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Risk factors for death among adults with severe asthma

Theodore A Omachi, MD MBA[1], **Carlos Iribarren, MD MPH PhD**[2], **Urmimala Sarkar, MD MPH**[3], **Irina Tolstykh**[2], **Edward H. Yelin, PhD**[4], **Patricia P. Katz, PhD**, **Paul D. Blanc, MD MSPH**[1,5], and **Mark D. Eisner, MD MPH**[1,3,5]

[1]Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of California, San Francisco

[2]Division of Research, Kaiser Permanente, Oakland, CA

[3]Division of General Internal Medicine, Department of Medicine, University of California, San Francisco

[4]Institute for Health Policy Studies and Division of Rheumatology, Department of Medicine, University of California, San Francisco

[5]Division of Occupational and Environmental Medicine, Department of Medicine, University of California, San Francisco

Abstract

Background—Mortality risk in adult asthma is poorly understood, especially the interplay between race, disease severity, and health-care access.

Objective—To examine mortality risk factors in adult asthma.

Methods—In a prospective cohort study of 865 adults with severe asthma in a closed-panel managed-care organization, we used structured interviews to assess baseline sociodemographics, asthma history, and health status. Subjects were followed until death or end of study, with a two-year average follow-up time. We used Cox proportional hazards regression to evaluate the impact of sociodemographics, cigarette smoking, and validated measures of perceived asthma control, physical health status, and severity-of-asthma on the risk of death.

Results—We confirmed 123 deaths, a mortality rate of 6.7 per 100 person-years. In analysis adjusted for sociodemographics and tobacco history, higher severity-of-asthma scores (hazard ratios [HR], 1.11 per ½ standard deviation increase in severity-of-asthma score; 95% confidence interval [CI], 1.01 - 1.23) and lower perceived asthma control scores (HR, 0.91 per ½ standard deviation increase in perceived asthma control score, 95% CI, 0.83 - 0.99) were each associated with risk of all-cause mortality. In the same adjusted analysis, African American race was not associated with an increased mortality risk relative to white race (HR 0.63; 95% CI 0.35 - 1.12).

Conclusions—In a large managed-care organization in which access to care is unlikely to vary widely, greater severity-of-asthma scores and poorer perceived asthma control scores are each associated with increased mortality risk among adults with severe asthma, but African Americans are not at increased risk of death relative to whites.

Corresponding Author: Theodore A. Omachi, MD, MBA, University of California, San Francisco, 350 Parnassus Avenue, Ste 609, San Francisco, CA 94117, Telephone (415) 476-7351, Fax (415) 476-6426, omachi@ucsf.edu.
Theodore A. Omachi: omachi@ucsf.edu; Carlos Iribarren: carlos.iribarren@kp.org; Urmimala Sarkar: usarkar@medicine.ucsf.edu; Irina Tolstykh: irina.v.tolstykh@kp.org; Edward H. Yelin: ed.yelin@ucsf.edu; Patricia P. Katz; patti.katz@ucsf.edu; Paul D. Blanc; paul.blanc@ucsf.edu; Mark D. Eisner; mark.eisner@ucsf.edu.

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Keywords

asthma; mortality; risk factors; prospective studies; severity of illness index

INTRODUCTION

Death from asthma is a devastating potential outcome. Asthma-specific mortality is considered to be preventable if high-risk patients are identified and appropriately treated.[1] Existing research on adult asthma mortality is incomplete. Most studies of asthma mortality have been retrospective, with limited information on asthma severity or other measures of health status.[1-7] Moreover, they have relied on cause-of-death information from death certificates to identify asthmatic cohorts,[1-7] which introduces unavoidable inaccuracies in ascertainment.[8-12] The prospective studies that have examined risk factors for death in asthma have had little information on disease severity, virtually no information about race, and have mostly studied populations outside the United States.[13-20]

Within this context, retrospective studies have repeatedly observed racial and ethnic differences in asthma mortality, with mortality rates for African American subjects approximately four- to five- fold higher than those of other racial groups.[2-7] This apparent discrepancy has prompted the National Heart, Lung, and Blood Institute to make reducing racial disparities in asthma a research priority.[21] However, it has not thus far been possible to confirm or refute this association prospectively, in particular taking into account correlated sociodemographic characteristics, disease severity and control, and access to care.

In a prospective cohort analysis, we examined risk factors for mortality among adults with asthma among a large, racially diverse cohort. By recruiting patients after hospitalization for asthma, we focused on patients with more severe asthma which should have the effect of increasing statistical power to detect risk factors for mortality.[22, 23] It was therefore feasible in this modest-sized cohort to examine the impact of previously-validated measures of asthma severity and health status on the risk of all-cause mortality. Moreover, because the study cohort were all members of a single closed-panel health care system, we were able to investigate whether racial disparities in mortality persist among asthma patients with established access to health care and after controlling for socioeconomic status as well as disease severity and control.

METHODS

Overview

Our study obtained baseline survey information from Northern California Kaiser Permanente (KP) patients who had recently been hospitalized for asthma. After baseline survey, all subjects were treated according the usual care practices for asthma at KP. Subjects were followed until death, termination of KP membership, or end of study period. KP is a closed-panel integrated health system and the nation's largest nonprofit managed care organization. The demographic characteristics of Northern California KP members are similar to the overall Northern California population, except for the extremes of income distribution.[24] Our study was approved by the University of California, San Francisco Committee on Human Research and the Kaiser Foundation Research Institute's Institutional Review Board.

Subject recruitment

Subject recruitment methods have been previously described in detail.[25-27] Briefly, we identified all adult KP members, on a rolling monthly basis, hospitalized at any Northern

California KP hospital with either (1) a primary discharge diagnosis of asthma or (2) a primary discharge diagnosis of an acute asthma-related respiratory condition and a secondary discharge diagnosis of asthma. Persons with a primary or secondary discharge diagnosis for chronic bronchitis, emphysema, or chronic airway obstruction were excluded. The diagnosis of asthma was previously validated in a stratified random sample of 100 subjects.[26] The cohort included 865 subjects with severe asthma who completed interviews (53% of all eligible subjects). Subjects who did and did not participate were similar in terms of age, gender and race-ethnicity ($p>.20$ for all)..[26]

Measurements

Structured telephone interviews performed after hospital discharge ascertained age, sex, race-ethnicity, educational attainment, household income, marital status and tobacco history, as previously described.[25, 27, 29]

We measured asthma severity using a 13-item disease-specific severity-of-asthma score, which is based on frequency of current asthma symptoms (daytime or nocturnal), use of systemic corticosteroids, use of other asthma medications (other than systemic corticosteroids), and history of hospitalization and endotracheal intubation.[30, 31] Possible total scores range from 0 to 28, with higher scores reflecting more severe asthma. Previous work has established the reliability, concurrent validity, and predictive validity of the severity score, including its ability to predict future hospitalizations for asthma.[30-32]

General physical health status was measured using the Physical Component Scale based on the 12-item Short Form health survey (SF-12 Physical),[33] which has been shown to be valid for adults with asthma.[34] Higher scores reflect more favorable physical health status.

Perceived asthma control was measured using the Perceived Control of Asthma Questionnaire, a validated 11-item instrument.[27, 35] It assesses individuals' perceptions of their ability to manage their asthma and its exacerbations. Higher scores reflect greater perceived asthma control.

Study Outcome: Mortality

The primary study outcome was all-cause mortality after subject enrollment (which required survival to discharge from the index hospitalization prior to recruitment) and before December 31, 2004, which corresponded to the last available mortality information. We used all-cause mortality for our primary outcome rather than death specifically attributed to asthma on death certificates for two reasons: death certificate information may underestimate death due to asthma,[8-12] and asthma may play an indirect but clinically important role in other causes of death, such as cardiovascular disease, chronic obstructive pulmonary disease (COPD), and pneumococcal disease.[15, 36-38] We note that all-cause mortality has been a major endpoint, and usually the primary end-point, used in prior prospective studies of mortality in asthma.[13-19]

However, to complement the analysis of all-cause mortality, we also performed two additional analyses in which we used death from respiratory causes as the outcomes. In one model, the outcome was death in which a respiratory cause was listed on the death certificate as the underlying cause-of-death.[39] In a second model, the outcome was death in which a respiratory cause was either the underlying or a contributing cause-of-death.[40] We classified deaths as respiratory based on our a priori categorization of a complete list of International Classification of Disease, 10th Revision (ICD-10) codes that can be used as causes-of-death on death certificates.

To obtain vital status, we first used KP's computerized record system. For subjects who had terminated their KP membership and for whom we did not therefore have vital status, we obtained this information by performing a search of the National Death Index (NDI), a database which is abstracted from all death certificates from throughout the United States.[41] We also obtained underlying and contributing causes of death for all deceased subject from the NDI, listed according to the ICD-10.[42]

Statistical Analysis

We performed statistical analysis using Stata/SE software (version 9.2, College Station, TX). To evaluate sociodemographic characteristics and health status measurements as single predictors of death we used the t-test to compare means for continuous variables and the χ^2 test to compare two or more percentages for categorical variables.

In Cox proportional hazards regression models that adjusted for multiple potentially explanatory variables, person-time was censored for subjects who terminated KP membership or reached the end of the study period without mortality. The proportional hazards assumption was verified by obtaining scaled Schoenfeld residuals ($p>0.1$ for all variables in the model). We scaled our continuous health status measures by ½ of their standard deviation, which generally corresponds to a minimally clinically significant score change.[43]

To provide insight into the death rate of our cohort relative to a standardized population, we calculated a standardized mortality ratio (SMR) for our cohort relative to age and gender-matched California mortality rates from 2000-2004, the years in which our study took place.[44] This was achieved by dividing the number of observed deaths by the expected number of deaths in each age decile and gender-specific California stratum (for example, males aged 45-55). This SMR calculation was not incorporated into other statistical analyses.

Although the diagnosis of asthma was confirmed in a medical record review, we performed a sensitivity analysis in which we attempted to strictly ensure that all patients had asthma rather than COPD as their primary underlying diagnosis. We restricted this sensitivity analysis to subjects who were highly likely to have asthma because they either never smoked cigarettes during their lifetime or had onset of asthma symptoms during childhood (<10 years) before COPD can develop (n=426). We chose a priori this cut-off age of 10 years because most childhood asthma begins in early childhood.[45]

RESULTS

During the study period, 123 deaths occurred in our cohort of 865 adults hospitalized for asthma. The average age of our cohort at baseline was 60.3 (Standard Deviation [SD] = 16.3). Subjects were followed for an average of 781 days (SD=356), corresponding to a mortality rate of 6.7 per 100 person-years (95% CI 5.6 to 7.8 deaths per 100 person-years). The mortality rate per 100 person-years ranged from a low of 1.9 for subjects between 30 and 40 years old to a high of 17.8 for subjects greater than 80 years old. The age and gender standardized mortality ratio for our study cohort relative to the general California population was 367% (95% CI 307% to 438%).

The baseline characteristics as single predictors of mortality are summarized in Table 1. Age, cigarette smoking history, and marital status were statistically associated with mortality risk. Education ($p=0.055$) and household income ($p=0.053$) were not associated with mortality at the conventional level of statistical significance.

As shown in Table 1, race-ethnicity was not associated with all-cause mortality risk. Because of our a priori study interest in African American-associated risk,[21] we reanalyzed these data

comparing African Americans (n=154) to all others (n=711). In that analysis African American race was significantly associated with decreased risk (p = 0.044).

Greater asthma severity, poorer health status, and poorer perceived asthma control were each predictive of death when analyzed without other explanatory variables (Table 2).

The frequency of all deaths and mortality grouped by broad category of underlying cause is shown in Table 3. Respiratory causes were the single largest category of underlying cause-of-death. Underlying cause-of-death was attributed to asthma in only two cases, although asthma, including status asthmaticus, was listed as a contributing cause-of-death in an additional seven cases. When both underlying and contributing causes-of-death are considered, 78 (63%) of 123 deaths were respiratory-related.

In the adjusted Cox proportional hazard model of all-cause mortality (Table 4), higher baseline severity-of-asthma scores (HR 1.11 per ½ SD increment in score; 95% CI 1.01 to 1.23) and lower perceived asthma control scores (HR 0.91 per ½ SD increment in score; 95% CI 0.83 to 0.99) were each associated with a greater prospective risk of death. A history of former or current tobacco usage was associated with increased risk of death (HR 1.81; 95% CI 1.18 to 2.79). African American race was not associated with a higher risk of death relative to non-Latino white race (HR 0.64; 95% CI 0.36 to 1.14). In contrast, Latino, Asian, and "other race/ethnicity" were each associated with an increased point estimate of mortality relative to whites. The confidence intervals for these relatively small groups, however, were wide and included unity.

In our sensitivity analysis in which we attempted to more strictly ensure that all subjects had asthma rather than COPD as their primary underlying diagnosis, the point estimates for the hazard ratios of the severity-of-asthma score (HR 1.12; 95% CI 0.96 to 1.31) and perceived asthma control score (HR 0.91; 95% CI 0.79 to 1.06) were virtually unchanged, although the confidence intervals, using this smaller subset of data, were larger and included unity.

We also performed another set of analyses in which we used two alternative mortality outcomes in adjusted models: (1) underlying respiratory cause-of-death (n=44) and (2) underlying or contributing respiratory cause-of-death (n=78) (Table 5). In both analyses, the severity-of-asthma score was even more strongly associated with mortality (HR=1.54; 95% CI 1.31 to 1.81 for respiratory as underlying cause-of-death and HR=1.40; 95% CI 1.24 to 1.58 for respiratory as underlying or contributing cause-of-death). African American race was still related to a decreased point estimate of risk of death (HR=0.68; 95% CI 0.26 to 1.69 for respiratory as underlying and HR=0.75; 95% CI 0.38 to 1.49 for respiratory as underlying or contributing). Asian race became a stronger predictor of both death in which a respiratory cause was underlying (HR=3.94; CI 1.47 to 10.6) and death in which a respiratory cause was underlying or contributing (HR=2.71; 95% CI 1.20 to 6.13).

DISCUSSION

In this prospective cohort study of adults with severe asthma and comparable access to care, asthma severity and perceived asthma control were both risk factors for death. Thus, gradations of asthma severity, even within a cohort characterized by disease severe enough to have led to recent hospitalization, confers substantive all-cause mortality risk. Moreover, in examining death from a respiratory cause, asthma severity exhibits even more predictive power. This demonstrates internal consistency for this measure, since we would expect that a respiratory-specific measure would be a stronger predictor of a respiratory-related outcome.

Even taking asthma severity into account, the subjective perception of disease control independently conferred mortality risk. Improved perceived asthma control has previously

been demonstrated to be associated with decreased prospective risk of severe asthma attacks and health care utilization.[27, 35] Perceived asthma control, which is closely related to self-efficacy, is a patient's self-perception of his or her ability to manage asthma and its exacerbations.[35] Higher perceived control may result in improved disease control, either through improved self-management behaviors, improved medication adherence, or through unknown mechanisms.[27] Our data showing that higher perceived asthma control predicts lower mortality even after adjustment for asthma severity suggests that perceived control is playing an independent and an important role. Prior research in other chronic diseases models has shown that clinical outcomes can be improved by intervention programs focused on improving self-efficacy,[46, 47] which is confidence in one's ability to carry out a behavior necessary to reach a desired goal.[47] Further studies should investigate whether improving perceived asthma control can also reduce mortality risk.

Our observation that African American race was not a risk factor for mortality is all the more striking in this context, given that multiple prior studies have demonstrated a markedly higher risk of death from asthma among African Americans. There are several possible explanations for our findings. First, our study prospectively identified patients with asthma rather than relying on potentially less accurate cause-of-death information to define our cohort.[8-12] Second, within the closed panel managed care organization in which the cohort was studied, asthma patients likely had equivalent access to care, thus controlling for this potential confounding variable. One key aspect to such health care access may be asthma-specific disease management programs. During the last decade, KP Northern California has made a major effort to standardize and improve asthma care through disease management programs, including clinical guidelines, patient self management education, disease registries, risk stratification, proactive outreach, reminders, multidisciplinary care teams, and performance feedback to providers.[48]

We found that adults with severe asthma had a markedly higher mortality than the age- and gender-matched California population (SMR 367%). However, cause-of-death was specifically attributed to asthma in relatively few subjects. There are several explanations for these contrasting findings. Asthma may play an indirect role in death from other causes, such as cardiovascular disease, either via inflammatory pathways or as a result of the treatment of the asthma with such medications as bronchodilators.[37, 38] Alternatively, cause-of-death information on death certificates may be inaccurate, as numerous studies have concluded generally.[49, 50] Some authors have suggested that physicians may not consider cause-of-death accuracy to be a priority and that declining autopsy rates have exacerbated death certificate unreliability.[49, 50] Other studies have shown that deaths from asthma specifically are often mistakenly attributed to COPD.[8-11] It is therefore possible that some of the deaths attributed to COPD in our study were in fact due to asthma. Finally, although we cannot say whether asthma was responsible for the entire increase in mortality suggested by the standardized mortality ratio, the fact that the severity-of-asthma score was related to increased mortality suggests that patients' asthma did play a role.

Many more deaths were attributed to COPD than to asthma, which raises the question of whether some subjects may have had COPD rather than asthma on enrollment. However, the diagnosis of asthma was previously validated at baseline by an in-depth medical record review of a stratified random sample of 100 patients.[26] In addition, all subjects reported a physician diagnosis of asthma during the survey. Finally, in a sensitivity analysis in which we attempted to more strictly ensure that included subjects had asthma rather than COPD as their primary underlying diagnosis, the relationships of the severity-of-asthma score and perceived asthma control score to mortality were virtually unchanged. Although the confidence intervals were slightly wider, this is expected when an analysis is performed on a smaller subset of a study

population. Consequently, misclassification of COPD as asthma on enrollment does not appear to explain the results.

Despite its strengths, our study has limitations. Although we recruited a cohort with severe asthma, follow-up was relatively brief and death still remained an uncommon event. It is possible that the lack of associations, as seen with gender, were due to a lack of statistical power. In particular, the small number of Asian and Latino participants make it difficult to draw clear conclusions about their risk. This is unfortunate, because little has been published about the risk of death among asthmatic Asians, and our estimate of risk for Asians was the highest of any group. Despite the limitations of study size for the other groups, African Americans comprised nearly 1 in 5 of our cohort and, given the observed point estimate and 95% confidence intervals, African American race appears very unlikely to confer a higher risk of death. We also recruited a cohort with relatively severe asthma after hospitalization for this condition. As a consequence, our results will likely not apply to populations with mild asthma.

Overall, these results demonstrate an elevated risk of death among adults with severe asthma and show that the potentially modifiable factors of asthma severity and perceived asthma control are prospectively associated with death. This provides justification for interventional research to investigate whether reducing asthma severity and improving perceived control can improve asthma outcomes. The severity score's application in a clinical context requires further validation, but ultimately it may help to identify patients at highest risk of death. Finally, it is noteworthy that our study did not find higher rates of death for African American asthmatics. Establishing access to care, as all patients in our cohort had done, stands out as one factor which may improve racial disparities in asthma mortality.

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Table 1

Baseline sociodemographic characteristics and smoking status in relation to mortality risk among 865 patients with asthma*

Baseline Characteristic	Died (n=123)	Survived (n=742)	P-value†
Age, mean (SD), years	69 (14)	59 (16)	<.001
Sex			.17
Female	80 (13)	528 (87)	
Male	43 (16)	214 (94)	
Marital Status			.047
Married/Cohabitating	65 (12)	462 (88)	
Single	58 (17)	280 (83)	
Education			.055
College graduate or higher	20 (10)	179 (90)	
Some college or lower	103 (15)	563 (85)	
Race / ethnicity			.34
Non-Latino White	79 (15)	445 (85)	
African American	14 (9)	140 (91)	
Asian	9 (16)	47 (84)	
Latino	10 (14)	60 (86)	
Other	11 (18)	50 (82)	
Annual Household Income‡			.053
>$60,000	8 (8)	97 (92)	
≤$60,000	103 (15)	603 (85)	
Smoking history			.005
Current or former smoker	94 (17)	470 (83)	
Never smoker	29 (10)	272 (90)	

*Data are presented as number (row percentage) except where indicated otherwise.

†The *t* test was used for age and likelihood ratio χ^2 test for all other characteristics.

‡Number of subjects for annual household income does not add up to 865 because 54 subjects declined to state income.

Table 2

Baseline asthma severity and health status on the risk of death in asthma*

Score	Died mean (SD) n=123	Survived mean (SD) n=742	P-value
Severity-of-Asthma Score	12.8 (4.0)	11.8 (3.4)	0.005
SF12 Physical Score	31.7 (10.7)	35.5 (11.6)	0.001
Perceived Asthma Control	37.2 (3.5)	38.2 (4.3)	0.014

Abbreviations: SD, Standard Deviation; SF12, Short Form 12

* Higher severity-of-asthma scores reflect more severe asthma. Higher SF-12 Physical scores and higher Perceived Control of Asthma scores reflect more favorable health status

Table 3

Underlying cause-of-death among 123 adults with asthma

Underlying Cause-of-death	Number	Percent
Respiratory*	44	36%
Cardiovascular	34	28%
Cancer	21	17%
Other	24	20%
Total	123	100%

Respiratory group composed of: 2 asthma (ICD10 J45.9), 3 emphysema (ICD10 J43.9), 4 “other specified chronic obstructive pulmonary disease” (ICD10 J44.8), 27 “chronic obstructive pulmonary disease, unspecified” (ICD10 J44.9), 5 pneumonia, 1 aspiration pneumonitis, 1 secondary pulmonary hypertension, and 1 bronchiectasis. Contributing respiratory causes were listed on 34 of the non-primary respiratory cases.

Abbreviations: ICD10, International Classification of Disease, 10th Revision

Table 4

Risk factors for all-cause mortality (n=123) among 865 adults with severe asthma*

Factor	Unadjusted Hazard Ratio (95% Cl)	Adjusted Hazard Ratio (95% CI)
Demographic Characteristics		
Age†	1.23 (1.16 - 1.32)	1.28 (1.19 - 1.37)
Female sex	0.81 (0.56 - 1.18)	0.84 (0.55 - 1.26)
Married/Cohabitating	0.68 (0.48 - 0.97)	0.72 (0.49 - 1.05)
College Graduate	0.60 (0.37 - 0.96)	0.61 (0.37 - 1.00)
High Income (>$60,000)	0.50 (0.24 - 1.02)	0.74 (0.35 - 1.56)
Race / Ethnicity		
White non-Latino (referent)	1.0	1.0
African American	0.59 (0.34 - 1.05)	0.64 (0.36 - 1.14)
Latino	0.93 (0.48 - 1.79)	1.16 (0.60 - 2.26)
Asian	0.96 (0.48 - 1.92)	1.77 (0.88 - 3.57)
Other	1.21 (0.64 - 2.27)	1.68 (0.88 - 3.19)
Tobacco		
Current or Former Smoker‡	1.78 (1.17 - 2.7)	1.81 (1.18 - 2.79)
Health Status & Severity		
Asthma Severity Score§	1.09 (1.00 - 1.18)	1.11 (1.01 - 1.23)
SF12 Physical Score§	0.83 (0.76 - 0.92)	0.91 (0.82 - 1.02)
Perceived Asthma Control§	0.89 (0.82 - 0.96)	0.91 (0.82 - 0.99)

Abbreviations: CI, Confidence Interval; SF12, Short Form 12

*Unadjusted hazard ratios include each factor, with appropriate reference group, analyzed by itself in a Cox proportional hazard model for death. Adjusted hazard ratios include simultaneously all factors listed in the table.

†Hazard ratio per 5 year increment in age

‡When tobacco history is defined as Current Smoker, Former Smoker or Never Smoker, the adjusted HRs, with Never Smoker as the referent, were: Current Smoker (HR 2.52; 95% CI 1.25 - 5.08) and Former Smoker (HR 1.74; 95% CI 1.12 - 2.70).

§Higher Asthma Severity Scores reflect greater severity; higher SF-12 Physical and Perceived Asthma Control scores reflect better status. Hazard ratio expressed per ½ standard deviation change in score.

Table 5

Sensitivity analysis: respiratory causes of death

Factor	Respiratory underlying cause of death* (n=44) Adjusted HR (95% CI)	Respiratory underlying or contributing cause of death* (n=78) Adjusted HR (95% CI)
Demographic Characteristics		
Age†	1.48 (1.28 - 1.72)	1.42 (1.29 - 1.58)
Female sex	0.83 (0.41 - 1.69)	0.77 (0.45 - 1.30)
Married/Cohabitating	0.51 (0.27 - 0.99)	0.65 (0.39 - 1.06)
College Graduate	0.79 (0.35 - 1.76)	0.62 (0.34 - 1.17)
High Income (>$60,000)	N/A§	1.01 (0.44 - 2.33)
Race / Ethnicity		
White non-Latino (referent)	1.0	1.0
African American	0.68 (0.26 - 1.79)	0.75 (0.38 - 1.49)
Latino	1.10 (0.37 - 3.25)	1.08 (0.45 - 2.55)
Asian	3.94 (1.47 - 10.6)	2.72 (1.20 - 6.13)
Other	N/A§	0.23 (0.03 - 1.67)
Tobacco		
Current or Former Smoker	2.67 (1.17 - 6.10)	2.10 (1.16 - 3.80)
Health Status & Severity		
Asthma Severity Score‡	1.54 (1.30 - 1.81)	1.39 (1.24 - 1.58)
SF12 Physical Score‡	0.90 (0.74 - 1.10)	0.86 (0.75 - 1.00)
Perceived Asthma Control‡	0.91 (0.78 - 1.06)	0.91 (0.82 - 1.02)

Abbreviations: HR, Hazard Ratio; CI, Confidence Interval; SF12, Short Form 12

*Underlying cause-of-death is the disease that initiated the sequence of events leading to death. Contributing causes of death are significant conditions contributing to death but not resulting in the underlying cause.

†Hazard ratio per 5 year increment in age

‡Higher Asthma Severity Scores reflect greater severity; higher SF-12 Physical and Perceived Asthma Control scores reflect better status. Hazard ratio expressed per ½ standard deviation change in score

§Unable to calculate a hazard ratio because there were no deaths from an underlying respiratory cause in the “other race” group or in the high income group.