

Relation between objective measures of atopy and myocardial infarction in the United States

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Background: Although rodent studies indicate that atherosclerosis is a T_H1-mediated disease and that atopic T_H2 immunity is atheroprotective, findings in humans are conflicting. Total IgE (tIgE) is associated with atherosclerotic disease but has limited specificity for atopy.

Objective: Our aim was to determine the relation between atopy, as indicated by a broad panel of serum allergen-specific IgE (sIgE), and past myocardial infarction (MI) in a sample representative of the US population.

Methods: Data were analyzed from 4002 participants aged ≥20 years from the 2005-2006 National Health and Nutrition Examination Survey.

Results: Subjects reporting a history of MI had lower summed sIgE (5.51 vs 7.71 kU/L; $P < .001$) and were less likely to have ≥1 positive sIgE test (29.9% vs 44.6%; $P = .02$) or current hay fever (3.3% vs 7.6%; $P = .002$). After adjustment for age, sex, race/ethnicity, diabetes mellitus, hypertension, family history of MI, smoking, total/high-density lipoprotein cholesterol, body mass index, and C-reactive protein, the odds ratio (OR) for MI was 0.91 (95% CI, 0.85-0.97) per positive sIgE; 0.70 (95% CI, 0.57-0.85) per 2-fold increase in sum[sIgE]; and 0.82 (95% CI, 0.69-0.98) per 10% increase in the ratio of sum[sIgE] to tIgE. Analysis with 7 data-driven, prespecified allergen clusters found that house dust mite is the only allergen cluster for which sIgE is associated with reduced odds for MI (fully adjusted OR, 0.36; 95% CI, 0.20-0.64).

Conclusion: Serum sIgE is inversely related to MI in the US population in a manner independent of multiple coronary risk factors. (*J Allergy Clin Immunol* 2012;■■■■:■■■-■■■.)

Key words: Myocardial infarction, immune system, risk factors, atopy, immunoglobulin E

Adaptive immunity plays an important role in atherosclerotic cardiovascular disease (ASCVD). T lymphocytes are found

Abbreviations used

ASCVD:	Atherosclerotic cardiovascular disease
BMI:	Body mass index
CRP:	C-reactive protein
HDM:	House dust mite
MI:	Myocardial infarction
NHANES:	National Health and Nutrition Examination Survey
OR:	Odds ratio
sIgE:	Allergen-specific IgE
tIgE:	Total IgE
TC:	Total cholesterol

within atherosclerotic lesions, and their products, as well as those of the cells with which they communicate (ie, B cells, eosinophils), modify lesion progression.¹ Polarization of adaptive immune responses along either a T_H1 program, characterized by cell-mediated immunity and the signature cytokine IFN- γ , or a T_H2 program, typified by allergic responses and IL-4, IL-5, and IL-13, has been proposed to drive the pathogenesis of distinct categories of human disease. Because the T_H1 and T_H2 programs are mutually suppressive, interest in immune reprogramming as a therapeutic strategy has fueled efforts to define whether ASCVD is driven or suppressed by atopy and associated T_H2 immunity.

Findings on the relation between atopy and ASCVD have been conflicting. Most studies that have measured or manipulated T-cell cytokines have concluded that ASCVD is T_H1 predominant and that T_H2 immunity is atheroprotective. Thus, in mice, T_H2-biased strains have reduced atherosclerosis^{2,3} and enhancing T_H2 responses ameliorates disease.⁴⁻⁸ Similarly, patients with coronary artery disease have a predominance of T_H1 cells.^{9,10} By contrast, elevated serum total IgE (tIgE), a surrogate biomarker of atopy, has also been found to associate with ASCVD.¹¹⁻¹⁴ Complicating matters, however, the tIgE-ASCVD relation is independent of clinical allergy,^{12,13} and serum tIgE has been shown to poorly predict and indeed to dissociate from atopy in different disease contexts,^{12,15} likely because it is composed of allergen-specific and -independent IgE fractions that are statistically and physiologically unrelated.¹⁶ Moreover, because IgE is itself potentially proatherogenic through actions on mast cells and platelets,^{17,18} tIgE may be both nonspecific and confounded as a biomarker of atopy in investigations of ASCVD. Studies that used allergic symptoms to define atopy have also yielded mixed results^{12,19,20} and are complicated because allergic inflammation can, like nonallergic inflammation, promote vascular injury.²¹ Taken together, because allergy is a highly complex condition, reductionist approaches to defining atopy such as detection of allergen-specific IgE (sIgE) may be more specific and informative as population-level metrics for isolating and defining the relation between atopic immune programming and ASCVD.

The National Health and Nutrition Examination Survey (NHANES) 2005-2006 collected questionnaire and laboratory

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data on US citizens and was also the first nationwide assessment of serum tIgE and sIgE. We hypothesized that atopy, as defined by sIgE, would be inversely related to past myocardial infarction (MI) in the US population. Our primary goal was to test for a relation between atopy and self-reported, physician-diagnosed MI and to assess the independence of this relation from established coronary risk factors. Our secondary goal was to discriminate among allergens by investigating the relation of prespecified allergen clusters to past MI.

METHODS

Study population

Data were obtained from the NHANES 2005-2006, a national survey designed to assess the health and nutritional status of the civilian, noninstitutionalized US population. The NHANES 2005-2006 was approved by the National Center for Health Statistics Research Ethics Review Board, and all participants gave informed consent. Details of the plan and operation of NHANES are available online (<http://www.cdc.gov/nchs/nhanes.htm>). All participants who completed a household interview were also invited to undergo a Health Examination Component performed in the Mobile Examination Center. Of 4773 participants ≥ 20 years old who were examined in the Medical Examination Center, 4492 (94.1%) had serum tIgE measured, 4411 (92.4%) had data available for all 19 sIgEs, and 4409 (92.4%) had data for both. Analysis was limited to subjects with complete tIgE and sIgE data. The NHANES classifies participants into 5 main racial/ethnic groups: non-Hispanic white, non-Hispanic black, Mexican American, other Hispanic, other/multirace. Because of the heterogeneity of the other Hispanic and other/multirace categories, we included them as a combined group in analysis of the overall population but did not analyze them separately in stratified analyses.

Clinical outcomes

Personal history of doctor-diagnosed MI was assessed by questionnaire, with an affirmative answer to the question, "Has a doctor or other health professional ever told you that you had a heart attack (also called myocardial infarction)?"

sIgE and tIgE measurement

tIgE and sIgE were measured with the Pharmacia Diagnostics ImmunoCAP 1000 System (Kalamazoo, Mich). sIgE was measured to a panel of the following 19 allergens: *Alternaria alternata*, *Apergillus fumigatus*, Bermuda grass (*Cynodon dactylon*), birch (*Betula verrucosa*), cat dander, cockroach (*Blattella germanica*), dog dander, dust mite (*Dermatophagoides farinae*, *D pteronyssinus*), egg white, milk, mouse urine proteins, oak (*Quercus alba*), peanut (*Arachis hypogaea*), ragweed (*Ambrosia elatior*), rat urine proteins, Russian thistle (*Salsola kali*), rye grass (*Lolium perenne*), and shrimp (*Pandalus borealis*). The lower limit of detection was 2.0 kU/L for tIgE and 0.35 kU/L for sIgEs. Thus, a positive (ie, detectable) result for sIgEs was defined as ≥ 0.35 kU/L.

Covariates

Covariates were obtained from (1) questionnaire; (2) laboratory analyses of C-reactive protein (CRP), high-density lipoprotein cholesterol (HDL-C), and total cholesterol (TC); and (3) physical examination (height and weight measurements). Serum CRP was measured by latex-enhanced nephelometry. Serum TC and HDL-C were measured with a Hitachi 717 or 912 (San Jose, Calif). Body mass index (BMI) was measured as weight (kg) divided by height in meters squared (kg/m^2).

Statistical analyses

Odds ratios (ORs) for the association between sIgE (independent variable) and MI (dependent variable) were estimated by logistic regression, treating

sIgE in the following 2 ways: (1) as the number of positive sIgE tests and (2) as the sum of sIgE values to all allergens. For the latter, $\text{sum}[\text{sIgE}]$ was log-transformed because the distribution of summed sIgE (excluding sums below detection) was highly skewed (range, 4.85-1189.00 kU/L; median, 9.64 kU/L). ORs for the tIgE-MI relation were estimated per $\log_{10}$ change in tIgE.²² Given racial/ethnic and sex differences in atopy and ASCVD and in risk factor-ASCVD relations, stratification of analyses by race/ethnicity and sex was prespecified. Covariates in adjusted models included age (linear, 1-year increment), sex, race/ethnicity (total population only), householder education, history of hypertension, history of diabetes mellitus, smoking (never, past, current), history of close relative with an MI occurring at age < 50 years, serum TC/HDL-C, BMI, and log-transformed CRP. NHANES assigns 0.25 kU/L to undetected sIgEs and 1.41 kU/L to undetected tIgE. To avoid the sum of imputed sIgE values exceeding imputed tIgE, in analyses of $[\text{sum}(\text{sIgE})/\text{tIgE}]$ and $[\text{tIgE} - \text{sum}(\text{sIgE})]$, 1.41 kU/L was assigned as a ceiling for the sum of undetected sIgEs, to which detected sIgEs were added to yield $\text{sum}[\text{sIgE}]$. When all sIgEs and tIgE were undetected, $[\text{sum}(\text{sIgE})/\text{tIgE}]$ was set at 1 and $[\text{tIgE} - \text{sum}(\text{sIgE})]$ at 0. The relation to MI of 7 clusters of sIgEs that we have previously identified with hierarchical clustering, factor analysis, and multidimensional scaling^{22,23} (see Table IV) was also assessed, both partially adjusting (for covariates above), and fully adjusting for these covariates plus the mutual presence of all other clusters. All analyses were adjusted for the NHANES complex sampling design with the use of Taylor series linearization methods through SAS statistical software (version 9.2; SAS Institute, Cary, NC) survey procedures (SURVEYFREQ, SURVEYMEANS, SURVEYLOGISTIC) according to NHANES specifications. Statistical significance was set at $P \leq .05$ for the main effects and $P \leq .10$ for interactions.

RESULTS

Table I shows the features of 4002 subjects aged ≥ 20 years in the NHANES 2005-2006 for whom data were available for the shown questionnaire items and biochemical variables, including serum tIgE and all 19 sIgEs; Table E1 (in the Online Repository available at www.jacionline.org) compares the characteristics of this study population with 771 subjects aged ≥ 20 years who were excluded because of missing data. Excluded subjects had higher CRP and lower sIgE positivity than study subjects. No significant difference was observed in MI prevalence between subjects who did versus did not have a full sIgE panel measured (see Table E2 in this article's Online Repository at www.jacionline.org), or between subjects who had complete data for both tIgE and sIgE versus subjects who were lacking data for either tIgE or sIgE (see Table E3 in this article's Online Repository at www.jacionline.org). Of the 4002 study subjects, 159 (3.97%) reported a history of physician-diagnosed MI. Subjects with a history of MI, compared with subjects without a history of MI, tended to be older, men, and were more likely to have a history of hypertension, diabetes mellitus, smoking, and a close family member with a history of an MI that occurred before age 50 years. BMI and serum CRP were also higher among subjects with a history of MI. Although subjects with a history of MI had a higher mean serum tIgE concentration, subjects without MI were more likely to have ≥ 1 positive sIgE tests, had a higher mean sum of serum sIgE values (ie, higher allergen-specific component of tIgE), and had a > 2 -fold higher prevalence of current hay fever.

Hypothesizing that atopy (independent variable) would have a "dose-responsive" relation to MI (dependent variable),²⁴ we analyzed the atopy-MI relation, treating atopy as a quantitative variable in 2 different ways. First, we analyzed the relation between the number of positive (ie, detected) sIgE tests and MI with the use of multivariate logistic regression (Table II). In the overall population, after adjustment for covariates, including

TABLE I. Characteristics of the study population

Characteristic	Total population*	MI, yes*	MI, no*	P value†
Population (no.)	4002	159	3843	
Age (y)	46.5 (0.8)	65.1 (1.0)	45.9 (0.8)	<.001
Age category (%)				<.001
20-39 y	37.5 (1.6)	3.5 (2.0)	38.7 (1.5)	
≥40 y	62.5 (1.6)	96.5 (2.0)	61.3 (1.5)	
Sex (%)				.05
Male	47.8 (0.7)	59.3 (4.7)	47.4 (0.7)	
Female	52.2 (0.7)	40.7 (4.7)	52.6 (0.7)	
Education (%)				<.001
<9th grade	6.3 (0.8)	6.7 (1.4)	6.3 (0.8)	
9th to <12th grade	11.3 (1.3)	20.9 (4.4)	11.0 (1.3)	
High school or GED	24.6 (1.0)	39.6 (6.1)	24.1 (1.0)	
Some college	30.9 (1.1)	18.1 (3.2)	31.4 (1.2)	
College graduate	26.8 (2.3)	14.6 (4.2)	27.2 (2.3)	
Hypertension (%)	29.6 (1.1)	66.6 (4.4)	28.3 (1.1)	<.001
Diabetes mellitus (%)	7.7 (0.5)	29.9 (4.9)	7.0 (0.6)	<.001
Close relative with MI at age <50 y (%)	15.5 (0.8)	25.4 (4.0)	15.2 (0.9)	.03
BMI (kg/m ²)	28.5 (0.3)	29.6 (0.5)	28.5 (0.2)	.04
Smoking status (%)				.001
Never	51.4 (1.5)	26.2 (4.6)	52.3 (1.5)	
Former	24.9 (0.9)	49.3 (5.6)	24.1 (1.1)	
Current	23.6 (1.3)	24.6 (3.9)	23.6 (1.3)	
CRP‡ (mg/dL)	0.18 (0.01)	0.26 (0.02)	0.18 (0.01)	<.001
TC (mg/dL)	199.3 (0.8)	179.6 (3.4)	199.9 (0.9)	<.001
HDL-C (mg/dL)	54.8 (0.4)	51.2 (2.0)	54.9 (0.4)	.08
tIgE‡ (kU/L)	40.93 (1.51)	55.13 (7.27)	40.51 (1.56)	.05
sIgE, ≥1 positive (%)	44.2 (1.1)	29.9 (4.8)	44.6 (1.1)	.02
sIgE, no. positive (%)				<.001
0	55.8 (1.1)	70.1 (4.8)	55.4 (1.1)	
1	10.3 (0.5)	13.0 (4.3)	10.2 (0.6)	
2	9.4 (0.6)	4.0 (1.8)	9.6 (0.6)	
≥3	24.5 (1.2)	12.9 (2.2)	24.8 (1.2)	
Sum of sIgE§ (kU/L)	7.62 (0.21)	5.51 (0.12)	7.71 (0.22)	<.001
Current hay fever (%)	7.5 (0.7)	3.3 (0.6)	7.6 (0.7)	.002

GED, General Educational Development.

*Parenthetical values are standard errors.

†Determined by χ^2 test of homogeneity or *t*-test of main effect for cardiovascular outcomes.

‡Geometric mean reported as log-transformed value is used as a covariate in adjusted logistic regression models.

age, race/ethnicity, sex, householder education, diabetes mellitus, hypertension, family history of MI before age 50 years, smoking status, BMI, serum ratio of TC to HDL-C, and CRP, the OR of each incremental positive sIgE for MI was 0.91 (95% CI, 0.85-0.97). We found essentially the same result with the use of different covariates for smoking (pack-years or serum cotinine) and socioeconomic status (poverty-to-income ratio or household income), as well as using multiple adjustments for both smoking and socioeconomic status in the same model (householder education plus poverty-to-income ratio, and smoking history plus serum cotinine; see Table E4 in this article's Online Repository at www.jacionline.org). In addition, the results were unchanged if we adjusted for age with the use of (1) both linear and quadratic terms, (2) 10-year categories, or (3) 2 age categories (<60 years old, ≥60 years old; data not shown). On age-stratification, an inverse relation was seen both in 20- to 59-year-old subjects and ≥60-year-old subjects, although statistical significance was lost in the former age category (see Table E5 in this article's Online Repository at www.jacionline.org). The inverse relation between the number of positive sIgE tests and MI was generally consistent

across racial/ethnic strata (*P* for interaction = .40). However, a significant interaction with sex was noted, with the inverse relation observed in women but not in men. Stratification by both age (20-59 years vs ≥60 years) and sex found that age did not significantly modify the sIgE-MI relation within either men or women and that a similar inverse sIgE-MI relation was seen in both age strata of women (see Table E6 in this article's Online Repository at www.jacionline.org). Finally, when we treated atopy as a dichotomous variable instead (ie, ≥1 positive sIgE), the unadjusted OR of atopy for MI in the study population was 0.53 (95% CI, 0.34-0.83), but this relation was attenuated (OR, 0.75; 95% CI, 0.46-1.23) after adjustment for covariates.

As shown in Table E7 (in the Online Repository available at www.jacionline.org), of the 4002 study subjects, 168 (4.2%) reported use of antihistamines and 228 (5.7%) reported use of corticosteroids (topical, inhaled, and/or systemic). No significant difference was observed in past MI between antihistamine users and nonusers. However, 19 (6.0%) of corticosteroid users compared with 140 (3.1%) of corticosteroid nonusers reported past MI (*P* = .04). To examine whether corticosteroid use was

TABLE II. Unadjusted and adjusted ORs for the association between the number of positive sIgE tests detected from a panel of 19 allergens and MI

	No.	MI % (SE)	Unadjusted OR (95% CI)	Interaction P value	Adjusted OR* (95% CI)	Interaction P value*
All	4002	3.3 (0.4)	0.84 (0.78-0.90)		0.91 (0.85-0.97)	
Race/ethnicity				.48		.40
Non-Hispanic white	2021	3.9 (0.5)	0.82 (0.73-0.92)		0.88 (0.79-0.98)	
Non-Hispanic black	889	2.4 (0.6)	0.92 (0.85-1.00)		0.98 (0.88-1.08)	
Mexican American	813	1.1 (0.2)	0.89 (0.74-1.06)		0.88 (0.67-1.15)	
Sex				.01		.01
Male	1914	4.1 (0.6)	0.87 (0.81-0.94)		0.97 (0.90-1.05)	
Female	2088	2.6 (0.4)	0.66 (0.54-0.80)		0.73 (0.61-0.87)	

*Adjusted for age, sex, ethnicity/race (non-Hispanic white, non-Hispanic Black, Mexican American, others), education of household reference person (<9th grade, 9th to 12th grade and no diploma, high school graduate or General Educational Development, some college, college degree), diagnosis of diabetes mellitus, diagnosis of hypertension, family history of MI before age 50 years, smoking status (never, past, current), BMI (continuous raw score), TC/HDL (continuous), CRP (continuous log₁₀ transformed).

TABLE III. Unadjusted and adjusted ORs for the association between the log₂ change of sum of sIgE values from a panel of 19 allergens and MI

	No.	MI % (SE)	Unadjusted OR (95% CI)	Interaction P value	Adjusted OR* (95% CI)	Interaction P value*
All	4002	3.3 (0.4)	0.54 (0.45-0.64)		0.70 (0.57-0.85)	
Race/ethnicity				.35		.25
Non-Hispanic white	2021	3.9 (0.5)	0.50 (0.38-0.65)		0.63 (0.48-0.84)	
Non-Hispanic black	889	2.4 (0.6)	0.65 (0.46-0.90)		0.78 (0.52-1.17)	
Mexican American	813	1.1 (0.2)	0.65 (0.35-1.21)		0.67 (0.30-1.51)	
Sex				.14		.06
Male	1914	4.1 (0.6)	0.59 (0.48-0.71)		0.82 (0.65-1.02)	
Female	2088	2.6 (0.4)	0.35 (0.18-0.67)		0.44 (0.26-0.77)	

*Adjusted for age, sex, ethnicity/race (non-Hispanic white, non-Hispanic black, Mexican American, others), education of household reference person (<9th grade, 9th to 12th grade and no diploma, high school graduate or General Educational Development, some college, college degree), diagnosis of diabetes mellitus, diagnosis of hypertension, family history of MI before age 50 years, smoking status (never, past, current), BMI (continuous raw score), TC/HDL (continuous), CRP (continuous log₁₀ transformed).

influencing the sIgE–MI relation, we performed a sensitivity analysis in which we repeated the analysis in Table II after first excluding corticosteroid users. As shown in Table E8 (in the Online Repository available at www.jacionline.org), the findings were minimally changed, still showing a significant inverse relation between sIgE and MI.

On stratifying the analysis between number of sIgEs and MI by serum tIgE concentration with the use of a common clinical cut point (100 kU/L), we noted no significant interaction with tIgE on formal testing. However, sIgE was inversely related to MI only among subjects with serum tIgE ≥100 kU/L (see Table E9 in this article's Online Repository at www.jacionline.org). Similar to prior reports, we found that tIgE was itself positively related to MI (adjusted OR per log₁₀ change in tIgE was 1.41; 95% CI, 1.01-1.98; see Table E10 in this article's Online Repository at www.jacionline.org). Like the sIgE–MI relation, the tIgE–MI relation was essentially unchanged if age was adjusted instead with the use of (1) both linear and quadratic terms, (2) 10-year categories, or (3) 2 age categories (<60 years, ≥60 years; data not shown). However, on stratified analysis, the positive association between tIgE and MI was only significant among nonatopic subjects (ie, subjects with no detectable sIgE; see Table E10 in this article's Online Repository at www.jacionline.org), suggesting that this positive relation is driven by non-sIgE.

To further confirm and explore the relation between atopy and MI, we next analyzed the relation, treating atopy as the sum of sIgE values. As shown in Table III, a statistically significant

inverse relation was found between sum[sIgE] and MI that persisted after adjustment for coronary risk factors. Similar to our treatment of atopy as the number of positive sIgEs (Table II), no interaction was observed between summed sIgE and race/ethnicity, whereas a significant interaction with sex was again observed. In an effort to normalize sIgE to tIgE, we divided sum[sIgE] by tIgE, constructing an atopic IgE index, similar to previous reports.^{25,26} As shown in Table IV, a 10% increase in this ratio was associated with an adjusted OR of 0.82 (95% CI, 0.69-0.98) for MI. This sum[sIgE]/tIgE–MI relation was essentially unchanged if age was instead adjusted with the use of (1) both linear and quadratic terms, (2) 10-year categories, or (3) 2 age categories (<60 years, ≥60 years old; data not shown). Conversely, a significant, direct relation was found between non-sIgE (ie, tIgE – sum[sIgE]) and MI, although this relation was somewhat attenuated on full adjustment (see Table E11 in this article's Online Repository at www.jacionline.org). Finally, given the reduced prevalence of current hay fever among subjects that had experienced an MI (Table I), we also analyzed the relation between current hay fever and MI. Notably, current hay fever was also inversely related to MI in a manner that persisted after adjustment for all covariates in Table II (adjusted OR, 0.52; 95% CI, 0.29-0.97); however, these results should be interpreted with caution because of the small number of subjects with current hay fever and MI.

We have previously reported that sIgEs group into clusters that share similarities in biological and statistical properties^{22,23} and

TABLE IV. Unadjusted and adjusted ORs for the association between (sum [sIgE]/tIgE) and MI*

	No.	MI % (SE)	Unadjusted OR (95% CI)	Interaction P value	Adjusted OR (95% CI)†	Interaction P value‡
All	4002	3.3 (0.4)	0.70 (0.55-0.88)		0.82 (0.69-0.98)	
Ethnicity				.93		.75
Non-Hispanic white	2021	3.9 (0.5)	0.68 (0.52-0.89)		0.82 (0.67-0.99)	
Non-Hispanic black	889	2.4 (0.6)	0.62 (0.28-1.38)		0.81 (0.44-1.50)	
Mexican American	813	1.1 (0.2)	0.47 (0.14-1.57)		0.65 (0.33-1.29)	
Sex				.82		.69
Male	1914	4.1 (0.6)	0.73 (0.51-1.07)		0.86 (0.70-1.04)	
Female	2088	2.6 (0.4)	0.68 (0.44-1.04)		0.75 (0.52-1.10)	

*[(Sum sIgE)/tIgE] ratio, an index of atopic IgE, was multiplied by 10, so ORs and 95% CI for MI correspond to a 10% change in ratio.

†Adjusted for age, sex, ethnicity/race (non-Hispanic white, non-Hispanic black, Mexican American, others), education of household reference person (<9th grade, 9th to 12th grade and no diploma, high school graduate or General Educational Development, some college, college degree), diabetes mellitus, hypertension, family history of MI before age 50 years, smoking status (never, past, current), BMI (continuous raw score), TC/HDL-C ratio (continuous), CRP (continuous log₁₀ transformed).

TABLE V. Unadjusted and adjusted ORs for the association between sIgE positivity within allergen clusters and MI

Allergen cluster	Unadjusted OR (95% CI)	Partially adjusted*† OR (95% CI)	Fully adjusted‡ OR (95% CI)
Food (egg, milk)	0.78 (0.37-1.64)	0.71 (0.31-1.61)	0.74 (0.31-1.78)
Mold (<i>Alternaria</i> , <i>Aspergillus</i>)	0.62 (0.33-1.18)	1.00 (0.57-1.76)	1.18 (0.57-2.42)
Plant§	0.52 (0.30-0.90)	1.00 (0.61-1.65)	1.14 (0.64-2.04)
Mite (<i>D farinae</i> , <i>D pteronyssinus</i>)	0.35 (0.20-0.58)	0.47 (0.26-0.86)	0.36 (0.20-0.64)
Roach (cockroach, shrimp)	0.87 (0.54-1.41)	1.08 (0.57-2.03)	1.70 (0.85-3.39)
Pet (dog, cat)	0.69 (0.35-1.37)	0.80 (0.40-1.60)	0.94 (0.39-2.22)
Rodent (mouse, rat)	0.61 (0.17-2.11)	0.77 (0.23-2.62)	1.03 (0.20-5.35)

OR and 95% CI for MI for a positive sIgE within indicated allergen clusters. Full study population (N = 4002; MI prevalence, 3.3% [SE, 0.4]) was analyzed for all clusters.

*Adjusted for age, sex, ethnicity/race (non-Hispanic white, non-Hispanic black, Mexican American, others), education of household reference person (<9th grade, 9th to 12th grade and no diploma, high school graduate or General Educational Development, some college, college degree), diagnosis of diabetes mellitus, diagnosis of hypertension, family history of MI before age 50 years, smoking status (never, past, current), BMI (continuous raw score), TC/HDL ratio (continuous), CRP (continuous log₁₀ transformed).

†Partially adjusted to only include allergen cluster of interest.

‡Fully adjusted to include all allergen clusters.

§Included rye grass, Bermuda grass, oak, birch, ragweed, peanut, thistle.

that these clusters associate independently with allergic disease.²² To determine whether specific allergen classifications account for (ie, underlie) the overall relation between sIgE and MI, we tested the relation between 7 prespecified allergen clusters²² and MI. As shown in Table V, on adjustment for coronary risk factors, house dust mite (HDM; ie, *D farinae* and *D pteronyssinus*) was the only allergen cluster significantly related to MI (OR, 0.47; 95% CI, 0.26-0.86); in other words, having a positive HDM-specific IgE was associated with a >50% reduction in the odds of MI. Of note, this significant relation between mite-specific IgE and MI persisted after adjustment for all other allergen clusters (Table V), indicating its independence from other allergens. The relation moreover remained significant after Bonferroni correction to account for the 7 allergen cluster comparisons tested (data not shown).

DISCUSSION

Notwithstanding criticisms that have been raised against the T_H1/T_H2 paradigm and its application to human disease, good evidence exists that T_H1 and T_H2 immune programs are mutually suppressive. Moreover, the potential for T_H2 responses to exogenous antigens to reprogram T_H1 disease responses to endogenous antigens has been clearly shown. For example, T_H2-biased preimmunization to keyhole limpet hemocyanin ameliorates experimental autoimmune encephalomyelitis through reprogramming autoreactive T cells from T_H1 to T_H2.²⁷ In support of mutual

T_H1/T_H2 antagonism in human disease, reduced rates of sIgE and allergic disease have been reported in rheumatoid arthritis and multiple sclerosis,²⁸⁻³⁰ T_H1-biased diseases. Experimental data derived from rodents indicate that ASCVD is also T_H1 biased, suggesting possible avenues for immunotherapy, but the limited human data are conflicting. Herein, we provide evidence that atopy, as objectively defined by sIgE, is inversely related to past MI in the US population in a manner that is independent of a long list of established coronary risk factors.

Our findings help to explain the seeming paradox that human ASCVD is T_H1 predominant²⁻¹⁰ and yet positively associated with tIgE.¹¹⁻¹⁴ We find that sIgE (inverse) and non-sIgE (direct) have opposite relations to MI, with tIgE (their sum) concordant with the latter fraction. This may be viewed as analogous to the relations of HDL-C (inverse), non-HDL-C (direct), and TC (direct) to MI. We speculate that the direct relation of tIgE to MI stems from the well-described capacity of IgE itself to promote vascular injury through actions on cell types that display its receptor, FcεR (eg, mast cells, platelets).^{17,18} sIgEs also bind to FcεR and are presumably not intrinsically different at a molecular level from non-sIgEs. Thus, we do not propose that sIgE protein is itself likely to be antiatherogenic. Rather, we posit that sIgE may be a quantitative biomarker of atheroprotective T_H2 programming. That is, sIgE may track quantitatively with more “proximal” master regulators of the T_H2 program (eg, IL-4) that are atheroprotective (to a degree that outstrips possible FcεR-dependent proatherogenic effects of sIgE protein) through antagonizing

T_H1 immunity. Indeed, we found that tIgE predicts MI only among nonatopic subjects. Conversely, the inverse relation of sIgE to MI was only evident among subjects with elevated tIgE. This may suggest that in atopics (among which, by definition, sIgE accounts for a higher fraction of tIgE), tIgE may track with the magnitude of atheroprotective atopic programming.¹⁵ It is important to emphasize, however, that our data allow us only to speculate on these important mechanisms, and that future investigation is thus warranted.

We find, remarkably, that HDM sIgE positivity is associated with a 64% reduction in odds of past MI in a fully adjusted model. By comparison, the INTERHEART study reported a 15% odds reduction per 1-SD increase in HDL-C.³¹ Our finding that the relation of sIgE to MI is specific to HDM should be taken with caution because it was a secondary analysis and thus requires independent validation. These data do not allow us to confidently propose that a cardioprotective effect of atopy is restricted to HDM, as opposed to more generalized allergens. Moreover, the HDM-specific findings may have limited generalizability to geographic areas where dust mite allergen and sensitization to it are less common. Nevertheless, HDM allergens do have unique immunologic properties. HDM elicits different memory T-cell and immunoglobulin profiles/responses than other allergens.^{32,33} Pre-immunization of mice with *D. farinae*, but not some other antigens, inhibited T_H1 -biased collagen-induced arthritis and did so in a dose-responsive fashion.²⁴ Patients with rheumatoid arthritis have lower HDM-specific IgE than controls.²⁸ Because HDM allergens are homologous to host cholesterol transport proteins,^{34,35} it is also intriguing to speculate that HDM-specific antibodies might also affect atheroprotective cholesterol trafficking through cross-reactivity.

The inverse relation between sIgE was limited to women. This finding should also be interpreted with caution because men displayed a relation between sum[sIgE] and MI that fell just short of statistical significance (Table III). Nonetheless, fairly extensive published data indicate that women have enhanced T_H2 responses,³⁶⁻³⁹ perhaps explaining how atopy in women could be quantitatively or even qualitatively different in its relation to MI. Indeed, transfer of female bone marrow cells, compared with male counterparts, confers enhanced repair of atherosclerotic lesions in mice likely because of enhanced T_H2 function.⁴⁰ Female-specific gene-IgE and gene-atopy associations have been reported,⁴¹⁻⁴³ suggesting distinct molecular pathways to atopy in women. Male and female $CD4^+$ T cells display nonoverlapping genomic correlations to IgE⁴⁴ and distinct genomic signatures on allergen exposure.⁴⁵ A growing body of literature also suggests that ASCVD is itself pathophysiologically different in women.⁴⁶ Because the Framingham Risk Score performs less well at predicting ASCVD in women, there is an urgent need for female-specific MI predictors.^{47,48}

Limitations of our report deserve mention. Because our analysis was cross-sectional, the temporality, causality, and directionality of the sIgE-MI relation are uncertain. We cannot exclude the possibility of reverse causation, which could hypothetically occur, for example, if after MI subjects changed their behavior or environment in a fashion that altered allergen sensitization. However, this scenario seems unlikely. Given that the study subjects excluded because of missing data had higher CRP values and lower sIgE positivity than the study population (Table E1), we cannot fully exclude selection bias from having contributed to our findings. In addition, despite the robustness of our findings to

multiple different adjustments for smoking, socioeconomic status, and age, we cannot exclude the possibility of residual confounding. In a cross-sectional analysis such as this, we are also unable to distinguish the contributions of disease incidence and survival to our outcome of past (ie, nonfatal) MI. We did not adjust our primary finding (sIgE-MI relation) for multiple testing because our analyses were performed in stages, and the sIgE-MI relation was found to be significant in our initial, primary analysis of the overall population. Self-reported MI as an outcome misses "silent" MIs and excludes other forms of obstructive coronary artery disease (eg, exertional angina) as well as subjects who may have experienced an MI if not for revascularization. Although self-report also carries the risk of introducing bias, such bias might be expected to produce or exaggerate a positive association between atopy and MI; for example, if atopic patients are in more frequent contact with the medical care system. In any event, multiple prior reports have used NHANES data to analyze MI as an outcome, and reports from NHANES and elsewhere indicate good validity of self-reported MI.^{49,50} Recent studies have also implicated the T_H17 program in ASCVD.⁵¹ The implications of our findings for this pathway, as well as for T-regulatory cells, also implicated in atherosclerosis, are uncertain.

Although translation of our findings to the clinical scenario would be premature, several interesting clinical questions nevertheless arise. Because the T_H2 cytokine IL-5 ameliorates ASCVD in part through induction of antioxidantized low-density lipoprotein antibodies,^{2,52} does sIgE track with, and/or environmental allergen exposure modify, levels of these atheroprotective autoantibodies? Do changes in allergen exposure and/or antiallergy therapy modify MI risk? Would a composite variable such as [(tIgE - sIgE)/sIgE] more optimally predict MI risk?

In conclusion, we report the first analysis of the relation of sIgE to past MI. In the US population, sIgE is inversely and independently related to past MI. Future studies in rodent models are warranted to determine whether T_H2 -biased immunization to exogenous antigens may reduce atherosclerosis. If future clinical studies confirm the present study's findings in a prospective fashion, sIgE may warrant further evaluation in clinical MI risk stratification.

Clinical Implications: An inverse relation between atopy, as defined by sIgE, and past MI in the US population was reported. Atopy may be an independent protective factor against MI.

REFERENCES

- Hansson GK, Hermansson A. The immune system in atherosclerosis. *Nat Immunol* 2011;12:204-12.
- Binder CJ, Hartvigsen K, Chang MK, Miller M, Broide D, Palinski W, et al. IL-5 links adaptive and natural immunity specific for epitopes of oxidized LDL and protects from atherosclerosis. *J Clin Invest* 2004;114:427-37.
- Schulte S, Sukhova GK, Libby P. Genetically programmed biases in T_H1 and T_H2 immune responses modulate atherogenesis. *Am J Pathol* 2008;172:1500-8.
- Huber SA, Sakkinen P, David C, Newell MK, Tracy RP. T helper-cell phenotype regulates atherosclerosis in mice under conditions of mild hypercholesterolemia. *Circulation* 2001;103:2610-6.
- Fredrikson GN, Andersson L, Soderberg I, Dimayuga P, Chyu KY, Shah PK, et al. Atheroprotective immunization with MDA-modified apo B-100 peptide sequences is associated with activation of T_H2 specific antibody expression. *Autoimmunity* 2005;38:171-9.
- Khallou-Laschet J, Tupin E, Caligiuri G, Poirier B, Thiebaut N, Gaston AT, et al. Atheroprotective effect of adjuvants in apolipoprotein E knockout mice. *Atherosclerosis* 2006;184:330-41.

7. Laurat E, Poirier B, Tupin E, Caligiuri G, Hansson GK, Bariety J, et al. In vivo downregulation of T helper cell 1 immune responses reduces atherogenesis in apolipoprotein E-knockout mice. *Circulation* 2001;104:197-202.
8. Miller AM, Xu D, Asquith DL, Denby L, Li Y, Sattar N, et al. IL-33 reduces the development of atherosclerosis. *J Exp Med* 2008;205:339-46.
9. Benagiano M, Azzurri A, Ciervo A, Amedei A, Tamburini C, Ferrari M, et al. T helper type 1 lymphocytes drive inflammation in human atherosclerotic lesions. *Proc Natl Acad Sci U S A* 2003;100:6658-63.
10. Methe H, Brunner S, Wiegand D, Nabauer M, Koglin J, Edelman ER. Enhanced T-helper-1 lymphocyte activation patterns in acute coronary syndromes. *J Am Coll Cardiol* 2005;45:1939-45.
11. Criqui MH, Lee ER, Hamburger RN, Klauber MR, Coughlin SS. IgE and cardiovascular disease. Results from a population-based study. *Am J Med* 1987;82:964-8.
12. Langer RD, Criqui MH, Feigelson HS, McCann TJ, Hamburger RN. IgE predicts future nonfatal myocardial infarction in men. *J Clin Epidemiol* 1996;49:203-9.
13. Sinkiewicz W, Blazejewski J, Bujak R, Kubica J, Dudziak J. Immunoglobulin E in patients with atherosclerotic heart disease. *Cardiol J* 2008;15:122-8.
14. Korkmaz ME, Oto A, Saraclar Y, Oram E, Oram A, Ugurlu S, et al. Levels of IgE in the serum of patients with coronary arterial disease. *Int J Cardiol* 1991;31:199-204.
15. Gergen PJ, Arbes SJ Jr, Calatroni A, Mitchell HE, Zeldin DC. Total IgE levels and asthma prevalence in the US population: results from the National Health and Nutrition Examination Survey 2005-2006. *J Allergy Clin Immunol* 2009;124:447-53.
16. Jackola DR, Blumenthal MN, Rosenberg A. Evidence for two independent distributions of serum immunoglobulin E in atopic families: cognate and non-cognate IgE. *Hum Immunol* 2004;65:20-30.
17. Joseph M, Capron A, Ameisen JC, Capron M, Vorng H, Pancre V, et al. The receptor for IgE on blood platelets. *Eur J Immunol* 1986;16:306-12.
18. Ishizaka T, Ishizaka K. Activation of mast cells for mediator release through IgE receptors. *Prog Allergy* 1984;34:188-235.
19. Kim J, Purushottam B, Chae YK, Chebrolo L, Amanullah A. Relation between common allergic symptoms and coronary heart disease among NHANES III participants. *Am J Cardiol* 2010;106:984-7.
20. Knoflach M, Kiechl S, Mayr A, Willeit J, Poewe W, Wick G. Allergic rhinitis, asthma, and atherosclerosis in the Bruneck and ARMY studies. *Arch Intern Med* 2005;165:2521-6.
21. Kounis NG. Kounis syndrome (allergic angina and allergic myocardial infarction): a natural paradigm? *Int J Cardiol* 2006;110:7-14.
22. Salo PM, Calatroni A, Gergen PJ, Hoppin JA, Sever ML, Jaramillo R, et al. Allergy-related outcomes in relation to serum IgE: results from the National Health and Nutrition Examination Survey 2005-2006. *J Allergy Clin Immunol* 2011;127:1226-35.e7.
23. Calatroni A, Arbes S Jr, Gergen PJ, Mitchell HE, Zeldin DC. Classification of 19 allergen-specific IgE antibodies tested in NHANES 2005-2006. *J Allergy Clin Immunol* 2009;123:S193.
24. Honda A, Ametani A, Matsumoto T, Kaminogawa S. Suppression of collagen-induced arthritis in DBA/1J mice by preimmunization with house dust mite extract. *Biosci Biotechnol Biochem* 2001;65:1063-70.
25. Eckman JA, Sterba PM, Kelly D, Alexander V, Liu MC, Bochner BS, et al. Effects of omalizumab on basophil and mast cell responses using an intranasal cat allergen challenge. *J Allergy Clin Immunol* 2010;125:889-95.e7.
26. Di Lorenzo G, Mansueto P, Pacor ML, Rizzo M, Castello F, Martinelli N, et al. Evaluation of serum s-IgE/total IgE ratio in predicting clinical response to allergen-specific immunotherapy. *J Allergy Clin Immunol* 2009;123:1103-10, 1110.e1-4.
27. Falcone M, Bloom BR. A T helper cell 2 (Th2) immune response against non-self antigens modifies the cytokine profile of autoimmune T cells and protects against experimental allergic encephalomyelitis. *J Exp Med* 1997;185:901-7.
28. Hartung AD, Bohnert A, Hackstein H, Ohly A, Schmidt KL, Bein G. Th2-mediated atopic disease protection in Th1-mediated rheumatoid arthritis. *Clin Exp Rheumatol* 2003;21:481-4.
29. Oro AS, Guarino TJ, Driver R, Steinman L, Umetsu DT. Regulation of disease susceptibility: decreased prevalence of IgE-mediated allergic disease in patients with multiple sclerosis. *J Allergy Clin Immunol* 1996;97:1402-8.
30. Verhoef CM, van Roon JA, Vianen ME, Bruijnzeel-Koomen CA, Lafeber FP, Bijlsma JW. Mutual antagonism of rheumatoid arthritis and hay fever: a role for type 1/type 2 T cell balance. *Ann Rheum Dis* 1998;57:275-80.
31. McQueen MJ, Hawken S, Wang X, Ounpuu S, Sniderman A, Probstfield J, et al. Lipids, lipoproteins, and apolipoproteins as risk markers of myocardial infarction in 52 countries (the INTERHEART study): a case-control study. *Lancet* 2008;372:224-33.
32. Wambre E, Bonvalet M, Bodo VB, Maillere B, Leclert G, Moussu H, et al. Distinct characteristics of seasonal (Bet v 1) vs. perennial (Der p 1/Der p 2) allergen-specific CD4(+) T cell responses. *Clin Exp Allergy* 2011;41:192-203.
33. Ciprandi G, De Amici M, Tosca MA, Negrini S, Puppo F, Marseglia GL. Immunoglobulin production pattern is allergen-specific in polysensitized patients. *Int J Immunopathol Pharmacol* 2009;22:809-17.
34. Ichikawa S, Takai T, Inoue T, Yuuki T, Okumura Y, Ogura K, et al. NMR study on the major mite allergen Der f 2: its refined tertiary structure, epitopes for monoclonal antibodies and characteristics shared by ML protein group members. *J Biochem* 2005;137:255-63.
35. Mueller GA, Edwards LL, Aloor JJ, Fessler MB, Glesner J, Pomes A, et al. The structure of the dust mite allergen Der p 7 reveals similarities to innate immune proteins. *J Allergy Clin Immunol* 2010;125:909-17.e4.
36. Okuyama K, Wada K, Chihara J, Takayanagi M, Ohno I. Sex-related splenocyte function in a murine model of allergic asthma. *Clin Exp Allergy* 2008;38:1212-9.
37. Giron-Gonzalez JA, Moral FJ, Elvira J, Garcia-Gil D, Guerrero F, Gavilan I, et al. Consistent production of a higher TH1:TH2 cytokine ratio by stimulated T cells in men compared with women. *Eur J Endocrinol* 2000;143:31-6.
38. Loza MJ, Foster S, Bleeker ER, Peters SP, Penn RB. Asthma and gender impact accumulation of T cell subtypes. *Respir Res* 2010;11:103.
39. Melgert BN, Postma DS, Kuipers I, Geerlings M, Luinge MA, van der Strate BW, et al. Female mice are more susceptible to the development of allergic airway inflammation than male mice. *Clin Exp Allergy* 2005;35:1496-503.
40. Zenovich AG, Panoskaltis-Mortari A, Caron GJ, Kolb AG, Fremming R, Nelson WD, et al. Sex-based differences in vascular repair with bone marrow cell therapy: relevance of regulatory and Th2-type cytokines. *Transplant Proc* 2008;40:641-3.
41. Gloria-Bottini F, Bottini N, Renzetti G, Bottini E. ACP1 and Th class of immunological disease: evidence of interaction with gender. *Int Arch Allergy Immunol* 2007;143:170-6.
42. Hunninghake GM, Lasky-Su J, Soto-Quiros ME, Avila L, Liang C, Lake SL, et al. Sex-stratified linkage analysis identifies a female-specific locus for IgE to cockroach in Costa Ricans. *Am J Respir Crit Care Med* 2008;177:830-6.
43. Yang KD, Liu CA, Chang JC, Chuang H, Ou CY, Hsu TY, et al. Polymorphism of the immune-braking gene CTLA-4 (+49) involved in gender discrepancy of serum total IgE levels and allergic diseases. *Clin Exp Allergy* 2004;34:32-7.
44. Hunninghake GM, Chu JH, Sharma SS, Cho MH, Himes BE, Rogers AJ, et al. The CD4+ T-cell transcriptome and serum IgE in asthma: IL17RB and the role of sex. *BMC Pulm Med* 2011;11:17.
45. Barrenas F, Andersson B, Cardell LO, Langston M, Mobini R, Perkins A, et al. Gender differences in inflammatory proteins and pathways in seasonal allergic rhinitis. *Cytokine* 2008;42:325-9.
46. Shaw LJ, Bugiardini R, Merz CN. Women and ischemic heart disease: evolving knowledge. *J Am Coll Cardiol* 2009;54:1561-75.
47. Schlendorf KH, Nasir K, Blumenthal RS. Limitations of the Framingham risk score are now much clearer. *Prev Med* 2009;48:115-6.
48. Bairey Merz CN, Shaw LJ, Reis SE, Bittner V, Kelsey SF, Olson M, et al. Insights from the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) study, part II: gender differences in presentation, diagnosis, and outcome with regard to gender-based pathophysiology of atherosclerosis and macrovascular and microvascular coronary disease. *J Am Coll Cardiol* 2006;47:S21-9.
49. Bergmann MM, Byers T, Freedman DS, Mokdad A. Validity of self-reported diagnoses leading to hospitalization: a comparison of self-reports with hospital records in a prospective study of American adults. *Am J Epidemiol* 1998;147:969-77.
50. Okura Y, Urban LH, Mahoney DW, Jacobsen SJ, Rodeheffer RJ. Agreement between self-report questionnaires and medical record data was substantial for diabetes, hypertension, myocardial infarction and stroke but not for heart failure. *J Clin Epidemiol* 2004;57:1096-103.
51. Eid RE, Rao DA, Zhou J, Lo SF, Ranjbaran H, Gallo A, et al. Interleukin-17 and interferon-gamma are produced concomitantly by human coronary artery-infiltrating T cells and act synergistically on vascular smooth muscle cells. *Circulation* 2009;119:1424-32.
52. Sampi M, Ukkola O, Paivansalo M, Kesaniemi YA, Binder CJ, Horkko S. Plasma interleukin-5 levels are related to antibodies binding to oxidized low-density lipoprotein and to decreased subclinical atherosclerosis. *J Am Coll Cardiol* 2008;52:1370-8.

TABLE E1. Characteristics of study population compared with participants excluded because of missing data

Characteristic	Total population (age ≥20 y)*	Excluded population*	Study population*	P value†
Population (no.)	4773	771	4002	
Age (y)	46.6 (0.7)	47.0 (1.1)	46.5 (0.8)	.68
Age category (%)				
20-39	38.0 (1.4)	40.8 (2.2)	37.5 (1.6)	.23
≥40	62.0 (1.4)	59.2 (2.2)	62.5 (1.6)	
Sex (%)				
Male	48.1 (0.6)	49.9 (1.8)	47.8 (0.7)	.32
Female	51.9 (0.6)	50.1 (1.8)	52.2 (0.7)	
Education (%)				
<9th grade	6.6 (0.8)	8.7 (1.4)	6.3 (0.8)	.16
9th to <12th grade	11.4 (1.3)	11.8 (1.9)	11.3 (1.3)	
High school or GED	25.1 (1.0)	28.0 (3.1)	24.6 (1.0)	
Some college	30.8 (1.0)	30.1 (2.2)	30.9 (1.1)	
College graduate	26.1 (2.1)	21.4 (2.2)	26.8 (2.3)	
Hypertension (%)	29.6 (1.1)	29.9 (1.9)	29.6 (1.1)	.87
Diabetes mellitus (%)	7.9 (0.5)	8.7 (1.1)	7.7 (0.5)	.46
Close relative with MI at age <50 y	15.5 (0.8)	15.5 (1.7)	15.5 (0.8)	.99
BMI (kg/m ²)	28.6 (0.2)	28.8 (0.3)	28.5 (0.3)	.41
Smoking status (%)				
Never	51.2 (1.4)	50.0 (2.2)	51.4 (1.5)	.67
Former	24.8 (1.0)	24.2 (2.4)	24.9 (0.9)	
Current	23.9 (1.2)	25.7 (2.2)	23.6 (1.3)	
CRP‡ (mg/dL)	0.19 (0.01)	0.24 (0.02)	0.18 (0.01)	<.001
TC (mg/dL)	199.0 (0.8)	197.2 (2.8)	199.2 (0.8)	.50
HDL-C (mg/dL)	54.6 (0.3)	53.2 (0.8)	54.8 (0.4)	.09
tIgE‡ (kU/L)	41.01 (1.55)	41.70 (3.76)	40.93 (1.51)	.82
sIgE, ≥1 positive (%)	43.7 (1.2)	39.2 (2.9)	44.2 (1.1)	.05
Current hay fever (%)	7.4 (0.7)	6.7 (1.3)	7.5 (0.7)	.57

GED, General Educational Development.

*Parenthetical values are SEs.

†P value result, comparing study population with excluded population, from χ^2 test of homogeneity or *t*-test of main effect for cardiovascular outcomes.‡Geometric mean reported because log₁₀ value is used as a covariate in the adjusted logistic regression models.

TABLE E2. Prevalence of MI among subjects with a full panel of sIgE measured compared with subjects with either a partial or no panel of sIgE measured

Characteristic	Total population	Full sIgE panel	Partial/no sIgEs	<i>P</i> value*
Population (no.)	4773	4411	362	
MI (%)	3.6 (0.4)	3.5 (0.4)	4.3 (1.6)	.62

Parenthetical values are SEs.

*Determined with χ^2 test of homogeneity.

TABLE E3. Prevalence of MI among subjects with tlgE and full panel of slgE measured compared with subjects missing data for either tlgE or slgE

Characteristic	Total population	Full IgE panel	Partial/no IgEs	<i>P</i> value*
Population (no.)	4773	4409	364	
MI (%)	3.6 (0.4)	3.5 (0.4)	4.2 (1.6)	.63

Parenthetical values are SEs.

*Determined with χ^2 test of homogeneity.

TABLE E4. Adjusted relation in overall study population between sIgE positivity and MI, using different adjustments for smoking and SES

Smoking covariate(s) in model	SES covariate(s) in model	OR (95% CI)
Never/former/current	HH education	0.91 (0.85-0.97)
Pack-years	HH education	0.93 (0.87-0.98)
Serum cotinine	HH education	0.90 (0.84-0.97)
Never/former/current	PIR	0.90 (0.84-0.96)
Never/former/current	HH income	0.90 (0.84-0.96)
Never/former/current, cotinine	HH income, PIR	0.91 (0.85-0.97)

HH, Householder (or household); PIR, poverty-to-income ratio; SES, socioeconomic status.

Adjusted for age, sex, ethnicity/race (non-Hispanic white, non-Hispanic black, Mexican American, others), smoking status (never, past, current) or pack-years of smoking or serum cotinine as indicated in table, education of household reference person (<9th grade, 9th to 12th grade and no diploma, high school graduate or General Educational Development, some college, college degree) or poverty-income ratio (continuous) or household income (continuous) as indicated in table, diabetes mellitus, hypertension, family history of MI, BMI (continuous), and TC/HDL-C (continuous).

TABLE E5. Age-stratified relation between sIgE positivity and MI

	No.	MI, % (SE)	Unadjusted OR (95% CI)	Interaction <i>P</i> value	Adjusted OR* (95% CI)	Interaction <i>P</i> value*
All	4002	3.3 (0.4)	0.84 (0.78-0.90)		0.89 (0.83-0.94)	
Age category				.79		.87
20-59 y	2796	1.4 (0.1)	0.87 (0.75-1.00)		0.92 (0.80-1.05)	
≥60 y	1206	10.2 (1.3)	0.89 (0.81-0.99)		0.88 (0.80-0.98)	

*Adjusted for age, sex, ethnicity/race (non-Hispanic white, non-Hispanic black, Mexican American, Others), education of household reference person (<9th grade, 9th to 12th grade and no diploma, high school graduate or General Educational Development, some college, college degree), diabetes mellitus, hypertension, family history of MI, smoking status (never, past, current), BMI (continuous), TC/HDL-C (continuous), and CRP (continuous log₁₀ transformed).

TABLE E6. Age- and sex-stratified relations between sIgE positivity and MI

	No.	MI % (SE)	Unadjusted OR (95% CI)	Interaction <i>P</i> value	Adjusted OR* (95% CI)	Interaction <i>P</i> value*
All	4002	3.3 (0.4)	0.84 (0.78-0.90)		0.91 (0.85-0.97)	
Sex/age				<.01		.09
Male/20-59 y	1290	1.3 (0.3)	0.95 (0.81-1.10)		1.04 (0.86-1.26)	
Male/≥60 y	624	14.9 (1.7)	0.91 (0.84-0.99)		0.94 (0.86-1.02)	
Female/20-59 y	1506	1.4 (0.3)	0.65 (0.49-0.85)		0.71 (0.47-1.07)	
Female/≥60 y	582	6.4 (1.5)	0.74 (0.55-0.99)		0.74 (0.50-1.08)	

*Adjusted for age (continuous in stratified model), sex, ethnicity/race (non-Hispanic white, non-Hispanic black, Mexican American, others), education of household reference person (< 9th grade, 9th to 12th grade and no diploma, high school graduate or General Educational Development, some college, college degree), diabetes mellitus, hypertension, family history of MI, smoking status (never, past, current), BMI (continuous), TC/HDL-C (continuous), and CRP (continuous log₁₀ transformed).

TABLE E7. MI prevalence among antihistamine and corticosteroid users in study population

Covariate	MI			P value
	Yes	No	Row total	
Any antihistamine use				
Yes, no. (%)	6 (2.3)	162 (97.7)	168 (100.0)	.502
No, no. (%)	153 (3.4)	3681 (96.6)	3834 (100.0)	
Total, no.	159	3843	4002	
Any steroid use				
Yes, no. (%)	19 (6.0)	209 (94.0)	228 (100.0)	.044
No, no. (%)	140 (3.1)	3634 (96.9)	3774 (100.0)	
Total, no.	159	3843	4002	

Antihistamine use refers to self-reported use of oral antihistamines. Steroid use includes subjects who reported use of oral, topical, and/or inhaled corticosteroids. The numbers are unweighted, and the row percentages are weighted. *P* values were determined with χ^2 test for difference of proportions.

TABLE E8. Unadjusted and adjusted ORs in corticosteroid nonusers for the association between the number of positive sIgE tests detected from a panel of 19 allergens and MI

	No.	MI % (SE)	Unadjusted OR (95% CI)	Interaction <i>P</i> value	Adjusted OR* (95% CI)	Interaction <i>P</i> value*
All	3774	3.1 (0.4)	0.80 (0.74-0.87)		0.88 (0.83-0.94)	
Ethnicity				.21		.09
Non-Hispanic White	1862	3.7 (0.6)	0.77 (0.67-0.89)		0.85 (0.76-0.94)	
Non-Hispanic Black	856	1.9 (0.5)	0.91 (0.84-0.98)		0.97 (0.89-1.07)	
Mexican American	789	1.1 (0.2)	0.89 (0.75-1.06)		0.87 (0.65-1.17)	
Sex				.12		.16
Male	1813	3.9 (0.7)	0.82 (0.75-0.90)		0.92 (0.84-1.02)	
Female	1961	2.4 (0.4)	0.68 (0.55-0.84)		0.77 (0.62-0.97)	

The 228 study subjects reporting use of corticosteroids were excluded from this analysis.

*Adjusted for age, sex, ethnicity/race (non-Hispanic white, non-Hispanic black, Mexican American, others), education of household reference person (<9th grade, 9th to 12th grade and no diploma, high school graduate or General Educational Development, some college, college degree), diagnosis of diabetes mellitus, diagnosis of hypertension, family history of MI before age 50 years, smoking status (never, past, current), BMI (continuous raw score), TC/HDL (continuous), CRP (continuous log¹⁰ transformed).

TABLE E9. Unadjusted and adjusted ORs for the association between the number of positive sIgEs detected from a panel of 19 allergens and MI stratified by tIgE

	No.	MI % (SE)	Unadjusted OR (95% CI)	Interaction <i>P</i> value	Adjusted OR* (95% CI)	Interaction <i>P</i> value*
All	4002	3.3 (0.4)	0.84 (0.78-0.90)		0.91 (0.85-0.97)	
tIgE				.18		.49
<100 (kU/L)	2761	3.2 (0.5)	0.87 (0.72-1.06)		0.99 (0.84-1.16)	
≥100 (kU/L)	1241	3.7 (0.7)	0.72 (0.63-0.82)		0.82 (0.72-0.94)	

*Adjusted for age, sex, ethnicity/race (non-Hispanic white, non-Hispanic black, Mexican American, others), education of household reference person (<9th grade, 9th to 12th grade and no diploma, high school graduate or General Educational Development, some college, college degree), diabetes mellitus, hypertension, family history of MI before age 50 years, smoking status (never, past, current), BMI (continuous raw score), TC/HDL ratio (continuous), CRP (continuous log₁₀ transformed).

TABLE E10. Unadjusted and adjusted ORs for the association between tlgE and MI stratified by slgE positivity from a panel of 19 allergens

	No.	MI % (SE)	Unadjusted OR (95% CI)	Interaction <i>P</i> value	Adjusted OR* (95% CI)	Interaction <i>P</i> value*
All	4002	3.3 (0.4)	1.38 (1.03-1.84)		1.41 (1.01-1.98)	
slgE				.07		<.01
0 positive	2196	4.2 (0.6)	2.76 (1.93-3.97)		2.07 (1.34-3.20)	
≥1 positive	1806	2.3 (0.4)	1.71 (1.04-2.80)		1.40 (0.72-2.71)	

*Adjusted for age, sex, ethnicity/race (non-Hispanic white, non-Hispanic black, Mexican American, others), education of household reference person (<9th grade, 9th to 12th grade and no diploma, high school graduate or General Educational Development, some college, college degree), diabetes, hypertension, family history of MI before age 50 years, smoking status (never, past, current), BMI (continuous raw score), TC/HDL-C ratio (continuous), and CRP (continuous log₁₀ transformed).

TABLE E11. Unadjusted and adjusted ORs for the association between non-sIgE (tIgE – sum [sIgE]) and MI

	No.	MI % (SE)	Unadjusted OR (95% CI)	Interaction P value	Adjusted OR*† (95% CI)	Interaction P value*†
All	4002	3.3 (0.4)	1.48 (1.05-2.08)		1.43 (0.97-2.13)	
Ethnicity				.89		.95
Non-Hispanic White	2021	3.9 (0.5)	1.68 (1.12-2.52)		1.41 (0.90-2.20)	
Non-Hispanic Black	889	2.4 (0.6)	1.53 (1.00-2.34)		1.47 (0.93-2.35)	
Mexican American	813	1.1 (0.2)	1.97 (0.92-4.25)		1.28 (0.85-1.92)	
Sex				.47		.52
Male	1914	4.1 (0.6)	1.29 (0.78-2.15)		1.36 (0.80-2.32)	
Female	2088	2.6 (0.4)	1.59 (1.21-2.09)		1.66 (1.14-2.43)	

*[tIgE – sum (sIgE)] difference was log₁₀-transformed, so ORs and 95% CIs for MI corresponded to a 10-fold change in non-sIgE.

†Adjusted for age, sex, ethnicity/race (non-Hispanic white, non-Hispanic black, Mexican American, others), education of household reference person (<9th grade, 9th to 12th grade and no diploma, high school graduate or General Educational Development, some college, college degree), diabetes mellitus, hypertension, family history of MI before age 50 years, smoking status (never, past, current), BMI (continuous raw score), TC/HDL-C ratio (continuous), CRP (continuous log₁₀ transformed).