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Association of allergic rhinitis, coronary heart disease, cerebrovascular disease, and all-cause mortality

Angelina M. Crans Yoon, MD [*]; Vicki Chiu, MS [†]; Jamal S. Rana, MD, PhD [‡,§]; Javed Sheikh, MD [*]

[*] Department of Allergy and Clinical Immunology, Kaiser Permanente Los Angeles, Los Angeles, California
[†] Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena, California
[‡] Department of Cardiology and Division of Research, Kaiser Permanente Northern California, Oakland, California
[§] Department of Medicine, University of California San Francisco, San Francisco, California

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ABSTRACT

Background: Inflammation is implicated in atherosclerotic cardiovascular disease. Allergic diseases also involve a systemic inflammatory state, which may potentiate cardiovascular disease.
Objective: To examine the association of allergic rhinitis, coronary heart disease (CHD), cerebrovascular disease (CVD), and all-cause mortality.
Methods: We conducted a retrospective, population-based, matched cohort study comparing the incidence of CHD, CVD, and all-cause mortality from January 1, 1999, through December 31, 2012, in patients with *International Classification of Disease, Ninth Revision*, documented allergic rhinitis matched 1:1 by age, sex, and ethnicity to a reference cohort without allergic rhinitis within Kaiser Permanente Southern California. Fully adjusted hazard ratios (HRs) were calculated. Further analyses for those with positive environmental allergen specific IgE (sIgE) test results within the allergic rhinitis cohort were also performed.
Results: Patients with physician-diagnosed allergic rhinitis (N = 110, 207 in matched cohort) had significantly lower risk for myocardial infarction (HR, 0.63; 95% confidence interval [CI], 0.59–0.67; $P < .001$), all CHD (HR, 0.81; 95% CI, 0.78–0.84; $P < .001$), CVD (HR, 0.67; 95% CI, 0.64–0.70; $P < .001$), and all-cause mortality (HR, 0.42; 95% CI, 0.40–0.43; $P < .001$). The results were similar after excluding patients with asthma. Patients with positive sIgE test result also had a decreased risk of all CHD (relative risk [RR], 0.87; 95% CI, 0.79–0.95; $P = .003$) but no association with cerebrovascular events (RR, 0.89; 95% CI, 0.77–1.02; $P = .10$) and all-cause mortality (RR, 1.16; 95% CI, 1.00–1.34; $P = .06$).
Conclusion: We found that the presence of allergic rhinitis was associated with decreased CHD, CVD, and all-cause mortality. This decreased risk was more pronounced after excluding patients with asthma. Patients with positive sIgE test results also had decreased risk of CHD.

Introduction

The role of inflammation in atherosclerotic cardiovascular disease (ASCVD) is well established.[1] Allergic diseases also involve a systemic inflammatory state, which may potentiate cardiovascular disease.[2,3] T lymphocytes have been implicated in the development of ASCVD and are directly found in atherosclerotic lesions.[4] In mouse models, T_H2-type inflammation seems to be protective against atherosclerosis, whereas T_H1-type inflammation promotes atherogenesis.[5–7]

Mast cells, which are found in large concentrations in the heart and vasculature, are another mechanism potentially linking allergic disease with ASCVD.[8–10] Proinflammatory mediators, such as tryptase, chymase, and histamine released by mast cells, are associated with coronary artery disease in small studies of patients with known coronary artery disease.[11–14] Total IgE levels have also been found to be elevated in patients with myocardial infarction (MI) or unstable angina, supporting a direct role for IgE in atherogenesis.[15]

Evidence potentially linking allergic disease to ASCVD in humans is conflicting. Several small studies have found an association among eosinophilia, positive skin test results, daily pollen burden, and cardiovascular disease.[16–20] Asthma has been associated with increased ASCVD and all-cause mortality; however, covariate allergy (broadly defined to include diagnoses of atopic dermatitis, anaphylaxis, and food allergy, in addition to allergic rhinitis [AR]) did not affect outcomes.[21,22] Allergic rhinitis has previously been associated with incident hypertension,[23] although those results were not duplicated in a similar study,[24] and self-

Reprints: Javed Sheikh, MD, Department of Allergy/Immunology, Kaiser Los Angeles Medical Center, 1515 N Vermont Ave, Fifth Floor, Los Angeles, CA 90027; E-mail: javed.sheikh@kp.org.
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reported allergic rhinoconjunctivitis symptoms were associated with increased coronary heart disease (CHD) in one National Health and Nutrition Examination Survey (NHANES) study.[25] However, a more recent study of NHANES 2005–2006 data found that having a positive allergen specific IgE (sIgE) test result was inversely related to having a history of an MI.[26]

The current understanding of how AR may relate to ASCVD is unclear. The primary objective of our study was to assess the incidence of ASCVD and all-cause mortality in patients with AR in a large, contemporary, real-world cohort. Our secondary objective was to assess allergen sIgE positivity within the cohort and evaluate its association with CHD, cerebrovascular disease (CVD), and all-cause mortality.

Methods

Study Design

We assembled a retrospective cohort of 110,207 patients with AR who were matched 1:1 by age, sex, and ethnicity to a reference cohort without AR within Kaiser Permanente Southern California, a large integrated health care system. We then compared the incidence of cardiovascular and cerebrovascular events and all-cause mortality from January 1, 1999, through December 31, 2012, using the Kaiser Permanente Southern California regional database and *International Classification of Diseases, Ninth Revision* (*ICD-9*), diagnosis codes. The study had a 7-year enrollment period from January 1, 1999, through December 31, 2005, and a 7-year follow-up period spanning January 1, 2005, through December 31, 2012. The maximum possible follow-up time was 13 years.

Inclusion criteria for the AR cohort were age older than 30 years and any diagnosis of AR (*ICD-9* code, 477) during the enrollment period. Patients were excluded if they had fewer than 2 outpatient visits for physician-documented AR within 12 months during the study enrollment period or if they did not have Kaiser Permanente membership for at least 1 year after the index date. Because Kaiser Permanente provides all levels of care, the diagnosis of AR could have been made in a primary care setting or by a specialist. Because most patients are seen in a primary care setting, most patients have their conditions diagnosed at this level. Within Kaiser Permanente Southern California, allergy and otolaryngology specialists are built into the network, so there is no bias toward tertiary care. These selection criteria were validated by manual review of 48 individual patient records. Median number of visits for AR during the study period was 4. Forty-six of 48 patients (95%) had medications prescribed for AR. Only 13 patients had in vitro sIgE testing for environmental allergens, of whom 12 (92%) had positive results, supporting an allergic cause of rhinitis. Medical record review of physician documentation was limited because electronic documentation only began in 2007; however, of 29 patients with encounters after 2007, 28 (96%) had supporting physician-documented text in the medical record, supporting AR diagnosis, such as physical examination findings.

Covariate asthma, diabetes, hypertension, cancer, autoimmune disease, renal disease, dyslipidemia, smoking status, human immunodeficiency virus, and obesity were determined by *International Classification of Diseases, Ninth Revision* (*ICD-9*), codes used for the ascertainment of these covariate diagnoses (eTable 1). Income and education data were estimated by geocoding the patient's census block, census block group, or zip code and cross-referencing to census data (Claritas Inc, San Diego, California). To assess incidence, we excluded patients from both cohorts if they had any prior cardiovascular or cerebrovascular events ascertained by *ICD-9* codes before the date of enrollment.

Primary outcomes assessed included CHD (MI, stable and unstable angina, other chronic ischemic heart disease, and revascularization procedures, such as percutaneous coronary intervention and coronary artery bypass surgery), CVD (cerebral hemorrhage and ischemic stroke), and mortality (subdivided into CHD related, CVD related, and other). Mortality data were drawn from an internal Kaiser Permanente database and cross-referenced with California state death records (recorded by *International Classification of Diseases, Tenth Revision* [*ICD-10*], codes). Patients without a specific cause of death were not included in the subgroups but were included in the all-cause mortality analysis. See eTable 1 for *ICD-9* codes for the outcomes and *ICD-10* codes for the cause of death.

Secondary analysis evaluated the association between sIgE positivity and the primary outcomes (condensed to all cardiovascular events, cerebrovascular events, and all-cause mortality for simplicity). Laboratory results for sIgE for an in vitro allergen environmental panel consisting of 13 of the most common environmental allergens encountered in southern California (eTable 2) were evaluated and considered to be positive if at least one of the test results was greater than or equal to 0.35 kU/L. This environmental allergen panel is commonly ordered as a screening test for environmental allergies within Kaiser Permanente Southern California. Patients had to have the complete panel performed to be included in this analysis.

The Kaiser Permanente Southern California Institutional Review Board approved this study. Informed consent was not required because this was a data-only study.

Statistical Analysis

To determine the incidence of ASCVD in both cohorts, the number of events was counted and the event rate per 100,000 person years was calculated for each outcome. Hazard ratios (HRs) for the primary outcomes were then calculated using survival analysis with a fully adjusted Cox proportional hazards model. Time 0 (index date) was the same between the cohort patients and their matched cohort controls. Patients were followed up until they reached a primary end point, unenrolled from the health plan, or the study end date, whichever was first.

For the secondary outcomes, the relative risks (RRs) of the primary end points within the AR cohort were assessed, comparing those with at least one positive sIgE test result with those with negative environmental panel results. Adjusted RRs were also calculated based on age, sex, and race in addition to the previously listed covariates because this subgroup was not compared with their matched cohort without AR because of absence of sIgE data on this control cohort. P values were calculated using χ^2 tests.

Data were analyzed using SAS statistical software, version 9.3 (SAS Institute Inc, Cary, North Carolina). A 2-tailed $P < .05$ was considered significant.

Results

A total of 110,207 patients were included in the AR cohort after applying the exclusion criteria. 65.8% were female, 37.8% white, 28.4% Hispanic, 10.1% black, 8.9% Asian, 1.5% other, and 13.2% unknown (Table 1). These demographics are similar to those of Los Angeles County.[27] The mean (SD) age was 47.9 (12.32) years. The AR cohort had a slightly higher estimated median percentage of high school graduates than controls (81.0% vs 79.5 %) and had a slightly higher median annual household income ($55,510 vs $53,333). These findings were both statistically significant ($P < .001$). A total of 16.6% of the patients in the AR cohort and 2.9% of the control cohort had asthma. The median number of annual outpatient visits for any diagnosis was 8.2 (interquartile range [IQR], 4.8–13.4) for the AR cohort and 3.9 (IQR, 1.5–7.6) for the reference cohort. The median follow-up time was 9.6 years (IQR, 5.9–12.3 years) for the AR cohort and 8.1 years (IQR, 2.4–11.3 years) for the reference cohort. Of note, the AR cohort had an increased incidence of traditional ASCVD risk factors, such as hypertension, dyslipidemia,