

Letter to the Editor

The developmental trajectory of pediatric asthma in 3- to-10-year-olds

To the Editor:

Longitudinal studies have suggested that early childhood asthma follows different temporal trajectories.¹⁻³ Children with early childhood recurrent wheezing frequently have “symptom- or disease-free” periods, followed by “relapse” of disease, or do not have diagnosed asthma for the first time until later childhood. Some children or young adults develop asthma for the first time later in life. However, the childhood trajectory and patterns of disease development and remittance are not well figuratively characterized. The objective of this study was to describe and figuratively present the pattern of first asthma diagnosis and remittance and to characterize the episodic nature of the disease by gender and race/ethnicity.

We conducted a population-based cohort study of 13,256 children born in the state of Tennessee during a 2-year period from 1995 to 1996 and continuously enrolled in a state-based health insurance plan, Tennessee Medicaid, until age 10 years. Asthma was diagnosed in the parent cohort from which these data are derived, during age 3.5 to 5.5 years by using an established modified Healthcare Effectiveness Data and Information Set algorithm incorporating diagnostic coding and asthma-specific medication use.^{4,5} Children with an *International Classification of Diseases, 9th Revision, Clinical Modification* diagnosis code of 493 (asthma) or children with asthma-specific prescription use in a 365-day period were considered to have asthma as has been previously described in greater detail.⁶⁻⁸ Our asthma definition had been validated as both sensitive and specific.⁶ In addition, our algorithm used to diagnose childhood asthma is similar to that used by other US Medicaid systems, a modified algorithm of the Council of State and Territorial Epidemiologists, which has been shown to have 90% sensitivity, 95% specificity, 94% positive predictive value, and 92% negative predictive value in identifying childhood asthma.⁹ In addition, we excluded children with diagnoses of chronic diseases including chronic lung, heart, airway, immunodeficiency, or neurologic disease.^{4,6-7} We further defined asthma period prevalence in 2-year blocks between ages 7 to 8 years (from the 6th to the 8th birthday) and between ages 9 to 10 years (from the 8th to the 10th birthday) using the same criteria. As children were classified as either having or not having asthma in each of the 3 age periods, 8 unique asthma diagnosis patterns were possible. Demographic differences in age at first asthma diagnosis were analyzed using the χ^2 test. R-software version 2.11.1 (www.r-project.org) was used for analyses, and a 2-sided 5% significance level was considered for statistical inference. The protocol was approved by the Institutional Review Board of Vanderbilt University and reviewed and approved by the Tennessee Department of Health and Bureau of TennCare.

Among the cohort of 13,256 children, the median gestational age was 39.1 weeks (interquartile range, 38.1-40.1 weeks) and the median birth weight was 3175 g (interquartile range, 2807- 3544 g). Fifty-two percent of children were males, and 59% had at least 1 living sibling at birth. The children were from urban (53%), suburban (21%), and rural regions (27%) of the state.

Twenty-five percent (3352) of the 13,256 children met the asthma definition between ages 3.5 and 10 years, with 7 distinct

disease development patterns (Fig 1). We figuratively presented these 7 patterns by using a novel lasagna plot, as the 8th pattern would be that of children never diagnosed with asthma in any of the 3 time periods. The x-axis is the age of follow-up, with columns representing the 3 age periods when asthma was diagnosed. The y-axis is the proportion of asthmatic children, with height of the row representing the proportion of the children in each disease pattern among children who were ever diagnosed with asthma. Children with asthma were more likely to be white (57% vs 46% in children without asthma; $P < .001$), males (58% vs 50% in children without asthma; $P < .001$), have had at least 1 bronchiolitis medical encounter during infancy (26% vs 15% in children without asthma; $P < .001$), and have mothers who smoked during pregnancy (30% vs 26% in children without asthma; $P < .001$). The proportions of children with asthma during age 3.5 to 5.5, 7 to 8, and 9 to 10 years were 14%, 15%, and 16%, respectively, which, in turn, represented 54%, 58%, and 63% of the 3352 ever-diagnosed asthmatic children by age 10 years. Twenty-four percent of the ever-diagnosed children with asthma had asthma throughout the follow-up period, while 20% were not diagnosed with asthma until age 9 to 10 years (Fig 1).

The proportion of children with asthma was consistently greater in boys than in girls in each of the 7 distinct disease development patterns (Fig 1). We further classified asthmatic children into 3 mutually exclusive groups by their age at first asthma diagnosis: 60% of children who first developed asthma between age 3.5 and 5.5 years were males, while the proportion of males decreased to 58% and 53% at ages 7 to 8 and 9 to 10 years, respectively. The gender difference shift with increasing female proportion of asthmatic children over increasing age groups was significant ($P = .01$). Fifty-five percent of children who first developed asthma between age 3.5 and 5.5 years were white, while the proportion of white children increased to 61% and 60% at ages 7 to 8 and at 9 to 10 years, respectively. There was a significant ($P = .009$) race/ethnicity shift with increasing proportion of white asthmatic children with advancing age, and a decreasing proportion of black asthmatic children (36%, 32%, and 33%, respectively) as well as those of other race/ethnicity (9%, 7%, and 7% respectively) with advancing age.

In summary, over half of the children who were ever diagnosed with asthma by age 10 years had the diagnosis by age 5.5 years, among whom 46% still had an asthma diagnosis at age 10 years. Overall, 24% of children had an asthma diagnosis during the entire study period and 20% were not diagnosed with asthma for the first time until age 9 to 10 years. Asthmatic children experienced patterns of disease remittance and relapse over time. Male gender is a risk factor for childhood asthma development until at least age 10 years. However, our study demonstrates the decreasing importance of male gender in asthma development with advancing age of first asthma diagnosis. Studies relying on an asthma diagnosis at a single age or age range would miss children who develop disease later during childhood, or have disease remittance. Because we define children as having asthma using both physician diagnosis and medication use, misclassification from physicians' reluctance to label/code a child with asthma, particularly at younger ages, should be minimized. In addition, as asthma was defined consistently over 3 age periods, misclassification due to diagnostic accuracy would be minimized.

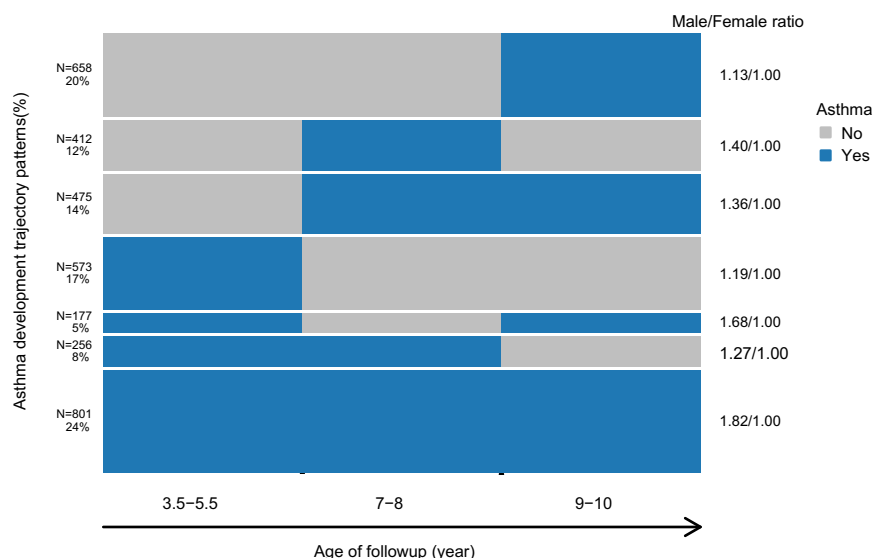


FIG 1. Developmental trajectory of asthma among 3352 children ever diagnosed with asthma before age 10 years. Children ever diagnosed with asthma are included in mutually exclusive disease development patterns. The x-axis represents the age periods during which asthma was diagnosed. The y-axis represents the proportion of children in each asthma diagnosis pattern; the row height represents the proportion of children with each disease pattern.

While this study is limited in utilizing physician diagnosis and medication utilization to determine asthma diagnosis and activity, it demonstrates the patterns of clinically evident disease and remittance in a population-based sample of children between ages 3.5 and 10 years.

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REFERENCES

- Butland BK, Strachan DP. Asthma onset and relapse in adult life: the British 1958 birth cohort study. *Ann Allergy Asthma Immunol* 2007;98:337-43.
- Stern DA, Morgan WJ, Halonen M, Wright AL, Martinez FD. Wheezing and bronchial hyper-responsiveness in early childhood as predictors of newly diagnosed asthma in early adulthood: a longitudinal birth-cohort study. *Lancet* 2008;372:1058-64.
- Roorda RJ, Gerritsen J, van Aalderen WM, Schouten JP, Veltman JC, Weiss ST, et al. Risk factors for the persistence of respiratory symptoms in childhood asthma. *Am Rev Respir Dis* 1993;148:1490-5.
- Wu P, Dupont WD, Griffin MR, Carroll KN, Mitchel EF, Gebretsadik T, et al. Evidence of a causal role of winter virus infection during infancy in early childhood asthma. *Am J Respir Crit Care Med* 2008;178:1123-9.
- Fuhlbrigge AL, Carey VJ, Finkelstein JA, Lozano P, Inui TS, Weiss ST, et al. Validity of the HEDIS criteria to identify children with persistent asthma and sustained high utilization. *Am J Manag Care* 2005;11:325-30.
- Hartert TV, Neuzil KM, Shintani AK, Mitchel EF Jr, Snowden MS, Wood LB, et al. Maternal morbidity and perinatal outcomes among pregnant women with respiratory hospitalizations during influenza season. *Am J Obstet Gynecol* 2003;189:1705-12.
- Hartert TV, Togias A, Mellen BG, Mitchel EF, Snowden MS, Griffin MR. Underutilization of controller and rescue medications among older adults with asthma requiring hospital care. *J Am Geriatr Soc* 2000;48:651-7.
- Hartert TV, Speroff T, Togias A, Mitchel EF Jr, Snowden MS, Dittus RS, et al. Risk factors for recurrent asthma hospital visits and death among a population of indigent older adults with asthma. *Ann Allergy Asthma Immunol* 2002;89:467-73.
- Wakefield DB, Cloutier MM. Modifications to HEDIS and CSTE algorithms improve case recognition of pediatric asthma. *Pediatr Pulmonol* 2006;41:962-71.

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