. Overweight was defined based on the US growth charts developed by the Centers for Disease Control.[9]
†White versus nonwhite.
‡Statistically significantly ($P < .05$) different compared with boys of the same age.

## Statistical methods

The $\chi^2$ test for categorical variables and analysis of variance for continuous variables were used to identify significant differences among age groups (6-8, 9-11, 12-14, and 15-17 years), stratified by gender. All analyses were performed using SAS Version 9.1 for Windows (SAS Institute, Cary, NC).

## RESULTS

### Demographic, clinical, and laboratory assessments

A total of 4756 patients were enrolled by 283 US study sites between January and October 2001. Of these, 1261 patients were greater than or equal to 6 years and less than or equal to 17 years at baseline. Demographic and clinical characteristics stratified by gender and baseline age group are shown in Table I. The proportion of white males was consistent among age groups (58% to 61%), whereas the proportion of white females ranged from 54% (9-11 years) to 80% (15-17 years). A significant difference was found among age groups in the proportion of female patients that were white versus nonwhite ($P = .0008$).

Most patients had moderate (55%) or severe (41%) asthma by physician assessment. The proportion of patients with severe asthma increased significantly across age groups in males ($P < .001$) but not females (Table I). No differences were found across age groups by treating physician specialist; more of the children and adolescents in TENOR were under the care of a pulmonologist than an allergist.

### HCU by number of long-term controllers

Overall, 62% of patients were using 3 or more long-term controllers. Across all measures of HCU in the 12-17–year age group, patients using 3 or more long-term controllers had greater HCU compared with those requiring 1 or 2 long-term controllers (Fig 1), although differences were not statistically significant. Of those using 3 or more long-term controllers, 53% of children and 44% of adolescents reported a corticosteroid burst and 25% of the children and 19% of adolescents had an ED visit

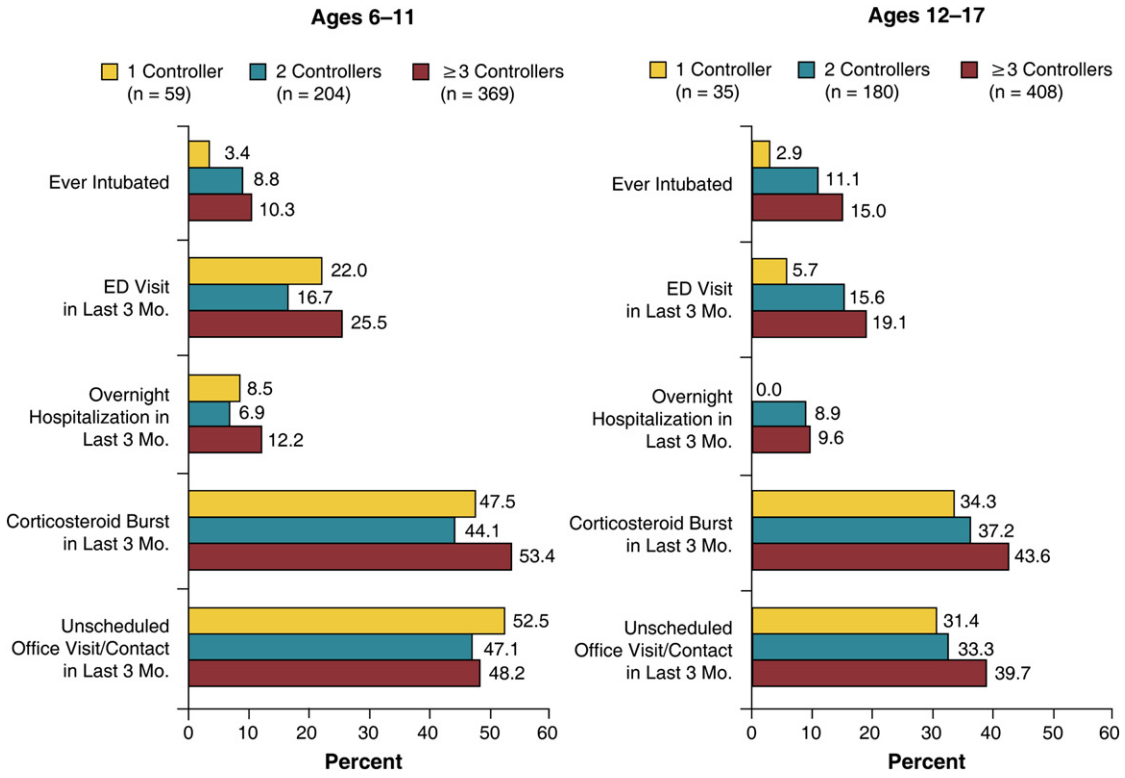


**FIG 1.** HCU by number of long-term controller medications in patients aged 6-11 years *(left panel)* and 12-17 years *(right panel)*. Long-term controllers included inhaled corticosteroids, long-acting β-agonists, leukotriene modifiers, methylxanthines, and cromolyn sodium or nedocromil. No statistically significant differences were found in rates of HCU by number of long-term controllers.

in the 3 months before the baseline visit. A history of intubation was reported in 10% to 15% of children and adolescents using 3 or more long-term controllers.

## Medication use

Overall, 96% of children and adolescents were using short-acting β-agonists, 95% inhaled corticosteroids, 74% long-acting β-agonists, 73% leukotriene modifiers, 15% systemic corticosteroids, 10% anticholinergics, 8% methylxanthines, and 9% cromolyn or nedocromil. For the combined gender groups, rates of use of inhaled corticosteroids (94% to 96%) and short-acting β-agonists (96% to 97%) were relatively consistent among age groups (Fig 2). Use of long-acting β-agonists and methylxanthines significantly increased across age groups ($P < .05$).

## Height and weight

For males, the mean weight for age ranged between the 65th and the 68th percentiles and the mean height for age ranged between the 45th and the 51st percentiles. For females, the mean weight for age ranged between the 67th and the 70th percentile and the mean height for age ranged between the 42nd and the 54th percentile; mean height for age was significantly different among age groups in females ($P < .01$) (Fig 3). Approximately 25% of children and adolescents in TENOR were considered overweight (weight for age $\geq$ 95th percentile) and a larger proportion of females (14% to 19%) than males (7% to 19%) were at risk for becoming overweight (weight for age >85th to <95th percentile).

## Serum IgE levels

Geometric means for total serum IgE levels were generally higher in males than in females across age groups; the differences between males and females were statistically significant for the 9-11–year and 15-17–year age groups ($P < .05$) (Table I). Mean total serum IgE was significantly different among age groups in males ($P < .01$) and females ($P < .05$).

## Spirometry

Lung function was lower in adolescents than in children, and spirometric measures were lower in males than females (Fig 4). Prebronchodilator percent predicted $FEV_1$/forced vital capacity (FVC) was 0.92 in males 6-8 years at baseline and 0.83 in males 15-17 years at baseline ($P < .05$); and was 0.94 in females 6-8 years at baseline and 0.87 in females 15-17 years at baseline ($P < .05$). Prebronchodilator percent predicted $FEV_1$ was 0.91 in males 6-8 years at baseline and 0.82 in males 15-17 years at baseline ($P < .05$); and was 0.94 in females 6-8 years at baseline and 0.84 in females 15-17 years at baseline ($P < .05$). Additional spirometry results are presented in Fig E1 in this article's Online Repository at www.jacionline.org.

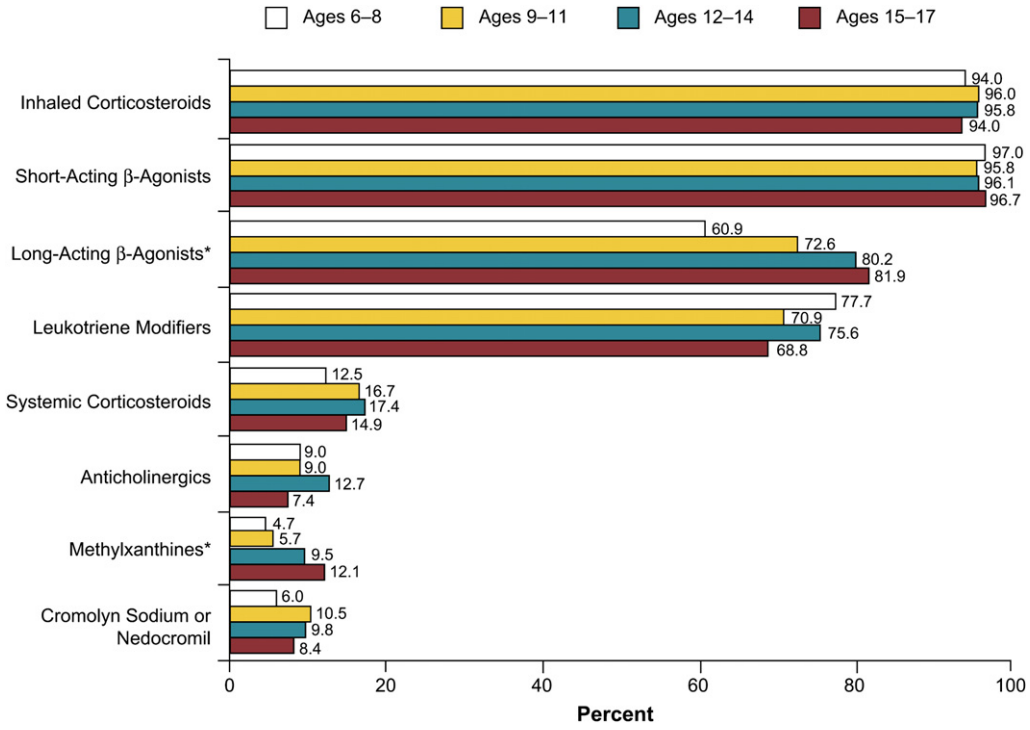


**FIG 2.** Medication use by age category. *Based on test for linear trend, a statistically significant age trend ($P < .05$) was observed for methylxanthines and long-acting β-agonists.

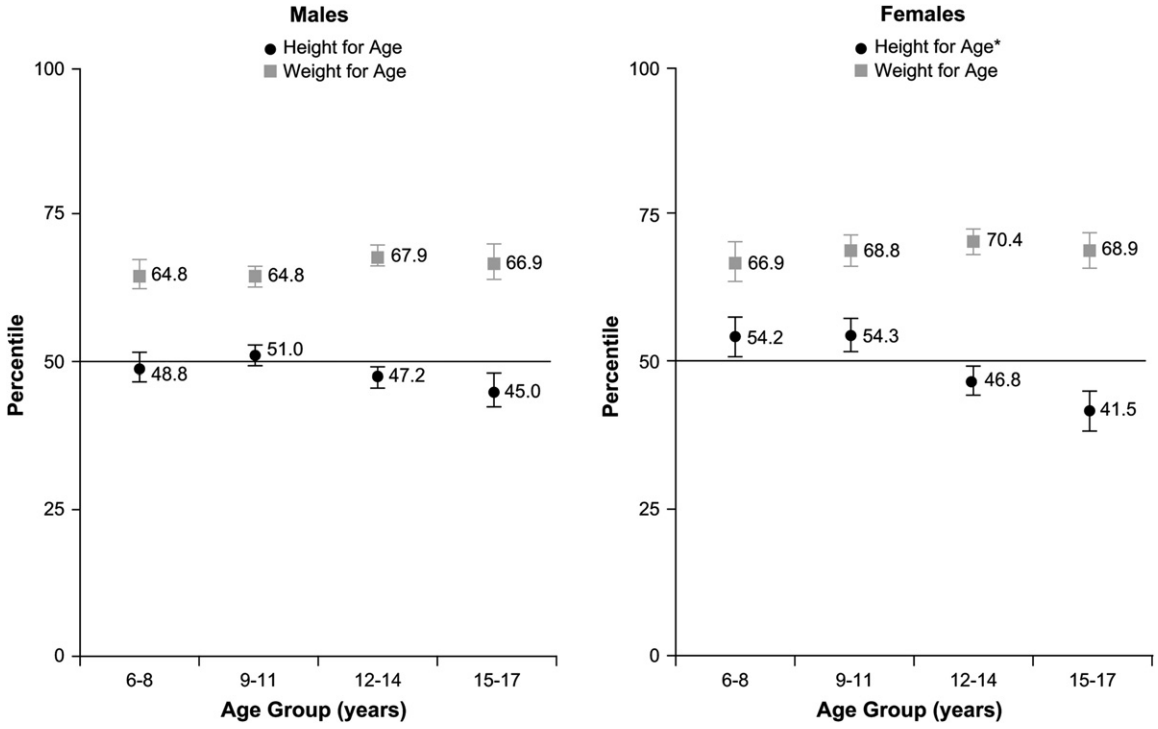


**FIG 3.** Height and weight for age in male *(left panel)* and female *(right panel)* pediatric and adolescent patients in TENOR. *Differences across height for age categories in females are statistically significant, $P = .0062$.

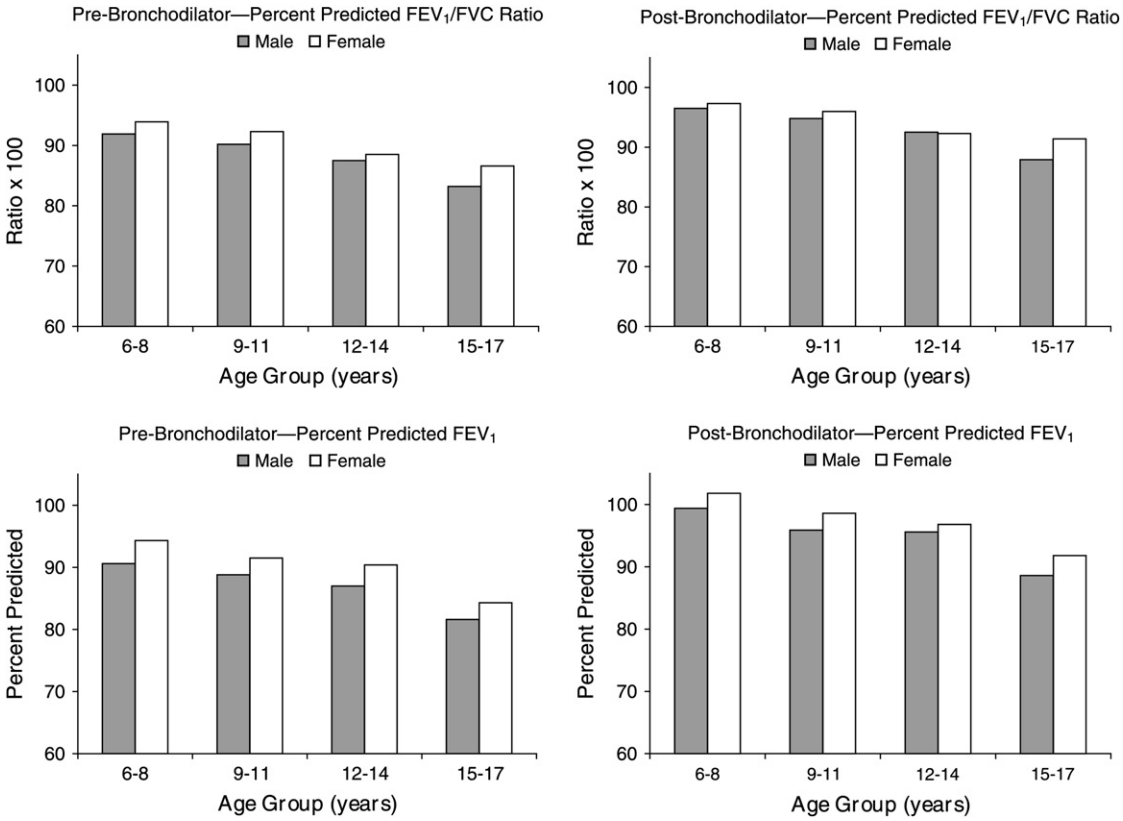


**FIG 4.** Prebronchodilator *(left panel)* and postbronchodilator *(right panel)* spirometry measures in male and female pediatric and adolescent patients in TENOR. Predicted values were calculated using formulas of Wang et al[9] and Hsu et al.[10] Based on test for linear trend, spirometry values are statistically significant ($P < .05$) across age categories.

## DISCUSSION

The TENOR study is one of the few observational studies to characterize the natural history of asthma in young patients with severe or difficult-to-treat asthma. In this cross-sectional analysis at baseline, most children and adolescents had moderate or severe asthma by physician assessment. Despite that almost two thirds of patients were using 3 or more long-term controllers, HCU in these patients was high. An increase in systemic corticosteroid use across the 3 youngest age groups was observed, and assessment of age-associated and gender-associated differences revealed that height for age decreased across age groups, especially in females. In general, the children and adolescents in TENOR were shorter and heavier compared with national averages. Lung function decreased with increasing age, and this trend seemed to be more pronounced in males than females.

Although a recent study showed that inhaled corticosteroids conferred a significant protective effect on the risk of hospitalization and ED visits in children with asthma,[11] the TENOR data demonstrate that high rates of HCU are still evident, despite the use of multiple asthma medications in most children and adolescents. Although the selection criteria for TENOR included patients with high HCU, these young patients continued to demonstrate high rates of asthma-related health care utilization throughout the 3-year study (data not shown). These findings could be interpreted to mean that physicians treat patients with higher morbidity with increased numbers of controller medications, but they do certainly suggest that the prescribed medications do not prevent morbidity adequately. Nonadherence with increased numbers of prescribed medications cannot be excluded. These findings demonstrate the possibility of an unmet need in asthma care for young patients with severe or difficult-to-treat asthma. They also lend support to the conclusions reached in recent reviews by leading experts in the field, which highlighted the need for a more global assessment of asthma severity that includes asthma-related HCU and medication use.[12-14] Similar conclusions were reached in a recent analysis of TENOR data in adults.[15]

In TENOR, height for age decreased across age groups, and this was particularly pronounced in females. We also observed an increase in systemic corticosteroid bursts across the 3 youngest age groups. Whether the decrease in height is related to the cumulative effect of systemic corticosteroid or high-dose inhaled corticosteroid use

requires further study. However, concerns about the side effects associated with long-term inhaled corticosteroid therapy, especially about delays in growth in children, have often been cited as a major factor in nonadherence with asthma guidelines.[16,17] Data from several prospective, randomized, double-blind placebo-controlled studies,[18-20] including the Childhood Asthma Management Program (CAMP),[18] have shown that budesonide 200 μg twice daily or beclomethasone dipropionate 200 μg twice daily were associated with small reductions in growth velocity in children soon after the onset of corticosteroid treatment but did not progress during follow-up for 1 or more years. Other reports, however, based on a nonrandomized study, have indicated that children treated with long-term budesonide attain normal adult height.[21,22]

Childhood obesity appears to be related to asthma, as supported by numerous publications.[23-26] An analysis of data from the Third National Health and Nutrition Examination Survey (NHANES III) showed that the prevalence of asthma rose significantly with increasing quartiles of body mass index (BMI) in children aged 4-17 years.[24] Other analyses from NHANES showed that physician-diagnosed asthma was almost 2-fold higher in children with BMI greater than or equal to the 85th percentile compared with those with BMI below this percentile,[25] and in children with BMI above the 95th percentile, the asthma risk was 3 times higher compared with those with BMI within the 25th-49th percentiles.[26] Data from CAMP also showed an association between asthma severity, as measured by the $FEV_1$/FVC ratio, and BMI in children with mild-to-moderate asthma.[23] In our population of severe or difficult-to-treat asthma, approximately 25% of children and adolescents were considered overweight. In contrast, the prevalence of overweight based on BMI at or above the 95th percentile in children aged 6-17 years in the NHANES was 11%.[27]

Physician-assessed severe/difficult-to-treat asthma in children and adolescents in TENOR is supported by lung function data. By most measures of spirometry, worse lung function was observed in the older children and adolescents. This is consistent with data from cohorts of children with asthma followed longitudinally.[18,28-32] In the CAMP study, 26% of children with mild-to-moderate asthma showed a significant reduction in percent predicted postbronchodilator $FEV_1$[30]; among the entire cohort, a gradual decline in the ratio of $FEV_1$/FVC was observed over 4 years despite treatment with budesonide or nedocromil.[18] Data from Sears et al[31] in a large cohort of children followed from age 9 years to adulthood showed that participants with persistent wheezing had consistently lower $FEV_1$/FVC ratios than those without persistent wheezing. Because of different clinical phenotypes of the cohorts enrolled into the above studies, the direct comparison of lung function values to the TENOR data is not possible. However, cross-sectional data from this TENOR analysis and another study,[33] as well as the longitudinal studies of children with asthma[28-32] described above, consistently demonstrate that lung function is compromised at an early age. Furthermore, the persistence of abnormalities and the worsening of lung function is observed over time in children and adolescents[28-31] and in young adults with a history of mild-to-moderate childhood allergic asthma.[34] Notably, similar to the TENOR data, Sears et al[31] also demonstrated lower lung function values in males compared with females.

Of note was the higher proportion of males than females across age groups in TENOR. This finding is consistent with general epidemiologic data and other pediatric studies, which show a higher prevalence of asthma in male pediatric and adolescent patients, whereas in adulthood, the prevalence of asthma is higher in females.[18,35-37] Reasons for the gender discrepancy in asthma by age are not entirely clear but have been attributed to hormonal changes during puberty or to gender-specific differences in environmental exposures such as diet, obesity, allergen exposure, or cigarette smoking.[38]

Several limitations of the current analysis should be mentioned. Data are cross-sectional and, therefore, provide a description of this cohort at a single point in time. Future planned analyses of TENOR will be based on data from repeated visits over the 3 years of this observational study and will be able to provide a description of changes in medication and health care resource use that occur over time. The impact of allergic sensitization, IgE, and obesity will also be addressed in a separate analysis.

It may be more difficult to obtain accurate and consistent results, particularly spirometry measures,[39] in young children than in older children and adolescents, possibly contributing to the differences observed among age groups. In addition, as they age, patients may have an increased awareness of those measures that relied partially on self-report, such as HCU, which could potentially lead to higher reporting in older age cohorts compared with younger age cohorts. Presumably, the parental assistance young children received during the baseline interview and when completing questionnaires should have mitigated this potential bias. Compliance with prescribed medications was based on patient self-report or parent report. Although patients with known cystic fibrosis were excluded, we cannot rule out the possibility that the TENOR cohort may contain some patients with other conditions misdiagnosed as asthma.

In conclusion, results of the current analysis of data from a large cohort showed that children and adolescents in TENOR demonstrated high rates of HCU, despite using multiple long-term controller medications. High proportions of these children and adolescents with severe or difficult-to-treat asthma were overweight, and most were at or below the median height for their age. Furthermore, data showed that older children and adolescents had worse lung function than younger children. The TENOR findings lend weight to the concept of asthma as a multifactorial disease with complex variations by age and gender. They also demonstrate the need for increased targeting of intervention programs and novel strategies to prevent loss of lung function and reduce health-care utilization in children with severe or difficult-to-treat asthma.

## REFERENCES

1. Dey AN, Bloom B. Summary health statistics for U.S. children: National Health Interview Survey, 2003. National Center for Health Statistics. Vital Health Stat 2005;10:1-78.
2. Beasley R. The burden of asthma with specific reference to the United States. J Allergy Clin Immunol 2002;109:S482-9.
3. Mannino DM, Homa DM, Akinbami LF, Moorman JE, Gwynn C, Redd SC. Surveillance for asthma—United States, 1980-1999. MMWR Surveill Summ 2002;51:1-13.
4. Antonicelli L, Bucca C, Neri M, De Benedetto E, Sabbatani P, Bonifazi F, et al. Asthma severity and medical resource utilisation. Eur Respir J 2004;23:723-9.
5. Dolan CM, Fraher KE, Bleecker ER, Borish L, Chipps B, Hayden ML, et al, for the TENOR Study Group. Design and baseline characteristics of The Epidemiology and Natural History of Asthma Outcomes and Treatment Regimens (TENOR) study: a large cohort of patients with severe or difficult-to-treat asthma. Ann Allergy Asthma Immunol 2004;92:32-9.
6. Ogden CL, Kuczmarski RJ, Flegal KM, Mei Z, Guo S, Wei R, et al. Centers for disease control and prevention 2000 growth charts for the United States: improvements to the 1977 National Center for Health Statistics version. Pediatrics 2002;109:45-60.
7. Borish L, Chipps B, Deniz Y, Gujrathi S, Zheng B, Dolan CM, for the TENOR Study Group. Total serum IgE levels in a large cohort of patients with severe or difficult-to-treat asthma. Ann Allergy Asthma Immunol 2005;95:247-53.
8. American Thoracic Society. Standardization of spirometry: 1994 update. Am J Respir Crit Care Med 1995;152:1107-36.
9. Wang X, Dockery DW, Wypij D, Fay M, Ferris B. Pulmonary function between 6 and 18 years of age. Pediatric Pulmonol 1993;15:75-88.
10. Hsu K, Hsi B, Thompson V, Hsieh G. Ventilatory functions of normal children and young adults: Mexican-American, white, and black. I. Spirometry. J Pediatr 1979;95:14-23.
11. Adams RJ, Fuhlbrigge A, Finkelstein JA, Lozano P, Livingston JM, Weiss KB, et al. Impact of inhaled antiinflammatory therapy on hospitalization and emergency department visits for children with asthma. Pediatrics 2001;107:706-11.
12. Moore WC, Peters SP. Severe asthma: an overview. J Allergy Clin Immunol 2006;117:487-94.
13. Apter AJ, Szefler SJ. Advances in adult and pediatric asthma. J Allergy Clin Immunol 2006;117:512-8.
14. Wenzel S, Szefler SJ. Managing severe asthma. J Allergy Clin Immunol 2006;117:508-11.
15. Miller MK, Johnson C, Miller DP, Deniz Y, Bleecker ER, Wenzel SE, for the TENOR Study Group. Severity assessment in asthma: an evolving concept. J Allergy Clin Immunol 2005;116:990-5.
16. Cabana MD, Rand CS, Becher OJ, Rubin HR. Reasons for pediatrician nonadherence with asthma guidelines. Arch Pediatr Adolesc Med 2001;155:1057-62.
17. Finkelstein JA, Lozano P, Shulruff R, Inui TS, Soumerai SB, Ng M, et al. Self-reported physician practices for children with asthma: are national guidelines followed? Pediatrics 2000;106:886-96.
18. The Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. N Engl J Med 2000;343:1054-63.
19. Simons FER, and the Canadian Beclomethasone Dipropionate-Salmeterol Xinafoate Study Group. A comparison of beclomethasone, salmeterol, and placebo in children with asthma. N Engl J Med 1997;337:1659-65.
20. Verberne AAPH, Frost C, Roorda RJ, van der Laag H, Kerrebijn KF, and the Dutch Paediatric Asthma Study Group. One year treatment with salmeterol compared with beclomethasone in children with asthma. Am J Respir Crit Care Med 1997;156:688-95.
21. Agertoft L, Pedersen S. Effect of long-term treatment with inhaled budesonide on adult height in children with asthma. N Engl J Med 2000;343:1064-9.
22. Agertoft L, Pedersen S. Effects of long-term treatment with inhaled corticosteroid on growth and pulmonary function in asthmatic children. Respir Med 1994;88:373-81.
23. Tantisira KG, Litonjua AA, Weiss ST, Fuhlbrigge AL, for the Childhood Asthma Management Program Research Group. Association of body mass with pulmonary function in the Childhood Asthma Management Program (CAMP). Thorax 2003;58:1036-41.
24. Von Mutius E, Schwartz J, Neas LM, Dockery D, Weiss ST. Relation of body mass index to asthma and atopy in children. The National Health and Nutrition Examination Study III. Thorax 2001;56:835-8.
25. Rodriguez MA, Winkleby MA, Ahn D, Sundquist J, Kraemer HC. Identification of population subgroups of children and adolescents with high asthma prevalence. Arch Pediatr Adolesc Med 2002;156:269-75.
26. Romieu I, Mannino DM, Redd SC, McGeehin MA. Dietary intake, physical activity, body mass index, and childhood asthma in the Third National Health and Nutrition Survey (NHANES III). Pediatr Pulmonol 2004;38:31-42.
27. Troiano RP, Flegal KM, Kuczmarski RJ, Campbell SM, Johnson CL. Overweight prevalence and trends for children and adolescents. The National Health and Nutrition Examination Surveys, 1963 to 1991. Arch Pediatr Adolesc Med 1995;149:1085-91.
28. Phelan PD, Robertson CF, Olinsky A. The Melbourne Asthma Study: 1964-1999. J Allergy Clin Immunol 2002;109:189-94.
29. Martinez FD. What have we learned from the Tucson Children's Respiratory Study? Paediatr Respir Rev 2002;3:193-7.
30. Covar RA, Spahn JD, Murphy JR, Szefler SJ. Progression of asthma measured by lung function in the Childhood Asthma Management Program. Am J Respir Crit Care Med 2004;170:234-41.
31. Sears MR, Greene JA, Willan AR, Wiecek EM, Taylor DR, Flannery EM, et al. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. N Engl J Med 2003;349:1414-22.
32. Rasmussen F, Taylor DR, Flannery EM, Cowan JO, Greene JM, Herbison P, et al. Risk factors for airway remodeling in asthma manifested by a low bronchodilator $FEV_1$/vital capacity ratio. A longitudinal population study from childhood to adulthood. Am J Respir Crit Care Med 2002;165:1480-8.
33. Jenkins HA, Cherniak R, Szefler SJ, Covar R, Gelfand EW, Spahn JD. A comparison of the clinical characteristics of children and adults with severe asthma. Chest 2003;124:1318-24.
34. Limb SL, Brown KC, Wood RA, Wise RA, Eggleston PA, Tonascia J, et al. Irreversible lung function in young adults with a history of childhood asthma. J Allergy Clin Immunol 2005;116:1213-9.
35. Osborne ML, Vollmer WM, Linton KLP, Buist S. Characteristics of patients with asthma within a large HMO. Am J Respir Crit Care Med 1998;157:123-8.
36. Taussig LM, Wright AL, Holberg CJ, Halonen M, Morgan WJ, Martinez FD. Tucson Children's Respiratory Study: 1980 to Present. J Allergy Clin Immunol 2003;111:661-75.
37. Sears MR, Burrows B, Flannery EM, Herbison GP, Hewitt CJ, Holdaway MD. Relation between airway responsiveness and serum IgE in children with asthma and in apparently normal children. N Engl J Med 1991;325:1067-71.
38. Debley JS, Redding GJ, Critchlow CW. Impact of adolescence and gender on asthma hospitalization: a population-based birth cohort study. Pediatr Pulmonol 2004;38:443-50.
39. Dockery DW, Berkey CS, Ware JH, Speizer FE, Ferris BG Jr. Distribution of forced vital capacity and forced expiratory volume in 1 second in children 6 to 11 years of age. Am Rev Respir Dis 1983;128:405-12.