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Age-related differences in asthma outcomes in the United States, 1988–2006

Chu-Lin Tsai, MD, ScD^{*}; George L. Delclos, MD, PhD^{*}; Jamie S. Huang, MPH^{*}; Nicola A. Hanania, MD, MS[†]; and Carlos A. Camargo, Jr, MD, DrPH[‡]

^{*} Division of Epidemiology, Human Genetics and Environmental Sciences, The University of Texas School of Public Health, Houston, Texas

[†] Section of Pulmonary and Critical Care Medicine, Department of Medicine, Baylor College of Medicine, Houston, Texas

[‡] Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

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ABSTRACT

Background: Relatively little is known about the effect of age on asthma outcomes in adults, particularly at a national level.

Objective: To investigate age-related differences in asthma outcomes in a nationally representative, longitudinal study.

Methods: We analyzed data from the Third National Health and Nutrition Examination Survey (1988–1994) with linked mortality files through 2006. Adults with physician-diagnosed asthma were identified and were divided into 2 age groups: younger adults (17–54 years of age) and older adults (55 years or older). The outcome measures were both cross-sectional (health care use, comorbidity, and lung function) and longitudinal (all-cause mortality).

Results: There were an estimated 9,566,000 adults with current asthma. Of these, 73% were younger adults and 27% older adults. Compared with younger adults, older adults had more hospitalizations in the past year, more comorbidities, and poorer lung function (eg, lower forced expiratory volume in 1 second) ($P < .05$ for all). During a median follow-up of 15 years, significant baseline predictors of higher all-cause mortality included older age (≥ 55 vs < 55 years old: adjusted hazard ratio [HR], 6.77; 95% confidence interval [CI], 3.15–14.54), poor health status (fair and poor vs excellent health status: adjusted HR, 10.07; 95% CI, 3.75–27.01), and vitamin D deficiency (vitamin D level < 30 vs ≥ 50 nmol/L: adjusted HR, 2.19; 95% CI, 1.05–4.58), whereas Mexican American ethnicity (adjusted HR, 0.31; 95% CI, 0.14–0.65) was associated with lower mortality. Controlling for age, asthma was not associated with increased all-cause mortality (adjusted HR, 1.28; 95% CI, 0.99–1.65).

Conclusion: Older adults with asthma have a substantial burden of morbidity and increased mortality. The ethnic differences in asthma mortality and the vitamin D–mortality link merit further investigation.

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Introduction

Asthma is an important public health problem in the United States and affects individuals across the entire age spectrum, from infants to older adults. Asthma in older adults is an emerging research issue because older age groups constitute the fastest growing segment of the US population.¹ Individuals 65 years or older are projected to increase from approximately 35 million in 2000 to more than 71 million by 2030.²

Despite this widely heralded demographic change, there remains a paucity of research on asthma in older adults. Recent reviews^{3,4} identified only one longitudinal epidemiologic study⁵ that addressed the natural history of asthma in older adults. That

study used a general population (nonasthma) as the comparator, as opposed to younger patients with asthma, so the effect of age could not be evaluated.⁵ A limited number of cross-sectional studies compared younger vs older patients with asthma,^{6,7} but none of them are based on a well-defined cohort with long-term follow-up.

Given these knowledge gaps in the literature, the objective of the present analysis was to investigate age-related differences in asthma outcomes in a nationally representative, population-based, longitudinal study. We hypothesized that older individuals with asthma would have higher morbidity (more health care use, more comorbidity, and worse lung function) at baseline and higher mortality during follow-up compared with younger adults.

Methods

Study Design and Setting

The National Center for Health Statistics conducted the Third National Health and Nutrition Examination Survey (NHANES III)

Reprints: Chu-Lin Tsai, MD, ScD, Division of Epidemiology, Human Genetics and Environmental Sciences, The University of Texas School of Public Health, 1200 Herman Pressler, Ste W610, Houston, TX 77030; E-mail: cltsai@post.harvard.edu.

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between 1988 and 1994, followed by the mortality assessment from enrollment through December 31, 2006. We performed a secondary analysis of this nationally representative, prospective cohort. The NHANES III used a stratified, multistage, clustered probability sample to represent the civilian noninstitutionalized population in the United States. Four-stage sampling was performed at different levels as follows: 81 primary sample units being mostly counties, the secondary stage being small area segments (city or blocks), the third stage being households and certain group quarters (eg, dormitories), and the final stage being selection of eligible members within a household. Once chosen, study participants were interviewed and underwent a comprehensive physical examination, including spirometric measurements, either in the household or a mobile examination center. Blood samples were also collected from participants for laboratory tests. Full details of the survey methods, including sampling, interview, examination, and laboratory measurements, have been described elsewhere.⁸ We received a waiver for this analysis from our institutional review board.

Study Population

From the larger data set of 33,994 participants of all ages, we included participants 17 years and older with physician-diagnosed current asthma. Individuals 17 years and older were considered adults according to the NHANES III definition.⁸ Current asthma was defined as an affirmative response to both questions, “Has a doctor ever told you that you had asthma?” and “Do you still have asthma?” Thus, 841 participants, who represented 9,566,000 adults with current asthma, were included in the final analysis.

Age

The primary exposure variable was age. For the purposes of characterizing the sample, individuals were categorized into 2 age groups (younger and older). Because most of the participants with current asthma tended to be young, we selected a slightly younger age cutoff (55 years, 75th percentile of the sample). As such, we considered individuals with age older than this cutoff as “older adults with asthma” as opposed to “elderly asthma” (ie, 65 years and older).

Information on Variables

The baseline demographic characteristics included age, sex, and self-reported race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, or other). Poverty was defined as a family's income less than the poverty threshold of a family of the same size. Current smoking was defined as having smoked at least 100 cigarettes in one's life and still smoking, former smoking as having smoked at least 100 cigarettes in one's life but not currently smoking, and nonsmoking as having smoked fewer than 100 cigarettes in one's life. Individuals with asthma were asked their age when a physician first told them that they had asthma. A number of comorbidities at baseline were assessed, such as physician-diagnosed diabetes, hypertension, heart failure, stroke, and cancer. Health care use was defined as the responses to the following questions: “During the past 12 months, how many times did you stay in a hospital overnight or longer?” and “During the past 12 months, how many times did you see a medical doctor or assistant?” Prescription medicine use in the past month was collected during the interview and, for each medication reported, the name of the product and the reason for using the medication were recorded. An interviewer also recorded the exact product name from the medication container label. We identified asthma medications using the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* code 493 associated with the drug.

After a physical examination, the examining physician rated an individual's health status on a 5-point scale of excellent, very good, good, fair, or poor. From the examination data, we calculated body

mass index as weight in kilograms divided by the square of height in meters. Bone mineral density (BMD) was measured by dual-energy x-ray absorptiometry. Osteoporosis status was defined as either femur neck BMD less than 0.56 g/cm² or total hip BMD less than 0.64 g/cm², according to the osteoporosis cutoffs reported in the NHANES III bone density study.⁹ Participants' blood samples were collected during the medical examination and were stored at –70°C until analysis. Serum 25-hydroxyvitamin D (25[OH]D) levels were measured by a radioimmunoassay kit (DiaSorin, Stillwater, Minnesota) at the National Center for Environmental Health (Atlanta, Georgia). To avoid potential inclement weather, the NHANES preferentially collected data in northern latitudes during summer and in southern latitudes in winter.¹⁰ The link of season and latitude in the NHANES controls for the variation in 25(OH)D levels by these 2 factors to some extent but limits the opportunity to study the independent effect of each factor. Because of this design, we created a dichotomous variable as “summer/higher latitude” and “winter/lower latitude” based on the previous literature.^{11,12} Serum 25(OH)D levels were categorized according to the Institute of Medicine report: sufficient in vitamin D (≥ 50 nmol/L), at risk of vitamin D inadequacy (30–49 nmol/L), and at risk of vitamin D deficiency (< 30 nmol/L).¹³

Pulmonary function tests were performed based on the 1987 American Thoracic Society recommendations.¹⁴ We defined airflow limitation as a forced expiratory volume in 1 second (FEV₁)/forced vital capacity (FVC) ratio of less than 0.7. Individuals with airflow limitation were considered to have chronic obstructive pulmonary disease (COPD).¹⁵ We used published predicted equations^{16,17} to estimate the predicted lung function and further classified participants with airflow limitation into mild (FEV₁, $\geq 80\%$ predicted), moderate (FEV₁, 50– $< 80\%$ predicted), and severe (FEV₁, $< 50\%$ predicted) COPD.¹⁵

Outcome Measures

The outcome measures were both cross-sectional (health care use, comorbidity, and lung function) and longitudinal (all-cause mortality). Mortality outcomes were determined by probabilistic matching between NHANES III and National Death Index data.¹⁸ Participants were classified as “dead” if matched or as “presumed alive” without a match. The underlying cause of death was coded using the *International Classification of Diseases, Tenth Revision (ICD-10)*. We attempted to analyze cause-specific mortality, but the number of observations was too small for meaningful subgroup analyses; thus, all-cause mortality was used as the primary outcome.

Statistical Analysis

Summary statistics are presented as proportions (with 95% confidence intervals [CIs]), means (with SDs), or medians (with interquartile ranges). Bivariate associations were examined using the *t* tests, Mann-Whitney tests, and χ^2 tests, as appropriate.

Survival time was calculated from the examination date through the date of death for those who died during the follow-up or through December 31, 2006, for those who were censored. Kaplan-Meier survival curves were plotted, and the log-rank test was used to test the equality of survivor functions between groups. Cox proportional hazards models were used to assess the factors associated with all-cause mortality. The proportional hazards assumption was confirmed by examining log-log plots of survival curves. Model variables were selected *a priori*¹⁹ or based on review of the medical literature.^{5,7,20–24} Model variables included age, sex, race, poverty, smoking status, duration of asthma, self-reported physical activity, physician's impression of health status, body mass index, serum 25(OH)D level, airflow limitation, and season and latitude. Statistical interactions between age categories and other covariates were tested by interaction terms to the

multivariable models. To better characterize the potential nonlinear relationship between age and all-cause mortality, we fit a multivariable restricted cubic spline model, and adjusted probabilities of mortality were plotted against the entire age spectrum.²⁵ In all analyses, appropriate sample weights were used to account for the complex sampling design and nonresponse using Stata SVY commands with the Taylor series linearization method. All hazard ratios (HRs) are presented with 95% CIs. All analyses were performed using Stata statistical software, version 12.0 (StataCorp, College Station, Texas). All *P* values are 2-sided, with *P* < .05 considered statistically significant.

To minimize the potential misclassification of asthma and COPD, we performed a sensitivity analysis by excluding all cases with

evidence of airflow limitation on spirometry and then repeating the main analysis for morbidity and all-cause mortality. We also performed an additional analysis to explore the “asthma effect” on survival (ie, the effect of asthma on survival independent of aging and other factors) in the adult population, controlling for the same set of potential confounders as in the aforementioned multivariable analysis.

Results

Baseline Characteristics

After the weighting procedures, there were an estimated 9,566,000 adults with current asthma. Table 1 lists the baseline

Table 1
Baseline characteristics of US adults with asthma, according to age group

Characteristic	Weighted sample size in thousands	Age 17–54 years (n = 7,005,000)	Weighted sample size in thousands	Age ≥55 years (n = 2,561,000)	<i>P</i> value
Demographics					
Age, mean (SE), y		34 (0.6)		67 (0.6)	
Female, %	4,270	61	1,396	55	.27
Race/ethnicity, %					
Non-Hispanic white	5,311	76	2,039	80	.62
Non-Hispanic black	933	13	280	11	
Mexican American	251	4	58	2	
Other	510	7	184	7	
Education, mean (SE), y		12.4 (0.17)		10.5 (0.26)	<.001
Metropolitan area, %	3,610	52	1,027	40	.06
Census region, %					
Northeast	1,753	25	495	19	.57
Midwest	1,499	21	661	26	
South	2,417	34	842	33	
West	1,336	19	563	22	
Access to care and use					
Poverty, %	1,274	19	406	17	.59
Insurance, %	5,916	87	2,404	98	<.001
Go to a particular place for health care, %	5,824	83	2,398	94	<.001
Have a primary care physician, %	4,986	86	2,135	89	.46
No. of all medications in the past month, mean (SE), times		2.5 (0.15)	4.4 (0.28)	—	<.001
No. of hospitalizations in the past year, mean (SE)		0.22 (0.03)		0.43 (0.08)	.02
No. of physician's office visits in the past year, mean (SE)		6.6 (0.71)		6.5 (0.50)	.99
Asthma-related factors and respiratory conditions					
Secondhand smoke at home, %	2,932	42	865	34	.10
Smoking status, %					
Never	3,104	44	806	31	<.001
Former	1,427	20	1,111	43	
Current	2,474	35	644	25	
Telephone use per week, mean (SE), No.		11 (0.72)		11 (1.32)	.65
Age of asthma diagnosis, mean (SE), y		17 (0.78)		45 (1.38)	<.001
Duration of asthma, mean (SE), y		18 (0.78)		22 (1.38)	.01
Shortness of breath when hurrying or walking up a hill, %	3,441	49	1,831	72	<.001
Stuffy, itchy, or runny nose in the past year, %	5,387	77	1,818	71	.18
Ever give up or avoid a pet because of allergies, %	1,862	27	277	11	<.001
Had cold or flu in the past year, %	5,671	81	1,631	64	<.001
Had sinusitis or sinus problems in the past year, %	3,776	54	1,350	53	.82
Had pneumonia in the past year, %	645	9	316	12	.35
Asthma severity and control					
Wheezing or whistling in the chest in the past year, %	5,176	74	1,909	75	.84
No. of wheezes in the past year, mean (SE), times		43 (9.01)	61 (15.56)		.26
Use 2 or more asthma medications in the past month, %	989	14	527	21	.09
No. of hospitalizations for episodes of wheezing or whistling in the past year, mean (SE)		0.13 (0.04)		0.18 (0.06)	.49
No. of physician's office visits or emergency department visits for episodes of wheezing or whistling in the past year, mean (SE)		1.26 (0.20)		1.27 (0.21)	.97
Physician-diagnosed comorbidities, %					
Arthritis	1,305	19	1,558	61	<.001
Congestive heart failure	61	1	518	20	<.001
Stroke	113	2	165	6	.01
Chronic bronchitis	2,032	29	1,183	46	.002
Emphysema	194	3	737	29	<.001
Hay fever	2,784	40	926	36	.57
Cancer, except skin cancer	306	4	262	10	.06
Diabetes	248	4	379	15	<.001
Hypertension	1,544	22	1,161	45	<.001
Myocardial infarction	141	2	500	20	<.001

patient characteristics of the weighted cohort by age group. Older adults comprised 27% of the asthma cohort. Younger and older adults with asthma did not differ by sex, race/ethnicity, poverty, metropolitan area, or region. Compared with younger adults, older adults with asthma were less educated, more likely to have insurance, more likely to go to a particular place for health care, used more medications, and had a slightly higher number of all-cause hospitalizations in the past year. With respect to asthma-related factors, older adults with asthma were less likely to be current smokers, were diagnosed as having asthma later in their lifetime, and had a longer duration of asthma. Regarding respiratory conditions, older adults with asthma were more likely to experience shortness of breath when hurrying, less likely to give up a pet due to allergies, and had less cold or flu in the past year. The frequency of wheezing and asthma-related medication use, hospitalizations, and ambulatory care visits were similar across the groups. With regard to comorbidities, in general, older adults with asthma had more comorbidities, with the exceptions of hay fever and cancer.

Table 2 gives the baseline health status and examination results of the cohort by age group. Compared with younger adults, older adults with asthma jogged or walked less, were found to have more locomotion abnormalities during the physical examination, and were more likely to be rated poorly on health status by examining physicians. Older adults with asthma also were more likely to be overweight or obese and were more likely to have osteoporosis documented by BMD. With respect to blood biomarkers, older adults with asthma had lower serum levels of cotinine, 25(OH)D, and C-reactive protein. With regard to lung function, older adults with asthma had a much lower FEV₁, FEV₁ percent predicted, and more severe airflow limitation compared with younger adults.

Follow-up

During a median follow-up of 15 years, there were 252 deaths (30%) in the unweighted cohort. Most deaths were related to cardiovascular disease (*n* = 87 [35%]), followed by respiratory disease (*n* = 58 [23%]) and cancer (*n* = 49 [20%]). Asthma was documented as the underlying cause of death in only 10 individuals

(4%). The multivariable associations between baseline characteristics and all-cause mortality are presented in Table 3. After adjusting for 11 potential confounders, significant baseline predictors of higher mortality included older age (≥ 55 vs < 55 years old: adjusted HR, 6.77; 95% CI, 3.15–14.54), poor health status (fair and poor vs excellent health status: adjusted HR, 10.07; 95% CI, 3.75–27.01), and vitamin D deficiency (vitamin D level < 30 vs ≥ 50 nmol/L: adjusted HR, 2.19; 95% CI, 1.05–4.58). When treating age as a continuous variable (eFig 1), there was an exponential increase in mortality beyond 55 years of age, adjusting for other confounders. Figure 1 demonstrates a sustained divergence of mortality risk between the vitamin D deficiency group (< 30 nmol/L) and other categories after approximately 4 years of follow-up. By contrast, female sex (adjusted HR, 0.64; 95% CI, 0.42–0.996) and Mexican American ethnicity (adjusted HR, 0.31; 95% CI, 0.14–0.65) were significantly associated with lower mortality in adults with asthma. We did not find statistically significant interactions in the multivariable analysis.

In the sensitivity analysis, by excluding 278 cases (33%) with airflow limitation, older adults with asthma still had significantly higher numbers of hospitalizations and comorbidities (except for cancer, hay fever, and stroke). For the multivariable model of mortality, all the significant associations became even stronger (away from the null), except that female sex was no longer significantly associated with lower mortality (adjusted HR, 0.59; 95% CI, 0.28–1.22).

We performed an additional analysis to assess the independent effect of asthma on survival. The results suggested asthma per se did not increase mortality risk (adjusted HR, 1.28; 95% CI, 0.99–1.65), after adjusting for age and other potential confounders. Older age remained a strong risk factor for mortality (adjusted HR, 9.64; 95% CI, 7.75–12.00).

Discussion

In this nationally representative sample of adults with asthma, we found significant baseline differences by age for asthma outcomes (ie, older asthma adults had more hospitalizations in the past year, more comorbidities, and poorer lung function compared

Table 2
Baseline health status and examinations of US adults with asthma, according to age group

Variable	Weighted sample size in thousands	Age 17–54 years (<i>n</i> = 7,005,000)	Weighted sample size in thousands	Age ≥ 55 years (<i>n</i> = 2,561,000)	<i>P</i> value
Self-reported level of physical activity (same or more active than others of same age/sex), %	4,597	67	1,664	68	.72
Jogged or ran in the past month, %	852	12	16	1	<.001
Walked a mile in the past month, mean (SE), No.		5.8 (0.6)		3.9 (0.6)	.01
Locomotion abnormalities during the examination (eg, limp or shuffle), %	190	3	262	11	<.001
Physician's impression of health status, %					
Excellent	3,219	47	385	16	<.001
Very good	1,873	28	488	20	
Good	1,274	19	803	33	
Fair	323	5	513	21	
Poor	112	2	279	11	
Body mass index, %					
<18.5	351	5	64	3	<.001
18.5–24.9	3,081	44	688	27	
25–29.9	1,511	22	906	36	
≥ 30	2,062	29	890	35	
Osteoporosis by DXA, %	96	2	446	19	<.001
Serum cotinine, mean (SE), ng/mL		95 (8.94)		75 (9.76)	.11
Serum 25-hydroxyvitamin D, mean (SE), nmol/L		73 (1.87)		66 (2.06)	.01
Serum C-reactive protein, mean (SE), mg/dL		0.43 (0.03)		0.60 (0.05)	.003
Peak expiratory flow, mean (SE), L/min		413 (7.9)		269 (13.1)	<.001
FEV ₁ , mean (SE), mL		3,036 (53)		1,868 (90)	<.001
FEV ₁ % predicted, mean (SE)		87 (0.97)		73 (2.52)	<.001
FEV ₁ /FVC < 0.7 , %	1,699	24	1,354	53	<.001

Abbreviations: DXA, dual energy x-ray absorptiometry; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity.

Table 3
Multivariable analysis of predictors of asthma mortality

Variable	Adjusted HR (95% CI)	P value
Age ≥ 55 y (vs age < 55 y)	6.77 (3.15–14.54)	<.001
Female	0.64 (0.42–0.996)	.048
Race/ethnicity		
Non-Hispanic white	1.00 (Reference)	
Non-Hispanic black	0.62 (0.36–1.09)	.10
Mexican American	0.31 (0.14–0.65)	.003
Other	0.63 (0.14–2.79)	.53
Poverty	1.57 (0.83–2.98)	.16
Smoking status		
Never	1.00 (Reference)	
Former	1.13 (0.62–2.06)	.69
Current	1.54 (0.84–2.81)	.16
Duration of asthma, per 10-year increase	1.004 (0.88–1.14)	.95
Self-reported level of physical activity (same or more active than others of same age/sex)	1.00 (0.56–1.77)	>.99
Physician's impression of health status		
Excellent	1.00 (Reference)	
Very good	2.57 (0.90–7.33)	.08
Good	3.97 (1.60–9.85)	.004
Fair and Poor	10.07 (3.75–27.01)	<.001
Body mass index		
<18.5	1.39 (0.31–6.24)	.66
18.5–24.9	1.00 (Reference)	
25–29.9	1.05 (0.47–2.33)	.91
≥ 30	0.72 (0.38–1.39)	.33
Serum 25-hydroxyvitamin D level		
Sufficient (≥ 50 nmol/L)	1.00 (Reference)	
Inadequate (30–49 nmol/L)	1.06 (0.65–1.75)	.81
Deficient (<30 nmol/L)	2.19 (1.05–4.58)	.04
Airflow limitation (FEV ₁ /FVC <0.7)	0.92 (0.46–1.84)	.81
Summer/higher latitude (vs winter/lower latitude)	1.39 (0.92–2.10)	.11

Abbreviations: CI, confidence interval; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; HR, hazard ratio.

with younger adults). Longitudinally, older adults with asthma had a 7-fold increased mortality compared with younger adults, independent of many potential confounders. We also found vitamin D deficiency and Mexican American race/ethnicity potentially played an important role in asthma mortality.

Our analysis estimated that more than 2 million older American adults had asthma at baseline (1988–1994), an estimate that is consistent with that from the National Health Interview Survey.²⁶ Given that older age groups are growing faster than the total US population,¹ using the present estimate, the projected number of older asthma patients will reach approximately 4 million by 2030.²

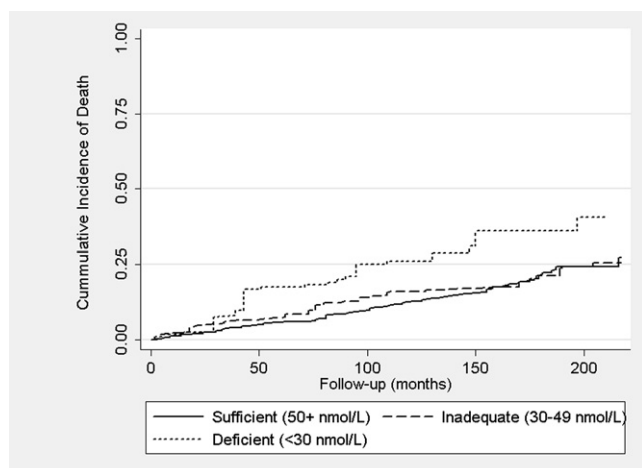


Figure 1. Kaplan-Meier survival curves for all-cause mortality by baseline serum 25-hydroxyvitamin D levels.

Our analysis found that within the asthma population, older adults have more morbidities and increased mortality than younger adults. An additional analysis suggests that, in the general population, the major risk factor for mortality was still older age, rather than asthma per se, which is consistent with most prior studies.^{5,21} With the aging of the US population, the societal burden of asthma can be expected to increase in the coming years.

Among the few clinical studies that compared younger vs older asthma,^{6,7} older asthma patients have been found to have greater respiratory symptoms, worse asthma control, and more comorbidities compared with their younger counterparts. They also are less educated and less likely to receive an action plan for asthma exacerbations.⁶ When older adults with asthma develop acute exacerbations, they may be less aware of asthma symptoms,²⁷ leading to their later presentation for care with more severe exacerbations. In this context, we recently found that older asthma patients have worse clinical outcomes (eg, higher in-hospital mortality and a longer hospital length of stay) than younger asthma patients.²⁰ In addition, asthma may be more severe in older adults because of the normal aging process,^{28,29} as indicated by a lower FEV₁. Our results found many age-related differences in baseline characteristics, such as age of onset, lower FEV₁, more breathlessness, and strikingly more comorbid conditions in older adults with asthma. Besides aging, the lower FEV₁ in the older asthma population could be a result of a longer duration of asthma and more former smokers.³⁰ The high prevalence of comorbid conditions underscores the importance of recognizing and treating these coexisting conditions in older adults with asthma.⁴

Despite these disadvantages in older adults with asthma, they may have better access to care and better asthma care than their younger counterparts.²² In the Epidemiology and Natural History of Asthma Outcomes and Treatment Regimens study,²² older adults with asthma actually did better than younger adults, as suggested by lower health care use and better quality of life in elderly patients, and the authors attributed this to more aggressive use of inhaled corticosteroids in elderly patients. In our study, despite worse lung function in older adults with asthma, asthma control appeared to be comparable between older and younger adults with asthma, suggesting that care appeared to be better for the older adults. Taken together, it appears that the aging processes in older adults with asthma may be counterbalanced by better access to care and better asthma care. However, the numbers of all-cause hospitalizations and medications in older adults with asthma were still higher, suggesting that nonasthma comorbid conditions may contribute to higher morbidity in older adults with asthma.

In addition to age, we also found that Mexican American ethnicity and vitamin D may play a role in asthma mortality. A previous US study examining racial/ethnic differences in asthma mortality found that Mexican American had the lowest mortality (9.2 per million) compared with other race/ethnicity groups (eg, 14.7 per million in whites; 40.9 per million in Puerto Ricans).³¹ The mortality differences may be partly explained by lower prevalence of asthma in Mexican Americans³²; however, our analysis found the mortality benefits remained even after Mexican Americans had developed asthma. This survival advantage in Mexican Americans persists after controlling for poverty, smoking, and several other important confounders, suggesting a phenomenon termed the “Hispanic paradox.”³³ Several postulated mechanisms have been proposed and may apply to our findings, including increased family support, healthy immigrant effect, and “salmon bias” (ie, ill immigrants tending to return to their country of birth). In addition to these general ethnic differences, recent studies also suggest asthma-specific ethnic differences in severity,³⁴ response to treatment,³⁵ and pharmacogenomics,³⁶ with favorable profiles in Mexican Americans compared with Puerto Ricans and African Americans.

Our analysis found that older adults with asthma had lower vitamin D levels than younger adults, which may explain several important age-related differences we observed. Serum 25(OH)D levels have been directly related to BMD, and low levels of 25(OH)D are inversely related to parathyroid hormone,³⁷ both of which may explain higher prevalence of osteoporosis in older adults with asthma. In addition, a growing body of research has suggested vitamin D may have noncalcemic effects on asthma pathogenesis, asthma control, treatment response, and exacerbation risk.³⁸ Specifically, through immunomodulation of innate and adaptive immunity, serum 25(OH)D may decrease the risk of viral infections and improve asthma control.³⁸ Our analysis extends these findings by suggesting a modestly increased risk of all-cause mortality with vitamin D deficiency (<30 nmol/L) in asthmatic adults. Potential mechanistic explanations may be that vitamin D deficiency increases the risk of upper respiratory tract infections, leading to asthma exacerbations,³⁹ decreases response to inhaled corticosteroids,⁴⁰ and is associated with impaired lung function.^{40,41} Alternatively, lower vitamin D levels have been found to be associated with cardiovascular mortality,^{42,43} and this mechanism may also explain the increased all-cause mortality in older adults with asthma. Regardless of the mechanisms, our findings are consistent with previous studies that link lower vitamin D levels and mortality in the general⁴⁴ or elderly population.⁴⁵ Our findings add to the existing literature because of the unique focus on adults with asthma and the extended follow-up to 2006.

This study has some potential limitations. First, it is possible that some patients with self-reported physician-diagnosed asthma may, in fact, have COPD. To address this misclassification issue, we conducted a sensitivity analysis, and the results did not materially change. Second, some of the baseline data may be subject to recall bias (eg, health care use in the past year), especially in elderly patients. Nonetheless, the findings are consistent with prior cross-sectional studies.^{6,7} Third, as with all observational studies, the observed association (eg, vitamin D–mortality link) may be a mixture of real and confounded association. Vitamin D deficiency may be a proxy for less time spent outdoors or unobserved frailty. Several ongoing, large randomized clinical trials may shed light on the potential therapeutic role of vitamin D in asthma.^{38,42} Fourth, asthma mortality was rare in this study, precluding us from examining factors associated with asthma-related mortality. This seems to be a perennial problem because a previous study also indicated that death certificate data are likely to underestimate actual asthma mortality.⁴⁶ Finally, the NHANES lacked detailed data on asthma severity (eg, nighttime awakening and interference with normal activity), so we were not able to finely classify the study population into intermittent and persistent asthma with varying degrees of severity.

In summary, in this nationally representative, longitudinal study, older adults with asthma appear to be phenotypically distinct from younger adults, with higher morbidity and all-cause mortality. The ethnic differences in asthma mortality and the vitamin D–mortality link merit further investigation. As the US population continues to age, the disease burden in older adults with asthma will continue to rise. Care of asthma in older adults needs to recognize these many age-related differences, and patient-tailored approaches would further improve clinical outcomes in older adults with asthma.

Supplementary Data

Supplementary data related to this article can be found at doi:10.1016/j.anai.2013.01.002

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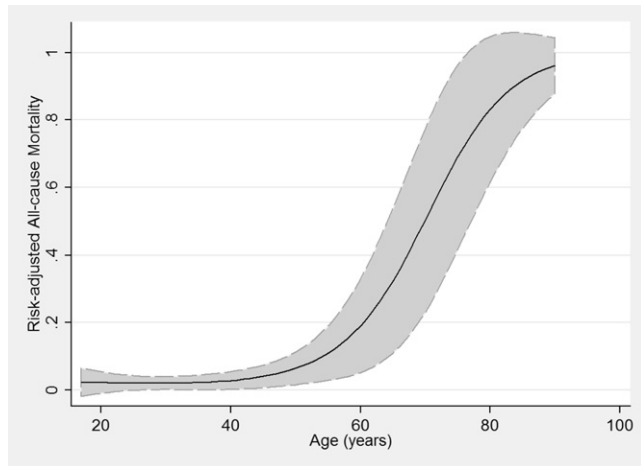


Figure 1. Risk-adjusted probabilities of all-cause mortality as a function of age. Data were fitted by a multivariable restricted cubic spline model. The 95% confidence intervals are indicated by the *dashed lines*. For those older than 90 years, the Third National Health and Nutrition Examination Survey recoded their age as 90 years.