

Letter to the Editor

The association between asthma and allergic disease and mortality: A 30-year follow-up study

To the Editor:

Over the last 30 years, rates of asthma and allergic disease have increased markedly in the United States.¹⁻³ Little is known about the long-term mortality burden of these conditions, which typically develop in children and young adults. It has been suggested that asthma and allergy may represent a state of systemic immunologic perturbation, perhaps with long-term consequences,⁴ and observational studies have linked allergic disease with cardiovascular disease⁵ and cancer.⁶ A better understanding of the mortality risk of asthma and allergy may direct resource allocation and inform disease mechanism. We therefore investigated data available from the first National Health and Nutrition Examination Survey Epidemiologic Follow-up Study (NHEFS) to determine the association between asthma, food allergy, and hay fever, and all-cause, cardiovascular, cancer, and respiratory mortality. We further explored whether asthma-mortality associations may be influenced by lung function in the subset of participants who performed spirometry.

The NHEFS included a US-based *full cohort* of 14,407 subjects aged 25 to 74 years who completed an interview and medical examination in 1971-1975. A *subcohort* of 6,913 underwent a more detailed health interview and examination, including questions on smoking and performance of spirometry (see Fig E1 in this article's Online Repository at www.jacionline.org). While the full cohort oversampled certain groups considered at risk for malnutrition, the subcohort is considered nationally representative. Follow-up occurred in 1982-1984, 1986, 1987, and 1992. The NHEFS ascertained mortality through December 31, 2006, based on deaths identified during previous follow-up and matching between NHEFS records and the National Death Index. Because a smoking history was not obtained on the full cohort at baseline, we used data obtained in 1982-1984 to ascertain smoking status. Missing education, income, and smoking data were imputed. See this article's Online Repository at www.jacionline.org for additional methods.

We used Cox proportional hazard regression models to determine the association between current asthma, food allergy, and hay fever, and all-cause and cause-specific mortality. All analyses were performed in STATA 12 (College Station, Tex) using age as the underlying time metric and the 1982-1984 survey as the start of follow-up. Analyses took place at the Research Data Center at the National Center for Health Statistics in Hyattsville, Maryland, because the mortality data through 2006 are considered restricted-use data.

At baseline, 3.6% of the subjects reported a history of doctor-diagnosed asthma, 4.5% reported food allergy, and 8.6% reported hay fever; 6800 (52.1%) died during follow-up. There were 2492 cardiovascular deaths, 1588 cancer deaths, and 539 respiratory deaths. Demographic characteristics of NHEFS subjects are listed in Table I.

In the full cohort, a history of asthma was associated with a statistically significant increase in respiratory and all-cause mortality. Asthma was not associated with other cause-specific mortality outcomes, and food allergy and hay fever were not

TABLE I. Demographic characteristics of NHEFS participants at baseline (1971-1974)

Characteristic	Full cohort (n = 13,042)	Subcohort (n = 5,132)
Age (y), %		
25-34	26.6	25.9
35-44	21.7	19.3
45-54	16.1	23.6
55-64	12.1	17.4
65-75	23.3	13.6
Race, %		
White	83.6	89.2
African American	15.2	10.8
Other	1.2	—
Sex (%)		
Male	39.6	45.3
Female	60.4	54.7
Education		
<10th grade/special school	37.3	30.7
11th-12th grade	38.5	41.8
College/graduate	23.5	27.2
Missing	0.6	0.2
Annual income (\$), %		
<5,000	25.5	18.9
5,000-<10,000	29.3	26.4
≥10,000-<15,000	20.9	24.0
≥15,000	20.4	27.1
Missing	3.7	3.5
Smoking status, %*		
Never	38.2	38.0
Ever	46.4	—
Current	—	19.6
Former	—	42.2
Missing	15.4	0.01
Pack years category, %*		
0	NA	41.4
<30		31.5
30-60		15.6
>60		7.5
Missing		3.9

NA, Not applicable/available.

*The full cohort includes all NHEFS participants who met inclusion/exclusion criteria. The subcohort includes all NHEFS participants who had additional spirometry performed and further information obtained on smoking history. For the full cohort, smoking status (never/ever) was obtained at the 1982-1984 survey. For the subcohort, smoking status (never/ever/current) and pack-years smoked were obtained at baseline. A smoking history was not obtained on all subjects at baseline. Please see this article's Online Repository at www.jacionline.org for methods and variable definitions.

associated with mortality of any cause (see Table E1 in this article's Online Repository at www.jacionline.org). The age-adjusted hazard ratio (HR) for asthma and respiratory mortality was 2.22 (95% CI, 1.47-3.35; Table II), which was similar after adjusting for sex, income, education, race, and smoking history and exclusion of subjects reporting a diagnosis of emphysema. In the subcohort, we found that the age-adjusted hazard of respiratory mortality associated with a history of asthma was 2.45 (95% CI, 1.25-4.78), which was similar after adjusting for demographic variables. However, after including smoking in the model, the HR associated with asthma declined to 2.01 (95% CI, 0.92-4.42).

TABLE II. HRs for asthma and all-cause and respiratory mortality, adjusting for demographic, smoking, and lung function characteristics

Condition	Respiratory mortality							
	Full cohort				Subcohort			
	1	2	3	4	1	2	5	6
Asthma	2.22 (1.47-3.35)*	2.26 (1.46-3.47)*	2.28 (1.50-3.47)*	2.22 (1.34-3.67)*	2.45 (1.25-4.78)*	2.51 (1.26-4.98)*	2.01 (0.92-4.42)	1.45 (0.67-3.14)
Mild obstruction								2.08 (1.34-3.24)*
Moderate to severe obstruction								5.86 (3.71-9.23)*
Restriction								1.65 (1.09-2.47)*

Model 1 is adjusted for age. Model 2 is adjusted for age, sex, income, education, and race. Model 3 is the same as model 2, additionally adjusted for smoking history obtained at the 1982-1984 survey (ever/never). Model 4 is the same as model 3, excluding subjects with a history of bronchitis or emphysema. Model 5 is the same as model 2, additionally adjusted for smoking history obtained at baseline (never/former/current) and pack-year history. Model 6 is the same as model 5, additionally adjusted for lung function category.

*Statistically significant ($P < .05$).

Further addition of lung function to the model resulted in an adjusted HR of 1.45 associated with asthma (95% CI, 0.67-3.14).

In the full cohort, the age-adjusted HR for all-cause mortality comparing those with and without a history of asthma was significantly elevated (HR, 1.23; 95% CI, 1.07-1.42). This remained significant after additionally adjusting for sex, income, education, race, and smoking history and excluding subjects reporting a diagnosis of emphysema. We did not find an association between asthma and all-cause mortality in the subcohort (age-adjusted HR, 1.07; 95% CI, 0.82-1.40). This discrepancy may be due to differences in the asthma-mortality relationship between the full cohort and the subcohort or a lack of power in this smaller sample size (for further discussion, and exploration of effect modification, see the Online Repository available at www.jacionline.org).

We examined the association between asthma and allergic disease and mortality in a population-based cohort with more than 30 years of follow-up. We identified an increased risk of respiratory and all-cause mortality associated with a doctor's diagnosis of asthma. Asthma was not associated with the other specific mortality causes we investigated, nor was food allergy or hay fever associated all-cause or cause-specific mortality. Although there was no indication of mortality risk in the United States due to allergic disease *per se*, asthma was associated with an increased risk of respiratory and all-cause mortality. In the subcohort in which more detailed data on smoking history were available, adjustment for confounding by smoking history attenuated the association between asthma and mortality, raising the possibility that residual confounding by smoking history may underlie some of the excess mortality risk seen in the full cohort. Incorporation of lung function into the model caused further attenuation of the association between asthma and respiratory mortality, suggesting that the asthma-mortality association may be driven largely by lung function abnormalities.

To our knowledge, this is the first report of an association between asthma and increased risk of respiratory and all-cause mortality. This contrasts with previous observations that identified null associations for asthma and all-cause mortality.^{7,8} However, 1 study included only young university students, and another, while nationally representative, did not have the benefit of a 30-year follow-up time. Our analyses within the subcohort suggest that the respiratory mortality burden of asthma is explained, at least in part, by lung function abnormalities, rather than by the general diagnosis of asthma. The factors that influence lung function decline in asthma are not well understood, and

further study may help determine whether strategies aimed at prevention of loss of lung function in asthma will have a mortality benefit.

The strengths of our study include the large sample size, long duration of follow-up, population-based design, and inclusion of smoking history as a covariate. We included only deaths occurring after the 1982-1984 follow-up, making it less likely that assessment of allergic disease, asthma, and pulmonary function was confounded by the presence of other medical complications. Most of our predictors were based on a history of a doctor's diagnosis of asthma or allergy, which may be limited by misclassification. However, our results are in general agreement with studies using skin testing as an objective measure of atopic disease that did not have the benefit of a long follow-up time.⁹ Our most prominent findings were with respiratory mortality, which unlike all-cause mortality is subject to potential misclassification, but we did detect a consistent significant increase in all-cause mortality associated with asthma in the full cohort. Because emphysema may be difficult to differentiate from asthma clinically, we performed sensitivity analyses excluding subjects with emphysema, which did not change our overall results. Since the NHEFS baseline visit, fewer Americans are smoking and improved asthma therapies have emerged, which may improve the long-term mortality associated with asthma and reduce lung function decline. Observing the long-term mortality risk of asthma in recent populations with more access to inhaled corticosteroids and long-acting bronchodilators will be of value to determine whether these agents can potentially modify the observed association between asthma and mortality.

In conclusion, we identified a significantly increased risk of respiratory and all-cause mortality in subjects with asthma. Analyses in the smaller subcohort with more information on smoking available suggests that residual confounding by smoking history may underlie at least some of this observation. There were no associations between asthma and cardiovascular or cancer mortality or other allergic disease and an increased risk of mortality from any cause. Our data do not support the theory that allergy is a systemic inflammatory disease leading to downstream immune dysregulation, cardiovascular disease, or cancer. Within the subcohort, excess respiratory mortality risk was largely explained by lung function abnormalities. Taken together, these findings are reassuring but suggest that better understanding of factors contributing to lung function decline and efforts to prevent this may have a mortality benefit in asthma.

TABLE II. (Continued)

All-cause mortality							
Full cohort				Subcohort			
1	2	3	4	1	2	5	6
1.23 (1.07-1.42)*	1.21 (1.05-1.39)*	1.22 (1.06-1.40)*	1.21 (1.03-1.42)*	1.07 (0.82-1.40)	1.08 (0.84-1.44)	1.07 (0.82-1.40)	1.00 (0.76-1.30)
							0.96 (0.79-1.15)
							1.57 (1.30-1.89)*
							1.30 (1.14-1.49)*

Jessica H. Savage, MD, MHS^{a,b}
 Elizabeth C. Matsui, MD, MHS^c
 Meredith McCormack, MD, MHS^d
 Augusto A. Litonjua, MD, MPH^{b,e,f}
 Robert A. Wood, MD^c
 Corinne A. Keet, MD, MS^c

from the NIH, and has received royalties from UpToDate. E. C. Matsui declares that she has no relevant conflicts of interest.

From ^athe Division of Rheumatology, Immunology, and Allergy, Brigham and Women's Hospital, and ^bHarvard Medical School, Boston, Mass; ^cthe Division of Pediatric Allergy and Immunology and ^dthe Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, Md; and ^eChanning Division of Network Medicine and ^fthe Division of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, Boston, Mass. E-mail: jrsavage@partners.org. This work was supported in part by a training grant from the National Institutes of Health (NIH) (grant no. 5T32AI007056-34), a grant from the American Academy of Allergy, Asthma & Immunology and Food Allergy Research and Education, and a KL2 Medical Research Investigator Training award (an appointed KL2 award) from Harvard Catalyst | The Harvard Clinical and Translational Science Center (National Center for Research Resources and the National Center for Advancing Translational Sciences) (NIH Award no. 1KL2 TR001100-01 to J.H.S.). The content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard Catalyst, Harvard University and its affiliated academic health care centers, or the NIH.

Disclosure of potential conflict of interest: J. H. Savage and C. A. Keet have received research support from the National Institutes of Health (NIH). M. McCormack has received research support from the National Institute of Environmental Health Sciences. A. A. Litonjua has received royalties from UpToDate and Springer. R. A. Wood has received consultancy fees from the Asthma and Allergy Foundation of America, is employed by Johns Hopkins University, has received research support

REFERENCES

1. Akinbami LJ, Moorman JE, Bailey C, Zahran HS, King M, Johnson CA, et al. Trends in asthma prevalence, health care use, and mortality in the United States, 2001-2010. NCHS Data Brief 2012;1-8.
2. Singh K, Axelrod S, Bielory L. The epidemiology of ocular and nasal allergy in the United States, 1988-1994. J Allergy Clin Immunol 2010;126:778-83.e6.
3. Sicherer SH, Munoz-Furlong A, Godbold JH, Sampson HA. US prevalence of self-reported peanut, tree nut, and sesame allergy: 11-year follow-up. J Allergy Clin Immunol 2010;125:1322-6.
4. Prescott SL. Early-life environmental determinants of allergic diseases and the wider pandemic of inflammatory noncommunicable diseases. J Allergy Clin Immunol 2013;131:23-30.
5. Knoflach M, Kiechl S, Mayr A, Willeit J, Poewe W, Wick G. Allergic rhinitis, asthma, and atherosclerosis in the Bruneck and ARMY studies. Arch Int Med 2005;165:2521-6.
6. McWhorter WP. Allergy and risk of cancer: a prospective study using NHANESI followup data. Cancer 1988;62:451-5.
7. Diaz-Guzman E, Khosravi M, Mannino DM. Asthma, chronic obstructive pulmonary disease, and mortality in the U.S. population. COPD 2011;8:400-7.
8. Galobardes B, McCarron P, Jeffreys M, Davey Smith G. Association between early life history of respiratory disease and morbidity and mortality in adulthood. Thorax 2008;63:423-9.
9. Gergen PJ, Turkeltaub PC, Sempos CT. Is allergen skin test reactivity a predictor of mortality? Findings from a national cohort. Clin Exp Allergy 2000;30:1717-23.

<http://dx.doi.org/10.1016/j.jaci.2014.01.028>

HUMAN STUDIES APPROVAL

Data collection for the NHEFS was approved by the National Center For Health Statistics (NCHS) Research Ethics Review Board. Analysis of de-identified data from the survey is exempt from federal regulations for the protection of human research participants. Analysis of restricted data through the NCHS Research Data Center is also approved by the NCHS Ethics Review Board.

STUDY DESIGN

The NHEFS is a national longitudinal study designed to investigate the relationships between clinical, nutritional, and behavioral factors assessed in the first National Health and Nutrition Examination Survey (NHANES I) and subsequent morbidity, mortality, and hospital utilization, as well as changes in risk factors, functional limitation, and institutionalization.^{E1} The NHEFS cohort includes all persons aged 25 to 74 years who completed a medical examination at NHANES I in 1971-1975 ($n = 14,407$). Four follow-up studies have been conducted to date. The 1982-1984 survey was designed to include all members of the NHEFS cohort and involved conducting personal interviews with subjects or their proxies; measuring pulse rate, weight, and blood pressure of surviving participants; collecting hospital and nursing home records of overnight stays; and collecting death certificates of decedents. Follow-up occurred in 1986, 1987, and 1992 using the same design and data collection procedures developed in the 1982-1984 NHEFS, with the exception that a 30-minute computer-assisted telephone interview was administered rather than a personal interview and no physical measurements were taken. The 1986 NHEFS was conducted for members of the NHEFS cohort who were aged 55 to 74 years at their baseline examination and not known to be deceased at the 1982-1984 NHEFS ($n = 3,980$). The 1987 NHEFS was conducted for the entire nondeceased NHEFS cohort ($n = 11,750$). The fourth wave of data collection, the 1992 NHEFS, includes the entire nondeceased NHEFS cohort ($n = 11,195$). Tracing rates for each completed wave ranged from 90% to 94% and interview rates ranged from 91% to 96% of those traced. By the 1992 follow-up, 96% percent of the study population had been successfully traced at least once.

VARIABLE DEFINITIONS

Demographic variables

Participants in the NHEFS completed an extensive questionnaire at baseline that included the demographic data of age, race, sex, income, and education level. We classified total annual family income and highest grade of school attended into ordinal variables, with similar numbers of subjects in each group. For income we used less than \$5,000, \$5,000 to less than \$10,000, \$10,000 to less than \$15,000, and more than \$15,000 per year as categories. An income of below \$4,275 was considered poverty for a family of four in 1972.^{E2} For education we used completion of less than 10th grade or special school, 11th to 12th grade, or attendance at college/graduate school as categories. Demographic variables with more than 2 categories were incorporated into the analytical models as categorical variables.

Participants were asked "has a doctor ever told you that you have any of the following conditions, and if so, do you still have it?" for asthma, allergies to food, hay fever, and chronic bronchitis or emphysema (referred to simply as emphysema in the main article). A history of allergic disease was considered positive if they reported a current diagnosis of the above conditions. For

bronchitis or emphysema, a history was considered positive if they reported any diagnosis.

Smoking history

Full cohort: A smoking history was obtained on all located, nondeceased subjects at the 1982-1984 follow-up. We classified subjects as ever smokers if they reported ever smoking at least 100 cigarettes and never smokers if they did not.

Subcohort: At the baseline visit, a smoking history was obtained only for participants in the subcohort. We considered participants to be former smokers if they reported any previous use of cigarettes (>100), cigars (>50), or pipes (>3 packages of tobacco) but no current use. Intensity of use was available for cigarettes only. We estimated pack-years of cigarette use by multiplying the average number of cigarettes smoked daily when the subject smoked the most by the number of years since starting smoking regularly (for current smokers) or the number of years between starting smoking and last smoking (for former smokers) and dividing the product by 20. Pack-years was incorporated into analyses as a categorical variable.

Pulmonary function data

Subjects who participated in the subcohort performed spirometry using a spirometer (Model 800; Ohio Medical Instrument Company, Inc, Cincinnati, Ohio). The procedures have been documented previously.^{E3} Values used in this analysis included forced vital capacity (FVC), FEV₁, and the FEV₁/FVC ratio. We determined predicted values of FEV₁ and FVC using published spirometric reference values for Caucasians and African Americans.^{E4} We excluded 56 subjects whose race was categorized as "other" given the lack of information on race and corresponding spirometric reference values.

A subject was considered to have obstructive lung disease if the FEV₁/FVC ratio was less than the predicted lower limit of normal FEV₁/FVC for age.^{E4,E5} Obstruction was considered mild (FEV₁ $\geq 70\%$ predicted) or moderate to severe (FEV₁ $< 70\%$ predicted). Subjects were considered to have restrictive disease if there was no evidence of obstruction and the FVC was less than 80% of the predicted value. The remaining subjects, without spirometric evidence of restriction or obstruction, were considered the reference group. We included only those subjects who had reliable spirometry results according to NCHS documentation.

Of the 6913 participants included in the subcohort, spirometry data were available only on 5544 subjects. Although all members of the subcohort were eligible for the spirometry portion of the examination, subjects were excluded from performing spirometry if a study physician did not provide permission, or if subjects could not generate acceptable data because of poor effort or difficulty comprehending instructions. Individual-level reasons for missing spirometry data are not available in the NHANES documentation.

Mortality data and outcomes

Mortality-related data through 2006 including final mortality status, age at death, age when last presumed alive, and underlying cause of death are restricted variables and therefore these data were accessed through the Research Data Center of the NCHS in Hyattsville, Maryland, after an approval process.

The National Death Index (NDI) obtains the cause of death from the death certificate, which is completed by an individual licensed to do so by the state where death takes place. The

underlying cause of death is provided on the death certificate in the best medical opinion of the certifier. Only one underlying cause of death may be listed by the certifying physician, though several immediate causes of death may be listed. The listed underlying cause of death is assigned an *International Statistical Classification of Diseases, 10th Revision (ICD-10)* (or the *International Classification of Diseases, Ninth Revision*, for deaths before 1999) diagnostic code by the NDI staff using a computerized nosology coding system. The cause of death variable used in this analysis was provided by the NDI and has 113 categories identified by *ICD-10* codes, where deaths before 1999 (which originally were coded using the *International Classification of Diseases, Ninth Revision*) were recoded by the NDI staff using *ICD-10* codes.

We examined all-cause, cardiovascular, cancer, and respiratory mortality. We used the *ICD-10* codes, available from the Research Data Center, to classify causes of death as follows: cardiovascular (eg, hypertension, ischemia, atherosclerosis, I00-I13, I20-I51, and I70-I78), cancer (eg, malignant and benign neoplasms, C00-C97 and D00-D48), and respiratory disease (eg, lower respiratory infection, emphysema, and asthma, J10-J18, J20-J22, and J40-J47).

EXCLUSION CRITERIA

We excluded 28 subjects from the full cohort who were listed as having an age of more than 100 years in 2006, in accordance with recommendations from the NCHS. We excluded an additional 1339 subjects who reported a history of tumor, congestive heart failure, myocardial infarction, or stroke at the baseline visit. These subjects were also excluded from the subcohort.

STATISTICAL METHODS

We tested the assumption of proportionality by examining log-log plots ($\log[-\log(\text{survival})]$ vs $\log$ of survival time) and using Schoenfeld residuals after model fitting. All analyses met the assumptions of proportionality.

We accounted for the complex survey design of the NHEFS by incorporating strata and primary sampling units into our analyses. To account for oversampling of some populations in the full cohort and ensure results are representative of the general population, we included sampling weights provided by NHANES in the analyses. However, because the incorporation of NHANES sample weights is controversial, we performed sensitivity analyses with and without sample weights.^{E6,E7} Results were similar in analyses performed with and without the sampling weights incorporated, and using the 1971-1975 visit or the 1982-1984 visit as the start of follow-up (data not shown). The unweighted results using the 1982-1984 survey as the start of follow-up are presented.

Missing data and imputation

Missing data for education, income, and smoking status at the 1982-1984 follow-up underwent multiple imputation using chained equations.^{E8} Education, income, and smoking status were imputed on the basis of sex, age, race, asthma and emphysema history, and a derived variable indicating whether the subject died before or after age 56 years, the age the youngest members of the cohort would be at the final follow-up time.

ADDITIONAL ANALYSES

Comparison of subjects selected for the subcohort who did and did not have spirometry data available

Because our point estimates for all-cause mortality associated with asthma were slightly different between the full cohort and the subcohort (age-adjusted HR in the full cohort, 1.23; 95% CI, 1.07-1.42; age-adjusted HR in the subcohort, 1.07; 95% CI, 0.82-1.40), we compared the mortality risk in subjects selected to be in the subcohort who did and did not have spirometry data available. We found that in models adjusted for age, sex, race, income, education, smoking status, and pack-years, subjects who completed spirometry were protected from all-cause mortality (HR, 0.84; 95% CI, 0.76-0.93). We next examined whether there was an interaction between asthma and spirometry performance on all-cause mortality, and we did not find that there was a significant interaction between spirometry performance and asthma on mortality ($P > .8$ for Asthma $\times$ Spirometry performance interaction). It is possible that in the subcohort, we are underpowered to detect the association between asthma and all-cause mortality. However, given that there are known differences between the full cohort and the subcohort on whom spirometry data are available (eg, the full cohort oversampled the elderly and those at risk for malnutrition while the subcohort was considered nationally representative, and the subcohort with spirometry data is protected from mortality compared with the subcohort without spirometry data), it is also possible that there are differences in the relationship between asthma and all-cause mortality between the 2 cohorts that we were unable to detect statistically.

Analysis of effect modification

We explored whether there was evidence of effect modification by age, sex, race, and smoking history on the association between asthma and mortality. We first generated interaction terms (eg, Asthma $\times$ Age) and included these in adjusted models. For age, we generated a dichotomous variable (≤ 40 years). We found that for respiratory mortality, there was a significant interaction between age and asthma on mortality in the full cohort, but not in the subcohort, and that younger subjects with asthma have a higher hazard of respiratory mortality than do older subjects with asthma. In the full cohort, in models adjusted for age, sex, income, education, race, and smoking status obtained at the 1982-1984 survey (ever/never), the hazard ratio for asthma among those aged 25 to 40 years was 5.88 (95% CI, 1.79-18.99). Among older subjects aged 41 to 75 years, the HR for asthma was 2.04 (95% CI, 1.36-3.08; P value for interaction of asthma and age = .03). In the subcohort, the adjusted HR for asthma among younger subjects was 3.00 (95% CI, 0.19-47.80) and among older subjects it was 2.00 (95% CI, 0.86-4.60; P value for interaction of asthma and age = .48). Because the interaction was not identified in the subcohort, it is possible that the effect modification by age on respiratory mortality is explained by smoking, as more information on smoking is available in the subcohort. We did not find evidence that there was an interaction between sex, race, and smoking history and asthma on all-cause and respiratory outcomes.

ADDITIONAL INFORMATION

The findings and conclusions in this article are those of the authors and do not necessarily represent the views of the Research Data Center, the NCHS, or the Centers for Disease Control and Prevention.

REFERENCES

- E1. Centers for Disease Control and Prevention. NHANES I epidemiologic followup study. Available at: <http://www.cdc.gov/nchs/nhanes/nhefs/nhefs.htm>. Accessed May 1, 2012.
- E2. US Department of Commerce. Characteristics of the low income population: 1972. Bureau of the Census, Washington, DC: Series P-60, Number 88; 1973
- E3. National Center for Health Statistics. Plan and operation of the Health and Nutrition Examination Survey, United States, 1971-1973. Washington, DC: National Center for Health Statistics; 1973.
- E4. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999;159:179-87.
- E5. Pellegrino R, Viedi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. *Eur Respir J* 2005;26:948-68.
- E6. Mannino DM, Buist AS, Petty TL, Enright PL, Enright SC. Lung function and mortality in the United States: data from the First National Health and Nutrition Examination Survey follow up study. *Thorax* 2003;58:388-93.
- E7. Ingram DD, Makuc DM. Statistical issues in analyzing the NHANES I Epidemiologic Followup Study. Series 2: data evaluation and methods research. *Vital Health Stat* 2 1994;1-30.
- E8. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med* 2011;30:377-99.

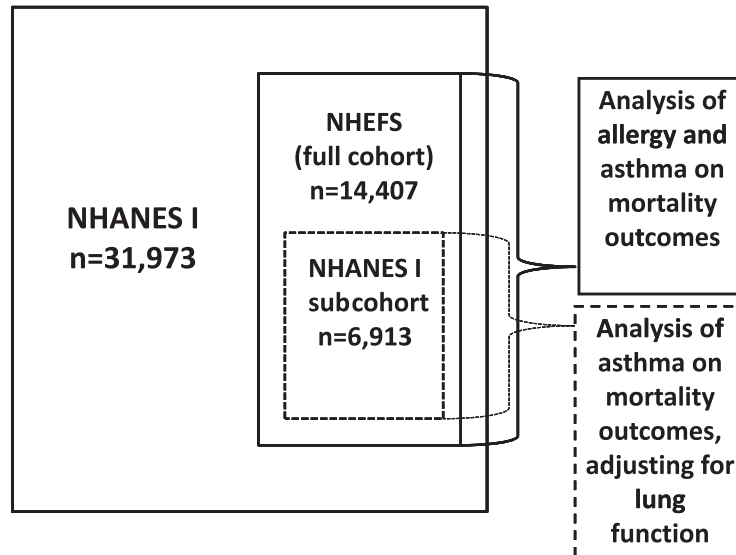


FIG E1. Overall study design. NHANES I took place in 1971-1975. The NHEFS followed all individuals aged 25 years or older who had a medical examination at NHANES I. The NHANES I subcohort had additional data collected including spirometry and detailed smoking history.

TABLE E1. HRs for mortality according to asthma or allergic disease status within the full cohort (N = 13,040)

Condition	Mortality			
	All-cause	Cardiovascular	Cancer	Respiratory
Asthma				
Age-adjusted hazard (95% CI)	1.23 (1.07-1.42)*	1.15 (0.93-1.41)	1.23 (0.92-1.60)	2.22 (1.47-3.35)*
Fully adjusted hazard (95% CI)	1.22 (1.06-1.40)*	1.13 (0.92-1.40)	1.23 (0.93-1.62)	2.28 (1.50-3.47)*
Food allergy				
Age-adjusted hazard (95% CI)	0.90 (0.79-1.02)	0.85 (0.69-1.05)	0.73 (0.53-1.02)	1.17 (0.75-1.81)
Fully adjusted hazard (95% CI)	0.95 (0.82-1.12)	0.88 (0.70-1.11)	0.81 (0.58-1.13)	1.36 (0.87-2.13)
Hay fever				
Age-adjusted hazard (95% CI)	0.97 (0.86-1.09)	0.87 (0.74-1.02)	0.96 (0.78-1.18)	1.09 (0.79-1.62)
Fully adjusted hazard (95% CI)	1.02 (0.90-1.15)	0.90 (0.77-1.06)	1.04 (0.84-1.28)	1.12 (0.78-1.61)

Full model adjusts for age, sex, income, education, race, and smoking status obtained at the 1982-1984 survey.

*Statistically significant ($P < .05$).