

Is allergen skin test reactivity a predictor of mortality?

Findings from a national cohort

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Summary

Background The importance of atopy on subsequent mortality is controversial. A clearer understanding is important as atopy is increasing worldwide.

Objective To determine the influence of allergen skin test reactivity on observed mortality of a national cohort.

Methods Baseline health status and atopic status (allergen skin testing) was measured as part of the second National Health and Nutrition Examination Survey (NHANES II), a representative sample of the US population, during the years 1976–80. Vital status and cause of death were assessed through December 31, 1992 for all examinees 30 years of age or older at baseline ($n = 9252$) as part of the NHANES II Mortality Study (NH2MS). The analytic sample contained 8179 men and women after excluding missing data. Allergen skin test reactivity was defined as weal ≥ 3 mm to one of eight 1 : 20 (w/v), 50% glycerinated ('No US Standard of Potency') allergens licensed by the FDA: house dust, cat, dog, Alternaria, mixed giant/short ragweed, oak, perennial rye grass, and Bermuda grass. Survival analyses were conducted using multivariate adjusted Cox regression models to evaluate the association between atopy and all-cause, cardiovascular, and cancer mortality.

Results There was no association between allergen skin test reactivity and all cause mortality: 30–44 years RR = 1.07 (95% CI 0.63–1.84); 45–59 years RR = 1.10 (0.78–1.55); 60–75 years RR = 1.07 (0.91–1.25). Results were unchanged when cancer or heart disease mortality were examined separately. The presence or absence of allergic symptoms, using the flare to define skin test reactivity, eliminating deaths in the first 5 years of follow-up, or eliminating individuals with pre-existing conditions did not alter the findings.

Conclusions Atopy, defined by allergen skin test reactivity, with or without symptoms, is not a predictor of subsequent mortality.

Keywords: atopy, survival, allergen skin test reactivity

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Introduction

It has been speculated for over 40 years that the atopic state has broader influence on health than just the allergic symptoms associated with it. In regards to cancer, atopy has been postulated to be either protective or detrimental owing to enhanced or deficient immune surveillance [1–3].

Atopy has also been postulated to play either a protective role in cardiovascular disease by decreased platelet aggregation [4] or be a risk factor via mast cell release of histamine provoking coronary artery spasm [5]. The conflicting findings of previous studies are due in part to methodological issues such as differing definitions of atopy, lack of objective measures for atopy, restricted selection of patients or outcomes, and failure to control for important cancer and cardiovascular risk factors such as smoking [1–3,6–24].

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Asthma and allergic diseases have been rising worldwide over the last several decades [25]. The potential effect of this change on future mortality needs to be understood. The recently available data on the approximately 14 years follow-up of the cohort participating in the second National Health and Nutrition Examination Survey (NHANES II) allowed the relation of atopy as defined by an objective measure, allergen skin testing, and subsequent mortality to be evaluated after controlling for other important predictors of mortality.

Methods

Survey

The second National Health and Nutrition Examination Survey (NHANES II) was conducted at 64 sampling sites by the National Center for Health Statistics during the years 1976–80. The NHANES II was a stratified multistage probability sample of the civilian noninstitutionalized civilian US population ages 6 months through 74 years of age. Standardized interview and examination procedures were used to collect a broad spectrum of health data on participants [26].

The NHANES II Mortality Study (NH2MS) was conducted on the 9252 NHANES II participants who were 30 years of age or older at the time of their examination. During the period 1976 through December 31, 1992 (median follow up time of 14.3 years) a total of 2145 deaths were identified [27]. Deaths were identified by matching personal identifiers to the National Death Index (NDI) for the years 1979–92 [28,29]. The NDI includes all deaths in the US from 1979 forward. Social security numbers were not available for matching. Previous studies have shown that 90% or more of all deaths can be identified from the NDI when social security numbers are not used as part of the matching criteria [30–32]. For the years 1976–78, mortality follow-up was conducted by matching personal identifiers to the Social Security Administration's Mortality Tapes Matching System (SSA). No data exist on the effectiveness of matching to the SSA without social security numbers. Based on US mortality rates for 1976, 142 deaths were expected during the years 1976–78; 84 deaths were identified [27].

Allergen skin testing

Allergen skin testing was performed by the prick-puncture method with a 25-gauge needle using eight 1 : 20 (w/v), 50% glycerinated ('No US Standard of Potency') allergens licensed by the Food and Drug Administration: house dust, cat, dog, *Alternaria*, mixed giant/short ragweed, oak, perennial rye grass, and Bermuda grass. A positive control

(histamine diphosphate) and a negative control (50% glycerol) were also applied [33]. The battery was used to elicit immediate hypersensitivity responses in the general US population, regardless of region. The battery was not intended to serve as a diagnostic evaluation of the allergic status of any individual tested.

Skin test reactions were measured 20 min after allergen administration. The analyses presented herein are based on the mean size of the weal reaction. The size of the weal was defined as the mean of the length and the width. Length was defined as the largest diameter parallel to the length of the arm. The width was defined as the diameter perpendicular to the length at the midpoint. A positive allergen skin test was defined as an average weal size of ≥ 3 mm. Overall, 16.3% of the sample had at least one positive allergen skin test. The rates of reactivity to the individual allergens were: house dust 5.6%, *alternaria* 1.8%, cat 2%, dog 2.2%, oak 4.1%, ragweed 8.4%, rye grass 6.9%, bermuda grass 3.1%.

Variable definitions

Smoking status was classified as the following: active smoker—sample person presently smoking; past smoker—sample person not now smoking but who had smoked more than 100 cigarettes during their lifetime; nonsmoker—sample person who had not smoked more than 100 cigarettes during their lifetime.

The poverty index was a standardized index derived from the total household income, family size, and the federal poverty level [34].

Mortality was based on death certificates. All cause mortality was death regardless of the underlying cause. Cancer mortality was deaths with the underlying cause of malignant neoplasm (ICD 9 CM 140–208). Heart disease mortality were deaths from hypertensive heart disease (402, 404–405), ischemic heart disease (410–414), diseases of the pulmonary circulation (415–417), and other forms of heart disease (420–429).

Statistical methods

Bivariate statistical testing was performed on categorical variables using Pearson chi-square. The analyses were performed under simple random sampling assumptions. Survival experience was evaluated using Cox Regression [35].

Results

Of the 9252 participants in the NH2MS, complete data for vital status, allergy skin testing, examination, and medical history variables were available for 8179 (88.4%). The two main reasons for missing data were incomplete allergy skin

Table 1 Distribution of allergen skin test reactivity and all cause mortality

	<i>n</i>	Sample		
		Percent distribution	Percent skin test positive†	Percent mortality
Total	8179		16.3%	22.9%
Weal				
Negative	6847	83.7%		23.8%
1 + Positive	1332	16.3%		18.5%***
Age (yrs)				
30–44	2328	28.5%	22.3%	3.4%
45–59	1941	23.7%	16.4%	13.7%
60–75	3910	47.8%	12.6%***	39.2%***
Race‡				
White	7208	88.1%	16.1%	23%
Black	841	10.3%	15.7%	23.3%
Sex				
Male	3888	47.5%	17.7%	28.8%
Female	4291	52.5%	15%***	17.7%***
Smoking				
Never	3315	40.5%	16.8%	18%
Past	2213	27.1%	15.8%	26.9%
Active	2651	32.4%	16%	25.8%***
Poverty level				
At/Below	1072	13.1%	13%	30.8%
Above	7107	86.9%	16.8%**	21.8%***
Education				
Grade school	2282	27.9%	12.1%	32.6%
High school	4058	49.6%	16.1%	21.2%
College	1839	22.5%	21.8%***	14.8%***
Health status				
Excellent/very good	3401	41.6%	19%	13.1%
Good	2491	30.5%	16%	22.4%
Fair/poor	2287	27.9%	12.5%***	38.2%***
BMI	8179	26.1		
Lower			15.5%	23.9%
Middle			17.1%	22.8%
Upper			16.2%	22.2%
Cholesterol	8179	226.3		
Lower			17.9%	20.0%
Middle			17.1%	22.8%
Upper			13.8%***	25.9%***
Systolic blood pressure	8179	134.7		
Lower			18.3%	13%
Middle			15.6%	21.8%
Upper			14.8%**	35%***

†Weal ≥ 3 mm. ‡Other race not shown separately owing to small sample size. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

testing for 55.8% (599), and missing income data 33.5% (359). Only 0.2% (2) individuals were missing information on vital status.

The distribution of allergen skin test reactivity and mortality by selected variables is presented in Table 1.

Allergen skin test reactivity was increased in the younger age groups, males, individuals living above poverty, those with higher levels of education, and those reporting excellent/very good health status, while allergen skin test reactivity was decreased in individuals with upper levels of

Table 2. Adjusted relative risk of mortality for allergen skin test-positive individuals*†

	All cause	Cancer	Cardiovascular
30–44 years olds (n = 2328)			
Deaths	80	25	19
Relative risk of death	1.07 (0.63, 1.84)	0.89 (0.33, 2.43)	1.50 (0.51, 4.36)
30–44 years old males (n = 1101)			
Deaths	54	10	17
Relative risk of death	0.94 (0.46, 1.90)	0.34 (0.04, 2.8)	1.22 (0.38, 3.93)
30–44 years old females (n = 1227)			
Deaths	26	15	2
Relative risk of death	1.48 (0.61, 3.59)	1.53 (0.47, 4.91)	NA
45–59 years olds (n = 1941)			
Deaths	266	101	82
Relative risk of death	1.10 (0.78, 1.55)	0.78 (0.42, 1.44)	1.87 (1.09, 3.21)
45–59 years old males (n = 913)			
Deaths	153	52	51
Relative risk of death	0.98 (0.63, 1.55)	0.83 (0.37, 1.87)	1.56 (0.79, 3.1)
45–59 years Old Females (n = 1028)			
Deaths	113	49	31
Relative risk of death	1.25 (0.74, 2.12)	0.72 (0.28, 1.83)	2.37 (0.99, 5.67)
60–75 years olds (n = 3910)			
Deaths	1531	373	605
Relative risk of death	1.07 (0.91, 1.25)	1.13 (0.84, 1.53)	1.06 (0.83, 1.37)
60–75 years old males (n = 1874)			
Deaths	911	233	359
Relative risk of death	1.02 (0.83, 1.24)	1.15 (0.79, 1.66)	0.93 (0.66, 1.3)
60–75 years old females (n = 2036)			
Death	620	140	246
Relative risk of death	1.16 (0.90, 1.48)	1.09 (0.65, 1.82)	1.31 (0.90, 1.91)

*Skin test positive (1 or more weals ≥ 3 mm) vs skin test negative. †Adjusted for age, sex, smoking, serum cholesterol, systolic blood pressure, poverty index, self-reported health status, and education level. In brackets, 95% Confidence Interval.

cholesterol and systolic blood pressure. All-cause mortality was decreased among individuals with at least one allergen skin test positive. All-cause mortality was increased in the older age groups, males, smokers, individuals living in poverty, those with lower education, poor self-reported health status, and increased cholesterol and systolic blood pressure.

Next Cox regressions were run to determine whether the protective effect of allergen skin test reactivity on all-cause mortality remained after controlling for the relevant confounders (Table 2). Because of the strong and opposite

effect that age had on allergen skin test reactivity (decreased with age) and all cause mortality (increased with age) the population was divided into tertiles based on age (30–44 years, 45–59 years, 60–75 years). Cox regression models evaluating the association between allergen skin test reactivity and mortality were run within each of the age stratas for the total population, then males and females separately. These models controlled for age, sex, smoking, serum cholesterol, systolic blood pressure, poverty index, self-reported health status, and education level. No association between allergen skin test reactivity and mortality (all cause, cancer,

or cardiovascular) was found in any of the age sex groups except for a borderline statistically significant increase in cardiovascular mortality among 45–59-year-olds with allergy skin test reactivity.

To determine the robustness of these results, the models were rerun with the following conditions: eliminating deaths in the first 5 years of follow-up, eliminating individuals with pre-existing cardiovascular disease or cancer at baseline, defining allergen skin test reactivity using the flare (≥ 10.5 mm), or defining allergen skin test reactivity as a sample person with self-reported allergic symptoms and allergic skin test reactivity. The results did not change significantly with these manipulations of the data.

Discussion

Atopy as defined by allergen skin test reactivity appears to have no role in subsequent mortality. The initial protective effect of atopy on mortality was merely a result of the opposite effect that age has on mortality and allergen skin test reactivity. This finding was unchanged when the leading causes of death (heart disease and cancer) were looked at separately or the definition of skin test reactivity was varied. The strengths of this cohort for evaluating this issue include the use of standardized allergen skin testing years before the development of cancer or cardiovascular disease; looking at broad categories of mortality to avoid the problem of multiple comparisons; the concomitant measurement of a number of important predictors of mortality; a follow-up of on average 14 years which should have been sufficient over this wide an age range for any important effect to be seen.

Power is always a concern in population studies. As might be expected the power in the entire sample, ages 30–75, was excellent while within age groups the power was largest in the older age groups. For example, the power to detect a relative risk of 1.25 for all causes mortality in the entire cohort, assuming a type 1 error or alpha level of 0.05, was >0.9 . In the youngest age group satisfactory power required a relative risk of 2 or larger while in the 60–75 years age group the power to detect a relative risk of 1.25 for all causes mortality, again, was 0.9 or above. The power to detect a significant difference also tended to be higher for CVD than for cancer. From this study it can not be ruled out that the atopic state is related to very specific forms of cancer or heart disease, but if such a relation exists it is a relatively minor contributor to mortality either in general or specifically to either cancer or heart disease.

The findings of previous cross-sectional studies looking at the association of atopy with cancer tend to find atopy associated with lower rates of cancer [1,6,8,9,16,18,22], although a few have reported no relationship [7,12,13,15]. As these studies deal with individuals who already have developed cancer, it is unclear if the reported association is

causal, or an artifact caused by under-reporting of allergy in the presence of a life-threatening disease.

Follow-up studies of individuals before they develop cancer do not suffer from this bias. No overall increased risk of developing cancer was noted in a 6-years follow-up of Seventh-day Adventist with a history of any allergy [2] nor in a 7-years follow-up of clinic patients with allergen skin test reactivity [3]. A 10-years follow-up of examinees in the first National Health and Nutrition Examination Survey, 1971–75, a sample of the US civilian population, reported an increased incidence of cancer (OR = 1.4, 95% confidence interval 1.1–1.77) among participants reporting any allergy [20]. The definition of allergy used in this study was quite broad and included 'asthma, hayfever, hives, food allergy, or other allergies'. All these studies [2,3,20] report further analyses looking at a wide variety of individual cancers and specific allergies. There tends to be no consistency in these findings implying the statistically significant associations are chance associations resulting from the multiple comparisons carried out.

In a group of studies looking specifically at asthma and the development of cancer no clear association emerges. Self-reported asthma was related to the development of lung cancer in males but not females in an 18-years follow-up of participants in the Alameda County Study [19]; similar findings were reported in a 29-years follow-up of men hospitalized for asthma during World War II in army hospitals [14]. Among approximately 78 000 Finnish adult asthmatics studied through the linkage of two registries, a number of cancers such as lung, rectum, bladder, and colon were increased while other cancers such as uterine, larynx, stomach, multiple myeloma, and leukaemia were decreased [23]. In contrast, self-reported asthma among individuals born between 1850 and 1899 who rented gym lockers at Harvard University was not associated with death from neoplasms in a follow-up conducted in 1967 [11]. A study of 2547 adult asthmatics in Britain found no increase in cancer deaths in all ages combined but a slight decrease in cancer deaths in patients under 45 years of age [24].

The few studies looking at allergies and cardiovascular disease tend to imply a role for allergies in the development of cardiovascular disease. Cross-sectional studies have reported an increase in the reported prevalence of allergies in nonsmoking adults with hypertension [10]; increased IgE in males with a history of MI, stroke, or large-vessel peripheral arterial disease, with no association found in women [17]; or elevated IgE in patients with acute MI or unstable angina in cardiac care units [21].

In summary the literature tends to support our findings of little or no association of atopy with mortality. The implications from our results are that the increasing trend of atopy with its associated immune deviation favouring a Th2-like cytokine profile [36] should not directly impact worldwide

mortality. The findings of this study should be of comfort for persons with atopy as we find no evidence that this condition will have a significant impact on their longevity. Although evidence of a mortality effect is lacking, the impact of atopic diseases on morbidity and health care costs are substantial and more than justify the increasing public health initiatives aimed at elucidating the potential aetiological exposures [37].

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