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

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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 disease (CVD) [5] 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 (NHANES I) 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.

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The NHEFS included a US-based *full cohort* of 14,407 subjects aged 25-74 years who completed an interview and medical examination in 1971-75. A *sub-cohort* of 6,913 underwent a more detailed health interview and examination, including questions on smoking and performance of spirometry (Supplementary Figure 1). While the full cohort oversampled certain groups considered at risk for malnutrition, the sub-cohort is considered nationally representative. Follow-up occurred in 1982-84, 1986, 1987, and 1992. NHEFS ascertained mortality through December 31, 2006 based upon 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 1982-84 to ascertain smoking status. Missing education, income, and smoking data were imputed. See the Appendix 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, TX) using age as the underlying time metric and the 1982-84 survey as the start of follow-up. Analyses took place at the Research Data Center at the National Center for Health Statistics in Hyattsville, MD, as the mortality data through 2006 is considered restricted-use data.

At baseline, 3.6% of subjects reported a history of doctor diagnosed asthma, 4.5% reported food allergy and 8.6% reported hay fever. 6,800 (52.1%) died during follow-up. There were 2,492 cardiovascular deaths, 1,588 cancer deaths, and 539 respiratory deaths. Demographic characteristics of NHEFS subjects are shown in Table 1.

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 associated with mortality of any cause (See Supplementary Table 1). The age-adjusted HR for asthma and respiratory mortality was 2.22 (95% CI 1.47-3.35, Table 2), which was similar after adjusting for gender, income, education, race, and smoking history, and exclusion of subjects reporting a diagnosis of emphysema. In the sub-cohort, 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). Further addition of lung function to the model resulted in an adjusted HR associated with asthma of 1.45 (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 gender, 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 sub-cohort (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 sub-cohort or a lack of power in this smaller sample size (please see supplementary materials for further discussion, and exploration of effect modification).

We examined the association between asthma and allergic disease and mortality in a population-based cohort with over 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 US due to allergic disease *per se*, asthma was associated with an increased risk of respiratory and all-cause mortality. In the sub-cohort where more detailed data on smoking history was 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 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, one 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 sub-cohort 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 if 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 1982-84 follow-up, making it less likely that assessment of allergic disease, asthma, and pulmonary function were confounded by the presence of other medical complications. Most of our predictors were based upon 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 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 sub-cohort 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 does not support the theory that allergy is a systemic inflammatory disease leading to downstream immune dysregulation, CVD, or cancer. Within the sub-cohort, 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Demographic characteristics of NHEFS participants at Baseline (1971-74).

	Full Cohort n=l3,042	**Sub-cohort n=5,132**
Age 25-34, % 35-44, % 45-54, % 55-64, % 65-75,%	26.6 21.7 16.1 12.1 23.3	25.9 19.3 23.6 17.4 13.6
Race White, % African American, % Other, %	83.6 15.2 1.2	89.2 10.8 --
Sex Male, % Female, %	39.6 60.4	45.3 54.7
Education <10th grade/ special school, % 11th - 12th grade, % college/graduate, % Missing, %	37.3 38.5 23.5 0.6	30.7 41.8 27.2 0.2
Income (annual) <$5,000, % $5,000-<$10,000, % ≥$10,000-<$l 5,000, % ≥$15,000 Missing, %	25.5 29.3 20.9 20.4 3.7	18.9 26.424.0 27.1 3.5
Smoking Status* Never, % Ever, % Current, % Former, % Missing, %	38.2 46.4 -- -- 15.4	38.0 -- 19.6 42.2 0.01
Pack years category* 0,% <30, % 30-60, % >60, % Missing, %	n/a	41.4 31.5 15.6 7.5 3.9

* The full cohort includes all NHEFS who met inclusion/exclusion criteria. The sub-cohort 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 sub-cohort, 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 Appendix for methods and variable definitions.

Table 2

Hazard ratios for asthma and all cause and respiratory mortality, adjusting for demographic, smoking, and lung function characteristics.

Outcome	**Respiratory Mortality**								**All Cause Mortality**							
Population	**Full Cohort**				**Sub-cohort**				**Full Cohort**				**Sub-cohort**			
Model	**1**	**2**	**3**	**4**	**1**	**2**	**5**	**6**	**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)	**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)
Mild obstruction								**2.08 (1.34-3.24)**								0.96 (0.79-1.15)
Moderate to severe obstruction								**5.86 (3.71-9.23)**								**1.57 (1.30-1.89)**
Restriction								**1.65 (1.09-2.47)**								**1.30 (1.14-1.49)**

Model 1 is adjusted for age. Model 2 is adjusted for age, gender, income, education, and race. Model 3 is the same as model 2, additionally adjusted for smoking history obtained at the 1982-84 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.

Values in boldface are statistically significant ($p<0.05$).