



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

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ARTICLE INFO

Article history:

Received for publication June 20, 2016.

Received in revised form August 3, 2016.

Accepted for publication August 18, 2016.

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.

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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-

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Disclosures: Authors have nothing to disclose.

<http://dx.doi.org/10.1016/j.anai.2016.08.021>

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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,

and obesity, compared with their reference cohort. The reference cohort had slightly increased prevalence of diabetes compared with the AR cohort (Table 1).

After adjusting for comorbidities, demographic differences, and frequency of outpatient visits, patients in the AR cohort had a significantly lower risk for MI (HR, 0.63; 95% CI, 0.59–0.67), and their total risk of all cardiovascular events was significantly decreased (HR, 0.81; 95% CI, 0.78–0.84). The AR cohort had a significantly decreased risk of CVD (HR, 0.67; 95% CI, 0.64–0.70) and a very significant decrease in all-cause mortality (HR, 0.42; 95% CI, 0.40–0.43), which did not significantly differ when CHD and CVD-related deaths were analyzed separately (Table 2).

Because asthma has been found to increase ASCVD in several studies,^{22,23} the analyses were repeated with all patients with any diagnosis of asthma before or during the study period excluded. This resulted in an AR cohort and a control cohort of 86,504 individuals each. The AR cohort without asthma also had a decreased risk of MI compared with their reference cohort (HR, 0.62; 95% CI, 0.58–0.67), with a decreased HR for all coronary events (HR, 0.79; 95% CI, 0.76–0.82) and a decreased risk of CVD (HR, 0.66; 95% CI, 0.63–0.70) and all-cause mortality (HR, 0.42; 95% CI, 0.41–0.44), which again did not differ by cause of mortality (Table 3).

Because our cohort was relatively young, the 3 aggregate outcomes were stratified by the ages of 30 to 49 years and 50 years or older at time of enrollment. Among younger adults there was a slightly less marked reduction in CHD risk among patients with AR compared with patients without AR. The difference in HRs between the 2 age groups was statistically significant but clinically and epidemiologically trivial (HR, 0.86 vs 0.84; $P = .048$). No significant

difference in the adjusted HRs was found between the age groups for CVD or mortality outcomes (eTable 3).

To examine the association between positive serum allergen sIgE test results and ASCVD outcomes, 17,159 patients in the AR cohort were identified who had the complete allergen sIgE environmental panel performed during the study period. Of these, 9,065 patients had at least 1 positive sIgE test result. Crude RRs were significantly decreased for aggregate outcomes of cardiovascular events, cerebrovascular events, and all-cause mortality. However, after adjusting for covariates, only cardiovascular events were still significantly decreased in the cohort who had at least 1 positive sIgE test result. Patients with positive sIgE test results had a significantly decreased adjusted RR of all cardiovascular events (RR, 0.87; 95% CI, 0.79–0.95) but not cerebrovascular events (RR, 0.89; 95% CI, 0.77–1.02) or all-cause mortality (RR, 1.16; 95% CI, 1.00–1.34) compared with those in the cohort with negative sIgE test results (Table 4).

Discussion

In this large matched cohort study, we found that adult patients with a physician diagnosis of AR have decreased risk of CHD, CVD, and all-cause mortality and that this association was maintained after excluding patients with coexisting asthma. Patients with AR who have positive in vitro allergy test results have a decreased risk of cardiovascular events compared with patients with AR without positive allergy test results but no difference in risk of cerebrovascular events or all-cause mortality.

Previously, a cross-sectional study by Jaramillo et al²⁶ found that patients with positive sIgE test results were less likely to have had a history of MI. Another large study found no association

Table 1
Cohort Characteristics^a

Characteristic	Allergic rhinitis cohort (n = 110,207)	Reference cohort (n = 110,207)	P value
Sex			
Female	72,530 (65.8)	72,530 (65.8)	
Male	37,677 (34.2)	37,677 (34.2)	
Ethnicity			
Asian/PI	9,766 (8.9)	9,766 (8.9)	
Black	11,165 (10.1)	11,165 (10.1)	
Hispanic	31,340 (28.4)	31,340 (28.4)	
Other	1,677 (1.5)	1,677 (1.5)	
Unknown	14,557 (13.2)	14,557 (13.2)	
White	41,702 (37.8)	41,702 (37.8)	
Age, y			
30–49	65,400 (59.3)	65,400 (59.3)	
50–69	38,194 (34.7)	38,194 (34.7)	
≥70	6,613 (6.0)	6,613 (6.0)	
Mean (SD)	47.9 (12.32)	47.9 (12.33)	
US Census tract estimated percentage of high school graduates, median (IQR)	81.0 (65.1–90.6)	79.5 (61.8–90.2)	<.001
US Census tract annual household income, median (IQR), US\$	55,510 (41,154–73,721)	53,333 (38,733–71,654)	<.001
Comorbidities			
Total before index date	52,771 (42.1)	48,585 (38.8)	
Asthma	18,283 (16.6)	3,207 (2.9)	<.001
Diabetes mellitus	6,363 (5.8)	6,865 (6.2)	<.001
Hypertension	22,986 (20.9)	16,891 (15.3)	<.001
Dyslipidemia	14,006 (12.7)	8,062 (7.3)	<.001
Renal disease	658 (0.6)	811 (0.7)	<.001
Malignant tumor	7,155 (6.5)	4,469 (4.1)	<.001
Autoimmune disease	2,959 (2.7)	1,886 (1.7)	<.001
HIV	163 (0.1)	146 (0.1)	.33
Obese (BMI >30)	11,019 (10.0)	6,117 (5.6)	<.001
Smoking	6,102 (5.5)	5,217 (4.7)	<.001
Annual outpatient visits, median (IQR)	8.2 (4.8–13.4)	3.9 (1.5–7.6)	<.001
Follow-up time, median (IQR), y	9.6 (5.9–12.3)	8.1 (2.4–11.3)	<.001

Abbreviations: BMI, body mass index (calculated as the weight in kilograms divided by square of height in meters); HIV, human immunodeficiency virus; IQR, interquartile range; PI, Pacific Islander.

^aData are presented as number (percentage) of patients unless otherwise indicated.

Table 2

Unadjusted and Adjusted HRs for Primary Outcomes Comparing the AR Cohort and Reference Cohort (n = 110,207 in Each Cohort)

Outcome	No. of events		Event rate per 100,000 person-years		Unadjusted		Adjusted ^a	
	AR cohort	Reference cohort	AR cohort	Reference cohort	HR (95% CI)	P value	HR (95% CI)	P value
Coronary heart disease								
Myocardial infarction	2,251	2,180	219	264	0.83 (0.78–0.88)	<.001	0.63 (0.59–0.67)	<.001
Stable and unstable angina	5,378	3,703	534	455	1.18 (1.13–1.23)	<.001	0.89 (0.85–0.93)	<.001
Chronic coronary heart disease	6,378	5,245	636	648	0.99 (0.95–1.02)	.47	0.73 (0.71–0.76)	<.001
Revascularization (CABG, PCI)	1,765	1,606	172	195	0.78 (0.71–0.86)	<.001	0.60 (0.54–0.66)	<.001
All coronary heart disease	9,040	6,877	916	858	1.08 (1.04–1.11)	<.001	0.81 (0.78–0.84)	<.001
Cerebrovascular disease								
Cerebral hemorrhage	805	822	78	99	0.91 (0.87–0.95)	<.001	0.68 (0.64–0.71)	<.001
Ischemic stroke	3,843	3,374	376	411	0.88 (0.83–0.95)	<.001	0.71 (0.66–0.76)	<.001
All cerebrovascular disease	4,295	3,824	421	466	0.89 (0.86–0.93)	<.001	0.67 (0.64–0.70)	<.001
Mortality								
CHD mortality	233	398	20	35	0.56 (0.48–0.66)	<.001	0.39 (0.33–0.47)	<.001
CVD mortality	247	407	21	35	0.59 (0.50–0.69)	<.001	0.42 (0.35–0.50)	<.001
Non-ASCVD mortality	4,837	7,591	394	635	0.62 (0.60–0.64)	<.001	0.42 (0.40–0.43)	<.001
All-cause mortality	5,733	9,196	464	763	0.61 (0.59–0.63)	<.001	0.42 (0.40–0.43)	<.001

Abbreviations: AR, allergic rhinitis; ASCVD, atherosclerotic cardiovascular disease; CABG, coronary artery bypass graft; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; PCI, percutaneous coronary intervention.

^aAdjusted for diabetes, hypertension, cancer, autoimmune disease, renal disease, dyslipidemia, smoking, human immunodeficiency virus, obesity, asthma, education, income, and annual outpatient visits.

between atopy and incidence of ischemic heart disease or stroke.²⁸ Our study found that patients with positive sIgE test results have a decreased risk of future CHD. Rather than supporting a direct link between protective effects of sIgE on ASCVD, these data indicate that AR with positive sIgE test results is associated with a decreased risk of CHD, with an unclear mechanism for the association.

Few studies have directly examined AR and mortality. A recent longitudinal study of asthma and mortality found that although patients with asthma had increased mortality, self-reported hay fever was not associated with increased (or decreased) mortality during a 30-year period.^{8,29} A recent Danish study found no association with positive allergen sIgE test results and mortality.³⁰ Our study adds further evidence that atopy is not associated with increased all-cause mortality, and the presence of AR was in fact associated with decreased risk.

To give a biological reason for the link between AR and the significantly decreased all-cause mortality observed would be speculative. The observation that patients in the AR cohort had

increased traditional cardiovascular risk factors and yet still had significantly decreased all-cause mortality compared with their matched controls argues for the robustness of this association. Moreover, this was independent of having a positive sIgE test result because patients with physician-diagnosed AR who had at least 1 positive sIgE test result had a slightly increased risk of all-cause mortality compared with patients who did not have a positive result for any of the 13 sIgE tests assessed. In our study, the frequency of physician visits in general was higher in the AR group. We adjusted for frequency of visits in the multivariate analysis; however, it is possible for residual effects of frequency of physician visits and increased health care use to have played a role on outcomes. One study examining health care use of patients with and without AR in our same patient population found that patients with rhinitis of either type had nearly twice as many visits for any medical diagnosis compared with patients without rhinitis,³¹ similar to the results in our study, supporting increased use of medical care as a plausible explanation of the observed mortality benefit.

Table 3

Adjusted HRs for Primary Outcomes Comparing the AR Cohort and Reference Cohort, Excluding Any Matched Pairs With Asthma Diagnosis in Either Cohort (n = 86,054 in Each Cohort)

Outcome	No. of events		Event rate per 100,000 person-years		Adjusted HR ^a (95% CI)	P value
	AR cohort	Reference cohort	AR cohort	Reference cohort		
Coronary heart disease						
Myocardial infarction	1,660	1,682	210	264	0.62 (0.58–0.67)	<.001
Stable and unstable angina	3,887	2,858	502	455	0.87 (0.82–0.91)	<.001
Chronic coronary heart disease	4,678	4,035	606	646	0.72 (0.69–0.75)	<.001
Revascularization (CABG, PCI)	1,364	1,236	173	194	0.58 (0.52–0.65)	<.001
All coronary heart disease	6,565	5,271	862	853	0.79 (0.76–0.82)	<.001
Cerebrovascular disease						
Cerebral hemorrhage	608	642	77	100	0.67 (0.63–0.70)	<.001
Ischemic stroke	2,863	2,608	365	412	0.70 (0.65–0.76)	<.001
All cerebrovascular disease	3,211	2,957	410	468	0.66 (0.63–0.70)	<.001
Mortality						
CHD mortality	172	308	19	34	0.39 (0.32–0.47)	<.001
CVD mortality	191	332	21	37	0.41 (0.34–0.49)	<.001
Other mortality	3,641	5,820	383	629	0.42 (0.41–0.44)	<.001
All-cause mortality	4,332	7,094	453	760	0.42 (0.41–0.44)	<.001

Abbreviations: AR, allergic rhinitis; ASCVD, atherosclerotic cardiovascular disease; CABG, coronary artery bypass graft; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; PCI, percutaneous coronary intervention.

^aAdjusted for diabetes, hypertension, cancer, autoimmune disease, renal disease, dyslipidemia, smoking, human immunodeficiency virus, obesity, education, income, and annual outpatient visits.

Table 4

Unadjusted and Adjusted RRs for Primary Composite Outcomes Comparing Patients With Positive Allergy Test Results With Those With Negative Allergy Test Results in the Allergic Rhinitis Cohort (n = 17,159)

Outcome	Unadjusted		Adjusted ^a	
	RR (95% CI)	P value	RR (95% CI)	P value
Coronary heart disease	0.65 (0.59–0.71)	<.001	0.87 (0.79–0.95)	.003
Cerebrovascular disease	0.58 (0.51–0.67)	<.001	0.89 (0.77–1.02)	.10
All-cause mortality	0.69 (0.60–0.80)	<.001	1.16 (1.00–1.34)	.057

Abbreviations: CI, confidence interval; RR, relative risk.

^aAdjusted for age, sex, race, diabetes, hypertension, cancer, autoimmune disease, renal disease, dyslipidemia, smoking, human immunodeficiency virus, obesity, asthma, education, income, and annual outpatient visits.

Interestingly, a small randomized, placebo-controlled study of patients with AR found that in patients treated for their AR with an intranasal steroid and an oral antihistamine had a significant reduction in their systolic blood pressure (mean [SD] change, 7.47 [4.3] mm Hg; $P = .006$) and decreased highly sensitive C-reactive protein level (mean [SD] change, 2.05 [1.08]; $P = .03$) at the end of an 8-week treatment period compared with placebo, which mirrored improvement in their quality of life scores.³² This finding suggests that treating AR symptoms may have some effect on these ASCVD risk factors. However, it is not entirely clear, and our study did not look at treatments for AR and their relation to improved outcomes. Therefore, we can only speculate that this may potentially be a link between having a diagnosis of AR and decreased ASCVD outcomes and mortality. Conversely, preliminary 5-year safety data indicated that treatment with omalizumab was associated with a slight increase in cardiovascular and cerebrovascular events, suggesting that specific anti-IgE treatment may be associated with some reversal of this protective effect.³³

Strengths of this study include its large population-based sample size, ethnic diversity, length of follow-up, and the availability of outcome measures. Limitations include that as an observational study causality cannot be inferred. In addition, because AR cases were matched with their controls at enrollment into the study, right-censoring may have been different within the pair based on when end points were reached. Right-censoring because of leaving the health plan may also have limited full data collection. Socioeconomic variables of household income and educational level were based on the patient's zip code or census block data, which is commonly used in health care research. There is always potential bias in using aggregate data; however, prior studies have found these to be valid approximations of individual-level data.³⁴ Neighborhood income and educational data may not exactly reflect a given individual's data; however, these data will accurately reflect the population distribution of that variable when used for studies that include very large populations, such as ours. Prior comparison, specifically of Kaiser Permanente Southern California data and US Census data, revealed equivalent representation of age, racial/ethnic, and socioeconomic groups.²⁷

In addition, as a data-based study, it is limited by physician-inputted diagnoses, which are subject to error but have been previously validated within the Kaiser Permanente system.²² The specific diagnosis of AR was also validated by medical record review; however, in the final cohort, even among those with the clinical diagnosis, sIgE test results were only positive in approximately half of the patients tested. This finding may reflect time or sampling bias of the initial confirmatory medical record review because only patients with electronic medical records (which were implemented in 2007) were reviewed. Non-AR may also have been captured by this diagnosis code because many patients may have had their conditions diagnosed in a primary care setting by history and physical examination alone without confirmation of a specific

allergy. Ideally, atopy (allergic status, such as by measurement of sIgE) would have been assessed in all patients; however, this was impractical because of the size and design of the study. Thus, the findings of this study may indicate that rhinitis in general is associated with decreased CHD, CVD, and mortality, regardless of atopic status.

We found that patients in a large managed care organization with a diagnosis of AR had a decreased risk of CHD, CVD, and all-cause mortality. This association was maintained after excluding patients with asthma. Patients with physician-documented AR and positive in vitro allergy test results had a decreased risk of cardiovascular events compared with patients with AR without positive allergy test results. This finding suggests that atopy may not be contributing to the increased cardiovascular events seen in patients with asthma in previous studies and may actually be protective against ASCVD. In addition, atopy may not be responsible for the decrease in all-cause mortality seen in patients with AR.

Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2016.08.021>.

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eTable 1

International Classification of Diseases, Ninth Revision (ICD-9), and International Classification of Diseases, Tenth Revision (ICD-10), Codes Used for the Ascertainment of Primary Outcomes and Covariate Diagnoses

Primary outcome or covariate diagnosis	ICD-9 or ICD-10 code(s)
Primary outcome^a	
Coronary vascular disease	
Myocardial infarction	410.xx
Stable and unstable angina	411.xx, 413.xx
Chronic coronary heart disease	412.xx, 414.xx
Revascularization procedures (percutaneous coronary intervention, coronary artery bypass surgery)	36.xx
Cerebrovascular disease	
Cerebral hemorrhage	430.xx, 431.xx, 432.xx
Ischemic stroke	433.xx, 434.xx, 438.xx
Covariate diagnoses	
Asthma	493.xx
Autoimmune disease	135.xx, 446.xx, 447.6, 695.4, 696.xx, 710.xx, 714.xx
Diabetes	250.xx
Dyslipidemia	272.xx
Human immunodeficiency virus	42.xx, V08
Hypertension	401.xx–405.xx
Malignant tumor	140.xx–165.xx, 170.xx–176.xx, 179.xx–209.xx, 235.xx–239.xx
Obesity	277.xx, 278.xx, V85.2–V85.4
Renal disease	580.xx–588.xx
Smoking	305.1, V15.82
Cause of death^b	
Coronary heart disease	I20–I25
Cerebrovascular disease	I60–I69

^aICD-9 codes.

^bICD-10 codes.

eTable 3

Adjusted HRs for Primary Composite Outcomes Stratified by Age at Study Enrollment (n = 110,207 in Each Cohort)

Outcome	Adjusted HR ^a 95% CI	<i>P</i> value	<i>P</i> value for interaction of age and HR
Coronary heart disease			
Age 30–49 y	0.86 (0.81–0.92)	<.001	.048
Age ≥50 y	0.84 (0.80–0.87)	<.001	
Cerebrovascular disease			
Age 30–49 y	0.65 (0.58–0.72)	<.001	.80
Age ≥50 y	0.72 (0.68–0.76)	<.001	
All-cause mortality			
Age 30–49 y	0.39 (0.36–0.43)	<.001	.58
Age ≥50 y	0.43 (0.41–0.45)	<.001	

Abbreviations: CI, confidence interval; HR, hazard ratio.

^aAdjusted for diabetes, hypertension, cancer, autoimmune disease, renal disease, dyslipidemia, smoking, human immunodeficiency virus, obesity, asthma, education, income and annual outpatient visits.

eTable 2

List of the 13 Environmental Allergens Comprising the Environmental Panel

Allergens
Bermuda grass (<i>Cynodon dactylon</i>)
Rye grass (<i>Lolium perenne</i>)
mugwort (<i>Artemisia vulgaris</i>)
Saltwort or Russian thistle (<i>Salsola kali</i>)
Elm tree (<i>Ulmus americana</i>)
Olive tree (<i>Olea europaea</i>)
Molds (<i>Cladosporium herbarum</i> , <i>Aspergillus fumigatus</i> , <i>Alternaria alternata</i>)
Dust mite (<i>Dermatophagoides pteronyssinus</i>)
Dog dander (<i>Canis familiaris</i>)
Cat dander (<i>Felis domesticus</i>)
Cockroach (<i>Blattella germanica</i>)