
Characterization of the duration from onset of asthma symptoms to asthma disease

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Background: Little is known about factors associated with progression of childhood asthma from onset of symptoms to index date determined by medical records.

Objective: To determine the duration between the onset of asthma symptoms to index date of asthma (ie, time when one met the criteria for asthma) and associated factors.

Methods: Study participants came from a sample of 839 healthy children, aged 5 to 12 years, who had participated in a previous study. Comprehensive medical record reviews were conducted to determine first documentation of asthma symptoms and index date of asthma. Factors were evaluated for an association with the duration from onset of asthma symptoms to index date of asthma.

Results: Of the study sample, 222 children met the criteria for asthma and had an available onset date of asthma symptoms. The median ages at onset of asthma symptoms and the index date were 5.6 and 7.6 years, respectively. The median duration between onset of asthma symptoms and index date was 2.9 months, and the mean was 17.2 months. There was a tendency for patients with a pet at home ($P = .047$), exercise-induced symptoms ($P = .04$), younger age at symptom onset ($P = .05$), and more severe asthma ($P = .05$) to have a shorter duration from onset of symptoms to index date.

Conclusions: The duration from onset of asthma symptoms to index date of asthma varies significantly depending on host and environmental factors. It does not necessarily correlate with commonly recognized risk factors for incidence or severity of asthma.

Ann Allergy Asthma Immunol. 2008;100:589–595.

INTRODUCTION

There are 2 important durations that precede the establishment of the diagnosis of asthma: (1) duration between onset of asthma symptoms and index date (when a patient first meets the criteria for diagnosis of asthma disease) and (2) duration between index date and the date of asthma diagnosis by a physician. We define the asthma index date as the earliest constellation of symptoms that meet predefined criteria for asthma regardless of whether a physician diagnosed the patient as having asthma. The first duration between onset of asthma symptoms and index date may be more closely related to disease of asthma and is important in understanding the natural history of asthma. The second duration, between index date of asthma and diagnosis of asthma, may be related to diagnosis of asthma and is important for determining access of asthmatic patients to therapeutic and preventive health services. The present study evaluated the duration between onset of asthma symptoms and index date of asthma

and the factors that influence progression from symptoms to index date.

Many previous studies^{1–7} on the natural history of asthma have evaluated epidemiologic and laboratory characteristics of asthmatic patients with regard to the progression of asthma after the time of diagnosis. Little is known about factors associated with progression of childhood asthma from onset of symptoms to index date.

Characterization of the duration between asthma symptom onset and index date will help clinicians better understand the clinical progress of various asthma symptoms among children who eventually develop asthma. This is an important concern because the diagnosis of asthma is often delayed, even after a child meets the criteria for asthma.^{8,9} Asthma is one of the most common chronic diseases in the United States, and it is critical that patients are identified and treated in a timely manner.¹⁰ It is important to provide an epidemiologic basis for future investigations as to why some people have varying rates of progression in development of asthma and what the immunologic mechanisms underlying the differential rate of progression to full-blown asthma are.

METHODS

Study Design and Setting

The study was a retrospective cohort study. Olmsted County, Minnesota, had a recorded population of 124,277 during the 2000 census. The population in Olmsted County was 90.3% white compared with 89.4% white in Minnesota and 75.1%

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Disclosures: Authors have nothing to disclose.

Funding Sources: The study was supported by a grant from Mayo Clinic.

Received for publication August 29, 2007; Received in revised form December 7, 2007; Accepted for publication December 11, 2007.

white in the United States. Characteristics of the Rochester, Minnesota, and Olmsted County populations were similar to those of the US white population, with the exception of more of the working population employed in the health care industry.^{11–13} Rochester is an excellent setting to conduct a retrospective cohort study because medical care is virtually self-contained within the community, with a unified medical record system for research.¹⁴ A recent study¹⁵ showed that 17.9% of children and adolescents in kindergarten through 12th grade in Olmsted County had ever had an asthma diagnosis.

Study Participants

The study protocol was approved by the institutional review boards at the Mayo Clinic and the Olmsted Medical Center. Study participants were obtained from a sample of 876 children who were enrolled in the Rochester Family Measles Project, which was a convenience sample recruited from the Rochester School District in Rochester. Briefly, the original study participants were healthy children aged 5 to 12 years when they were enrolled in the original study from schools in Rochester in 1993. Of the eligible original study cohort (n = 839) for our study, 50.7% were male and 93.8% were white. The mean and median ages at enrollment in the original study were 8.8 and 9.0 years, respectively. The demographic and clinical characteristics of the original participants were described in a previous study.¹⁶ In our study, between July 1, 2002, and June 31, 2006, the study participants were 14 years or older. Overall, the sex and ethnic distributions of the study cohort are similar to the demographic characteristics of the 1990 Olmsted County population, in which 51% of the residents were female and 96% were white.¹⁷

Ascertainment of Asthma Cases

We conducted comprehensive medical record reviews to determine the asthma status of study participants by applying predetermined criteria for asthma. Patients were considered to have definite asthma if a physician diagnosed asthma and/or if each of the following 3 conditions were present (they were considered to have probable asthma if only the first 2 conditions were present): (1) history of cough, dyspnea, and/or wheezing or history of cough and/or dyspnea plus wheezing on examination; (2) substantial variability in symptoms from time to time or periods of weeks or more when symptoms were absent; (3) 2 or more of the following: sleep disturbed by nocturnal cough and wheeze, nonsmoker (aged ≥ 14 years), nasal polyps, blood eosinophilia (eosinophil count $>300/\mu\text{L}$), positive wheal-and-flare skin test results or elevated serum IgE level, history of hay fever or infantile eczema or cough, dyspnea, and wheezing regularly on exposure to an antigen, pulmonary function test results showing one forced expiratory volume in 1 second (FEV_1) or forced vital capacity reading of less than 70% predicted and another with at least 20% improvement to an FEV_1 of more than 70% predicted or a methacholine challenge test result showing 20% or greater decrease in FEV_1 , and favorable

response to a bronchodilator. Patients were excluded from the study if any of the following conditions were present: pulmonary function test results that showed FEV_1 to be consistently less than 50% predicted or diminished diffusion capacity, tracheobronchial foreign body at or about the incidence date, hypogammaglobulinemia (IgG level < 2.0 mg/mL) or other immunodeficiency disorder, and wheezing occurring only in response to anesthesia or medications. The following diseases excluded the patient from study if they occurred before the incidence date: bullous emphysema or pulmonary fibrosis on chest radiograph, α_1 -antiprotease phenotype ZZ α_1 -antitrypsin, cystic fibrosis, and other major chest disease, such as juvenile kyphoscoliosis or bronchiectasis.

The criteria were developed during a previous study, and many previous studies on asthma epidemiology research have used these criteria to define asthma.^{12,16,18–21} We believe that our criteria for identifying and abstracting asthma cases should be suitable for this study. A previous study²² reported high interobserver reliability, and agreement rates among abstractors had a high degree of concordance.

Onset of Symptoms of Asthma

Asthma status, as previously defined, was determined first. Subsequently, the specific date of onset of symptoms of asthma was determined. The date of the onset of symptoms of asthma was defined as the date of the earliest symptoms of asthma in medical records. We considered symptoms of asthma to include wheezing (exercise or infection induced), spasmodic cough, bronchospasm (exercise or infection induced), shortness of breath or dyspnea, and chest tightness. An example of symptom onset of asthma would be a patient who had a wheezing episode associated with exposure to cat. The point at which a physician lists this episode as the first episode of wheezing ever was considered to be the date of symptom onset, but this subject has not yet met the criteria for asthma delineated previously. In this study, we excluded the asthmatic patients whose medical records did not have clear documentation about asthma symptoms in a way to determine the onset of asthma symptoms and type of symptoms.

Index Date of Asthma

The asthma index date was defined as the earliest constellation of symptoms, including cough, dyspnea, and/or wheezing, found in the medical record that met the previously described predetermined criteria for asthma.

We also developed specific criteria to estimate an approximate index date in patients in whom the onset of asthma was described in general terms. In this study, we consistently considered “a few years” to indicate 3 years before the date of the current physician encounter.

Independent Variables

The independent variables in this study included likelihood of asthma, sex, and race of the study patient; age at the onset of symptoms; maternal education level; severity of asthma according to the 2002 National Asthma Education and Preven-

tion Program guidelines; earliest symptoms of asthma; and number of viral and bacterial infections before the index date of asthma.

To determine the likelihood of asthma, we further classified the status of asthma when the criteria for asthma were met inside the medical record. Patients were classified as having definite or probable asthma.

Patients were categorized according to the severity of their asthma at the index date of asthma using the National Asthma Education and Prevention Program expert panel report²³ classifications: mild intermittent (2 days per week or 2 nights per month of asthma symptoms); mild persistent (>2 nights per month or >2 times per week but <1 episode per day of asthma symptoms); moderate persistent (daily daytime symptoms or 1 night per week of asthma symptoms); and severe persistent (continuous daytime symptoms or frequent nighttime symptoms).

The medicals records for each patient were examined to determine the highest level of education achieved by the patient's mother at enrollment in the original study.

The criteria for infectious diseases described later have been adopted and modified from a previous study.²⁴ Briefly, patients were considered to have respiratory or gastrointestinal tract illnesses (viral or bacterial) based on a physician-made diagnosis (ie, upper respiratory tract infection [URI], colds, common colds, viral infections or syndrome, bronchitis, bronchiolitis, croup, herpangina, gingivostomatitis, viral gastroenteritis, and rotavirus infection) and/or the specific criteria for the illnesses defined by the previous study. The number and dates of infections between birth and the asthma index date were abstracted.

Statistical Analysis

Factors were evaluated for an association with the duration between onset of asthma symptoms and index date of asthma using nonparametric methods given the skewed distribution of the durations. Continuously scaled factors were evaluated by estimating the Spearman rank correlation coefficient. Nominal and categorical factors (including the continuous factors categorized using the quartiles) were evaluated using the Kruskal-Wallis test. We also compared sociodemographic and clinical characteristics between the patients who were not included in this study because of the absence of symptom dates ($n = 54$) and those included in this study ($n = 222$) to evaluate transfer bias (ie, distorted sample because of exclusion of the patients). These included age, sex, ethnicity, asthma severity, pet ownership, and certainty of asthma. Continuously scaled factors were compared between the 2 groups using the Wilcoxon rank sum test. Nominal and categorical factors were evaluated using the χ^2 test or the Fisher exact test.

RESULTS

Study Cohort

Of the 876 children previously enrolled in the Rochester Family Measles Project, 839 had research authorization and

complete information for this study. Of the 839 children, 276 (32.9%) met the criteria for asthma before the age of 18 years, including 150 males (54.3%) and 259 whites (93.8%). However, at original study enrollment of the patients in the Rochester Family Measles Project, when the children were aged 5 to 13 years, the prevalence of asthma among the patients was 18.6% (156/839). Onset date of asthma symptoms and index date were available for 222 of the 276 children, and the results herein are presented based on these 222 children. Forty-five children (20.3%) met the criteria for asthma at the onset of asthma symptoms, and these were primarily based on physician diagnosis of asthma. The median ages at onset of asthma symptoms and index date were 5.6 and 7.6 years (mean [SD], 6.2 [4.7] and 7.6 [5.0] years), respectively. The median duration between onset of symptoms and index data was 2.9 months (interquartile range, 0.2–15.3 months), and the mean (SD) was 17.2 (32.2) months.

Table 1 summarizes the sociodemographic and clinical factors that were evaluated for an association with the duration between onset of asthma symptoms and index date. There was a tendency to have a shorter duration (ie, progress to asthma more rapidly) in patients with a younger age at symptom onset ($P = .05$), definite (vs probable) asthma ($P = .06$), nonwhite ethnicity ($P = .09$), more severe asthma ($P = .05$), exercise-induced wheezing or bronchospasm ($P = .04$), or pet present in the home ($P = .047$). Not associated with the duration between onset of asthma symptoms and index date of asthma were sex, birth weight, season of birth, maternal education at birth, family history of asthma or atopy, and frequency of viral or bacterial infections before the index date.

The patients who were excluded from this study because of the absence of symptom onset dates for asthma were slightly older in median age (8.3 vs 7.6 years; $P = .048$). Otherwise, there were no differences in sex ($P = .92$), ethnicity ($P = .69$), likelihood of asthma ($P = .28$), proportion of moderate or severe asthma ($P = .50$), and pet ownership ($P > .99$).

DISCUSSION

Although the natural history of asthma after diagnosis has been studied extensively, few studies evaluated the specific duration from onset of asthma symptoms to index date of asthma. Our results show that the progress from onset of asthma symptoms to index date is relatively rapid, from 2.9 (median) to 17.2 (mean) months. Considering many previous reports on underrecognition of asthma,^{9,25–28} the progress of asthma by parental or self-report alone might underestimate the rapidity of development of asthma. Progress from onset of asthma symptoms to asthma disease might be faster than what clinicians or parents realize.

According to our asthma criteria, 32.9% of our study cohort met the criteria for asthma, which seem to be high. However, Bisgaard and Szefer²⁹ found that 32% of 9,490 children, who were screened for respiratory symptoms in Europe and the United States, had recurrent clinically significant asthmalike symptoms (cough, wheezing, and/or breath-

Table 1. Factors Evaluated for an Association With the Duration Between Onset of Asthma Symptoms and Index Date

Factor	No. of patients	Duration between onset of asthma symptoms and index date, d				P value
		Median	Mean	SD	IQR range	
Age at onset of symptoms, y ^a						
<1.5	56	89.5	858.0	1426.7	21.5–1248.5	.09
1.5–<5.6	56	88.5	440.9	859.3	1.0–471.0	
5.6–<10.1	54	123.5	520.1	838.3	9.0–570.0	
≥10.1	56	49.0	276.5	497.7	0–343.0	
Sex						
Male	121	82.0	423.5	778.5	6.0–398.0	.49
Female	101	95.0	644.2	1175.1	7.0–589.0	
White race						
No	7	30.0	68.7	132.2	0–51.0	.09
Yes	209	95.0	528.9	1000.1	6.0–466.0	
Low birth weight (<2,500 g)						
No	166	102.0	577.0	1066.9	4.0–502.0	.93
Yes	6	77.0	297.3	431.8	16.0–535.0	
Season of birth						
Winter	72	97.0	585.4	1105.5	4.0–632.5	.93
Spring	61	108.0	519.3	927.0	7.0–466.0	
Summer	52	69.5	533.1	950.2	8.0–505.5	
Fall	37	82.0	399.0	886.0	10.0–321.0	
Maternal education at birth						
<High school	2	287.5	287.5	375.5	22.0–553.0	.60
High school	16	88.5	593.6	1040.2	0–563.5	
Some college	68	92.5	464.9	1050.5	11.0–365.0	
College degree	59	209.0	631.2	1024.8	9.0–712.0	
Family history of asthma						
No	110	79.5	551.3	1090.5	9.0–441.0	.89
Yes	105	108.0	499.2	856.3	6.0–553.0	
Family history of allergies						
No	92	79.5	401.2	788.5	0–411.0	.11
Yes	120	112.5	628.8	1109.4	15.0–662.5	
Likelihood of asthma						
Probable	96	140.0	616.1	1036.1	15.5–721.5	.06
Definite	126	73.0	453.6	938.4	1.0–379.0	
Maximal asthma severity during first evaluation						
Mild intermittent	119	144.0	633.5	1127.1	12.0–688.0	.05
Mild persistent	71	48.0	407.1	769.4	6.0–441.0	
Moderate or severe	13	9.0	319.5	904.3	1.0–117.0	
Earliest asthma symptoms						
URI-induced wheezing or bronchospasm	55	171.0	622.0	1007.3	27.0–743.0	.04
Exercise-induced wheezing or bronchospasm	14	41.0	221.6	531.3	0–167.0	
Spasmodic cough	41	47.0	590.2	1261.9	9.0–466.0	
Wheezing, bronchospasm, or other	38	386.5	814.1	1136.9	15.0–1018.0	
Presence of pet (cat or dog)						
No	13	117.0	444.1	520.2	48.0–688.0	.047
Yes	24	27.0	97.5	149.2	2.0–147.0	
No. of viral infections before index date per year†						
<0.37	56	47.5	283.4	555.7	0–323.5	.09
0.37–<0.90	55	128.0	577.4	992.1	6.0–570.0	
0.90–<1.63	55	185.5	781.6	1340.0	10.5–732.5	
≥1.63	56	78.0	452.9	830.1	21.0–456.0	
No. of bacterial infections before index date per year ^a						
<0.52	57	52.0	406.9	857.8	0–365.0	.49
0.52–<1.09	55	164.0	482.7	840.0	7.0–517.0	
1.09–<2.04	54	102.0	885.7	1413.5	4.5–1314.5	
≥2.04	56	99.0	317.2	517.2	15.0–385.0	

Table 1. Continued

Factor	No. of patients	Duration between onset of asthma symptoms and index date, d				P value
		Median	Mean	SD	IQR range	
No. of viral and bacterial infections before index date per year ^a						
<1.14	56	51.5	418.5	868.9	0–354.5	.39
1.14–<2.10	55	140.0	441.8	715.3	15.0–526.0	
2.10–<3.72	55	76.0	798.1	1411.5	1.0–742.0	
≥3.72	56	105.0	440.6	754.3	21.0–461.0	

Abbreviations: IQR, interquartile range; URI, upper respiratory tract infection.

^a The association between continuously scaled variables and duration was also assessed using the Spearman rank correlation: age at symptom onset, $r = -0.13$ ($P = .05$); number of viral infections before index date per year, $r = 0.09$ ($P = .19$); number of bacterial infections before index date per year, $r = 0.06$ ($P = .40$); and number of viral and bacterial infections before index date per year, $r = 0.07$ ($P = .32$).

lessness), 24% had persistent asthmalike symptoms, and only 22% had been diagnosed as having asthma. Thus, the relatively high prevalence of asthma in our study cohort may be reasonable by reflecting the proportion of children with recurrent asthmalike symptoms in our study population. In addition, Bisgaard and Szefer suggested that studies are needed to improve our ability to communicate the clinical symptoms reflecting early asthma, allowing research to move beyond wheeze for diagnosis. In this respect, our study results provide clinicians with a sense of the duration from the onset of asthma symptoms to the index date of asthma so that they are more cognizant in recognizing clinical presentations consistent with asthma in a timely fashion.

Our study results suggest that the progress from onset of asthma symptoms to index date of asthma depends on host and environmental factors. We found that different rates of the progress of asthma development depended on patients' initial asthma symptoms. For example, children who present with exercise-induced symptoms or spasmodic cough had median durations between symptom onset and index date of 41.0 and 47.0 days, respectively, whereas children who presented with viral URI-induced symptoms did not develop full-blown asthma until a median of 171.0 days later. Exercise-induced asthma occurs in up to 90% of asthmatic patients, and exercise can be a potent wheeze, cough, and asthma trigger.^{9,30,31} Considering activity and exercise are often aspects of the daily life of children, occurring on a more daily level than viral infections, it may not be surprising that children presenting with exercise-induced symptoms progress more rapidly to index date or reach physician diagnosis of asthma. Alternatively, because our study showed that more severe asthma correlates with more rapid progression, children with exercised-induced bronchospasm might be more likely to have more severe asthma.³ In contrast, children whose asthma is triggered only by viral URIs and who are symptom free between URIs were more likely to have mild intermittent asthma.³² Although exercise-induced bronchospasm or wheezing is more likely to reach the criteria for asthma compared with viral infection-induced bronchospasm, it needs to be determined if it is because of a differential

diagnostic tendency by physicians vs a different disease nature.

Presence of a pet (cat or dog) in the household was also associated with shorter duration between symptom onset and index date. Children growing up with a pet had a median time between symptoms and index date of only 27.0 days, one of the shortest durations of any of our studied variables. The relationship between pet exposure and atopy, sensitization, and asthma is controversial.^{4,33–39} Some studies have found that exposure to cats and dogs is associated with increased sensitization and asthma in childhood, whereas others have found it is not.^{4,33–36,38,40–42} However, patients with asthma have been frequently reported to have allergic triggers, such as pollens, molds, dust mites, cockroaches, or pets.^{37,43} It is possible that patients with pet exposure may progress more rapidly from onset of asthma symptoms to asthma disease because the household pet acts as a triggering factor for asthmalike symptoms or because physicians may be more likely to diagnose a patient with known household pets as having asthma.

Younger age at the onset of asthma symptoms approached significance in association with more rapid asthma development, although children older than 10 years also had rapid progress. Previous studies^{39,44} have found that children who are diagnosed as having asthma at a younger age tend to have more severe disease. The Tucson Children's Respiratory Study found that children with early-onset transient or persistent wheezing have worse lung function in adolescence than children with late-onset wheezing (starting at the age of 6 years).⁴⁵ Our study findings may suggest that the differential role of age of onset in relation to the progress of development of asthma depends on other factors.

Strengths of our study include ascertainment of asthma status and index date by predetermined well-established criteria for asthma. Because our study evaluated the duration between first asthma symptom documented in the medical record to the point at which the patient met criteria for asthma (index date), we did not have to rely on a subjective parent's report or self-report. In addition, we had epidemiologic ad-

vantages, including a self-contained health care environment with a unified medical records system.

There are also limitations to our study, including limitations inherent to the retrospective design. Of the 276 asthmatic children, the date of onset of asthma symptoms for 54 was not available in medical records, largely because they had moved into our study setting from other communities. Based on the comparison between the patients included in the study and those excluded, there were small differences in age. Other sociodemographic and clinical characteristics (sex, ethnicity, certainty of asthma, and pet ownership) were not different, ensuring that transfer bias is minimal or unlikely. Another limitation of our study is that the study cohort was 93.8% white and a relatively more educated population than the general population in the United States. Thus, the results need to be interpreted carefully in applying them to populations of other ethnicities and with different socioeconomic backgrounds. The results of a recent study⁴⁶ showed that socioeconomic status did not affect access and use of health care services when a child develops an acute illness in our study setting, reassuring that socioeconomic background is unlikely to affect our study results. The effects of race and ethnicity in progression of asthma symptoms are subject to further study. Finally, no medical and pharmacy claim data were available to our study, which might have been helpful for assessing the effect of treatment for asthma on the progress of asthma.

In conclusion, the duration from asthma symptom onset to asthma disease varies significantly depending on host and environmental factors. Clinicians and parents need to know the window period from onset of initial asthma symptoms to index date of asthma to be more cognizant of the nature of the progress of development of asthma. Factors associated with rapid progression toward development of asthma may not necessarily coincide with commonly recognized risk factors for the incidence or severity of asthma.

ACKNOWLEDGMENTS

We thank Titus Chang, MD, Martha Hartz, MD, Linda Lee, MD, Gregory Poland, MD, Ryan Smith, MD, Hirohito Kita, MD, and Rebecca Maki, RN, for their help and support for this project.

REFERENCES

1. Anderson HR, Bland JM, Patel S, Peckham C. The natural history of asthma in childhood. *J Epidemiol Community Health*. 1986;40:121–129.
2. Blair H. Natural history of childhood asthma: 20-year follow-up. *Arch Dis Child*. 1977;52:613–619.
3. Croner S, Kjellman NI. Natural history of bronchial asthma in childhood: a prospective study from birth up to 12–14 years of age. *Allergy*. 1992;47(pt 2):150–157.
4. Liu AH, Szeffler SJ. Advances in childhood asthma: hygiene hypothesis, natural history, and management. *J Allergy Clin Immunol*. 2003;111(suppl):S785–S792.
5. Martin AJ, McLennan LA, Landau LI, Phelan PD. The natural history of childhood asthma to adult life. *BMJ*. 1980;280:1397–1400.
6. Sears MR. Consequences of long-term inflammation: the natural history of asthma. *Clin Chest Med*. 2000;21:315–329.
7. Sears MR, Greene JM, Willan AR, et al. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. *N Engl J Med*. 2003;349:1414–1422.
8. Molis W, Kita H, Bagnieski S. Timeliness of diagnosis of asthma in children and associated factors. Paper presented at: Annual Meeting of American Academy of Allergy, Asthma, & Immunology; March 5, 2006; Miami, FL.
9. Jones A, Sykes A. The effect of symptom presentation on delay in asthma diagnosis in children in a general practice. *Respir Med*. 1990;84:139–142.
10. Masoli M, Fabian D, Holt S, Beasley R. The global burden of asthma: executive summary of the GINA Dissemination Committee report. *Allergy*. 2004;59:469–478.
11. Census Bureau: 1980 and 1990 Census of Population and Housing. Washington, DC: Census Bureau; 1983 and 1993. PHC80–2–305, US Dept of Commerce.
12. Yunginger JW, Reed CE, O'Connell EJ, Melton LJ III, O'Fallon WM, Silverstein MD. A community-based study of the epidemiology of asthma: incidence rates, 1964–1983. *Am Rev Respir Dis*. 1992;146:888–894.
13. Katusic SK, Colligan RC, Barbaresi WJ, Schaid DJ, Jacobsen SJ. Potential influence of migration bias in birth cohort studies. *Mayo Clin Proc*. 1998;73:1053–1061.
14. Kurland LT, Molgaard CA. The patient record in epidemiology. *Sci Am*. 1981;245:54–63.
15. Yawn BP, Wollan P, Kurland M, Scanlon P. A longitudinal study of the prevalence of asthma in a community population of school-age children. *J Pediatr*. 2002;140:576–581.
16. Juhn YJ, Kita H, Lee LA, et al. Childhood asthma and measles vaccine response. *Ann Allergy Asthma Immunol*. 2006;97:469–476.
17. 1980 and 1990 Census of Population and Housing. Washington, DC: Census Bureau; 1983 and 1993. Publication PHC80–2–305.
18. Silverstein M, Reed CE, O'Connell EJ, Melton L, O'Fallon W, Yunginger JW. Long-term survival of a cohort of community residents with asthma. *N Engl J Med*. 1994;331:1537–1541.
19. Hunt W, Silverstein M, Reed CE, O'Connell EJ, O'Fallon W, Yunginger JW. Accuracy of the death certificate in a population-based study of asthmatic patients. *JAMA*. 1993;269:1947–1952.
20. Juhn Y, Weaver A, Katusic S, Yunginger J. Mode of delivery at birth and development of asthma: a population-based cohort study. *J Allergy Clin Immunol*. 2005;116:510–516.
21. Yawn BP, Yunginger JW, Wollan PC, Reed CE, Silverstein MD, Harris AG. Allergic rhinitis in Rochester, Minnesota residents with asthma: frequency and impact on health care charges. *J Allergy Clin Immunol*. 1999;103(pt 1):54–59.
22. Beard M, Yunginger JW, Reed CE, O'Connell EJ, Silverstein MD. Interobserver variability in medical record review: an epidemiological study of asthma. *J Clin Epidemiol*. 1992;45:1013–1020.
23. NAEP Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma—Update on Selected Topics 2002. Bethesda, MD: National Institutes of Health; 2002. NIH publication 97–4051.
24. Lee GM, Salomon JA, Friedman JF, et al. Illness transmission in the home: a possible role for alcohol-based hand gels. *Pediatrics*. 2005;115:852–860.
25. Renwick DS, Connolly MJ. Prevalence and treatment of chronic airways obstruction in adults over the age of 45. *Thorax*. 1996;51:164–168.
26. Speight ANP, Lee DA, Hey EN. Underdiagnosis and undertreatment of asthma in childhood. *BMJ*. 1983;286:1253–1256.
27. Plaut TF, Hershey JE, Bendich DM. Is asthma misdiagnosed? *J Asthma*. 1986;23:23–24.
28. Yeatts K, Davis KJ, Sotir M, Herget C, Shy C. Who gets diagnosed with asthma? frequent wheeze among adolescents with and without a diagnosis of asthma. *Pediatrics*. 2003;111(pt 1):1046–1054.
29. Bisgaard H, Szeffler S. Prevalence of asthma-like symptoms in young children. *Pediatr Pulmonol*. 2007;42:723–728.
30. Randolph C. Exercise-induced asthma: update on pathophysiology, clinical diagnosis, and treatment. *Curr Probl Pediatr*. 1997;27:53–77.
31. Milgrom H, Taussig LM. Keeping children with exercise-induced

-
- asthma active. *Pediatrics*. 1999;104:e38. Available at: <http://pediatrics.aappublications.org/cgi/content/full/104/3/e38>. Accessed March 1, 2007.
32. Guill MF. Asthma update: epidemiology and pathophysiology. *Pediatr Rev*. 2004;25:299–305.
33. Perzanowski MS, Ronmark E, Platts-Mills TA, Lundback B. Effect of cat and dog ownership on sensitization and development of asthma among preteenage children. *Am J Respir Crit Care Med*. 2002;166:696–702.
34. Apelberg BJ, Aoki Y, Jaakkola JJ. Systematic review: exposure to pets and risk of asthma and asthma-like symptoms. *J Allergy Clin Immunol*. 2001;107:455–460.
35. Almqvist C, Egmar AC, Hedlin G, et al. Direct and indirect exposure to pets: risk of sensitization and asthma at 4 years in a birth cohort. *Clin Exp Allergy*. 2003;33:1190–1197.
36. Lindfors A, Wickman M, Hedlin G, Pershagen G, Rietz H, Nordvall SL. Indoor environmental risk factors in young asthmatics: a case-control study. *Arch Dis Child*. 1995;73:408–412.
37. Lindfors A, van Hage-Hamsten M, Rietz H, Wickman M, Nordvall SL. Influence of interaction of environmental risk factors and sensitization in young asthmatic children. *J Allergy Clin Immunol*. 1999;104(pt 1):755–762.
38. Remes ST, Castro-Rodriguez JA, Holberg CJ, Martinez FD, Wright AL. Dog exposure in infancy decreases the subsequent risk of frequent wheeze but not of atopy. *J Allergy Clin Immunol*. 2001;108:509–515.
39. Ratageri VH, Kabra SK, Dwivedi SN, Seth V. Factors associated with severe asthma. *Indian Pediatr*. 2000;37:1072–1082.
40. Nafstad P, Magnus P, Gaarder P, Jaakkola J. Exposure to pets and atopy-related diseases in the first 4 years of life. *Allergy*. 2001;56:307–312.
41. Platts-Mills T, Vaughan J, Squillace S, Woodfolk J, Sporik R. Sensitization, asthma, and a modified Th2 response in children exposed to cat allergen: a population-based cross-sectional study. *Lancet*. 2001;357:752–756.
42. Celedon JC, Litonjua AA, Ryan L, Platts-Mills T, Weiss ST, Gold DR. Exposure to cat allergen, maternal history of asthma, and wheezing in first 5 years of life. *Lancet*. 2002;360:781–782.
43. Mathur SK, Busse WW. Asthma: diagnosis and management. *Med Clin North Am*. 2006;90:39–60.
44. Higgins PS, Wakefield D, Cloutier MM. Risk factors for asthma and asthma severity in nonurban children in Connecticut. *Chest*. 2005;128:3846–3853.
45. Morgan WJ, Stern DA, Sherrill DL, et al. Outcome of asthma and wheezing in the first 6 years of life: follow-up through adolescence. *Am J Respir Crit Care Med*. 2005;172:1253–1258.
46. Juhn YJ, Johnson SK, Hashikawa AH, et al. The potential biases in studying the relationship between asthma and microbial infection. *J Asthma*. 2007;44:827–832.
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