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Relationship Between Objective Measures of Atopy and Myocardial Infarction in the United States

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Abstract

Background—Whereas rodent studies indicate that atherosclerosis is a T helper (Th)1-mediated disease and that atopic Th2 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 relationship between atopy, as indicated by a broad panel of serum allergen-specific immunoglobulin E (sIgE), and past myocardial infarction (MI) in a sample representative of the U.S. population.

Methods—Data were analyzed from 4,002 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; $P<0.001$), and were less likely to have ≥1 positive sIgE test (29.9% vs. 44.6%; $P=0.02$) or current hay fever (3.3% vs. 7.6%; $P=0.002$). After adjustment for age, gender, 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% confidence interval [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 using 7 data-driven, prespecified allergen clusters revealed 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 U.S. population in a manner independent of multiple coronary risk factors.

Keywords

Myocardial Infarction; Immune System; Risk Factors; Atopy; Immunoglobulin E

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Introduction

Adaptive immunity plays an important role in atherosclerotic cardiovascular disease (ASCVD). T-lymphocytes are found within atherosclerotic lesions, and their products, as well as those of the cells with which they communicate (i.e., B cells, eosinophils), modify lesion progression.¹ Polarization of adaptive immune responses along either a T helper (Th)1 program, characterized by cell-mediated immunity and the signature cytokine interferon- γ , or a Th2 program, typified by allergic responses and the interleukins-4, -5, and -13, has been proposed to drive the pathogenesis of distinct categories of human disease. As the Th1 and Th2 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 Th2 immunity.

Findings on the relationship between atopy and ASCVD have been conflicting. Most studies that have measured or manipulated T-cell cytokines have concluded that ASCVD is Th1-predominant and that Th2 immunity is atheroprotective. Thus, in mice, Th2-biased strains have reduced atherosclerosis,^{2, 3} and enhancing Th2 responses ameliorates disease.^{4–8} Similarly, coronary artery disease patients have a predominance of Th1 cells.^{9, 10} By contrast, elevated serum total immunoglobulin E (tIgE), a surrogate biomarker of atopy, has also been found to associate with ASCVD.^{11–14} Complicating matters, however, the tIgE-ASCVD relationship 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, as IgE is itself potentially pro-atherogenic 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 using allergic symptoms to define atopy have also yielded mixed results,^{12, 19, 20} and are complicated by the fact that allergic inflammation can, like non-allergic inflammation, promote vascular injury.²¹ Taken together, as 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 relationship between atopic immune programming and ASCVD.

The National Health and Nutrition Examination Survey (NHANES) 2005–2006 collected questionnaire and laboratory data on U.S. 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 U.S. population. Our primary goal was to test for a relationship between atopy and self-reported, physician-diagnosed MI, and to assess the independence of this relationship from established coronary risk factors. Our secondary goal was to discriminate among allergens by investigating the relationship 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 U.S. population. The NHANES 2005–2006 was approved by the NCHS Research Ethics Review Board, and all participants gave informed consent. Details of the plan and operation of NHANES are 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 4,773 participants 20 years old who were examined in the Medical Examination Center, 4,492 (94.1%) had serum tIgE measured, 4,411 (92.4%) had

data available for all 19 sIgEs, and 4,409 (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/Multi-race. Due to the heterogeneity of the Other Hispanic and Other/Multi-race 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)?”

Allergen-specific IgE and total IgE measurement

tIgE and sIgE were measured using the Pharmacia Diagnostics ImmunoCAP 1000 System (Kalamazoo, Michigan). sIgE was measured to a panel of 19 allergens: *Alternaria alternata*, *Aspergillus 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 (i.e., detectable) result for sIgEs was defined as ≥ 0.35 kU/L.

Covariates

Covariates were obtained from: 1) questionnaire; 2) lab analyses of CRP, high-density lipoprotein cholesterol (HDL-C), and total cholesterol (TC); and 3) physical examination (height, weight measurements). Serum C-reactive protein (CRP) was measured by latex-enhanced nephelometry. Serum TC and HDL-C were measured using a Roche Hitachi 717 or 912. 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 two 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 as 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 relationship were estimated per $\log_{10}$ change in tIgE.²² Given racial/ethnic and gender differences in atopy and ASCVD and in risk factor-ASCVD relationships, stratification of analyses by race/ethnicity and gender 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. In order 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 relationship 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 using Taylor series linearization methods through SAS statistical software (Version 9.2, 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 4,002 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 compares the characteristics of this study population to 771 subjects aged ≥ 20 years who were excluded due to missing data. Excluded subjects had higher CRP and lower sIgE positivity than study subjects. There was no significant difference in MI prevalence between subjects who did vs. did not have a full sIgE panel measured (Table E2), nor between subjects who: a) had complete data for both tIgE and sIgE; vs. b) were lacking data for either tIgE or sIgE (Table E3). Of the 4,002 study subjects, 159 (3.97%) reported a history of physician-diagnosed MI. Subjects with a history of MI, compared to those without a history of MI, tended to be older, male, and were likelier 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. Whereas subjects with a history of MI had a higher mean serum tIgE concentration, subjects without MI were likelier to have one or more positive sIgE tests, had a higher mean sum of serum sIgE values (i.e., 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' relationship to MI (dependent variable),²⁴ we analyzed the atopy-MI relationship, treating atopy as a quantitative variable in two different ways. First, we analyzed the relationship between the number of positive (i.e., detected) sIgE tests and MI using multivariate logistic regression (Table II). In the overall population, after adjustment for covariates, including age, race/ethnicity, gender, householder education, diabetes mellitus, hypertension, family history of MI before age 50 years, smoking status, BMI, serum TC/HDL-C ratio, 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 using 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)(Table E4). In addition, the results were unchanged if we adjusted for age using: a) both linear and quadratic terms; b) 10 year categories; or c) two age categories (<60 years old, ≥ 60 years old)(data not shown). Upon age-stratification, an inverse relationship was seen both in 20–59 year old subjects and ≥ 60 year-old subjects, although statistical significance was lost in the former age category (Table E5). The inverse relationship between the number of positive sIgE tests and MI was generally consistent across racial/ethnic strata (interaction $P=0.40$). However, a significant interaction with gender was noted, with the inverse relationship observed in females, but not males. Stratification by both age (20–59 years old vs. ≥ 60 years old) and gender revealed that age does not significantly modify the sIgE-MI relationship within either males or females, and that a similar inverse sIgE-MI relationship is seen in both age strata of females (Table E6). Finally, when we treated atopy as a dichotomous variable instead (i.e., ≥ 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 relationship was attenuated (OR 0.75 [95% CI, 0.46–1.23]) after adjustment for covariates.

As shown in Table E7, of the 4,002 study subjects, 168 (4.2%) reported use of antihistamines and 228 (5.7%) reported use of corticosteroids (topical, inhaled, and/or systemic). There was no significant difference in past MI between antihistamine users and nonusers. However, 19 (6.0%) of corticosteroid users as compared to 140 (3.1%) of corticosteroid nonusers reported past MI ($P=.04$). In order to examine whether corticosteroid use was influencing the sIgE-MI relationship, we performed a sensitivity analysis in which we repeated the analysis in Table II after first excluding corticosteroid users. As shown in Table E8, the findings were minimally changed, still showing a significant inverse relationship between sIgE and MI.

Upon stratifying the analysis between number of sIgEs and MI by serum tIgE concentration using a common clinical cutpoint (100 kU/L), we noted no significant interaction with tIgE upon formal testing. However, sIgE was inversely related to MI only among subjects with serum tIgE ≥ 100 kU/L (Table E9). 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], Table E10). Like the sIgE-MI relationship, the tIgE-MI relationship was essentially unchanged if age was adjusted instead using: a) both linear and quadratic terms; b) 10 year categories; or c) two age categories (<60 years old, ≥ 60 years old)(data not shown). However, upon stratified analysis, the positive association between tIgE and MI was only significant among non-atopic subjects (i.e., those with no detectable sIgE) (Table E10), suggesting that this positive relationship is driven by non-sIgE.

In order to further confirm and explore the relationship between atopy and MI, we next analyzed the relationship, treating atopy as the sum of sIgE values. As shown in Table III, a statistically significant inverse relationship 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), there was no interaction between summed sIgE and race/ethnicity, whereas a significant interaction with gender 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 relationship was essentially unchanged if age was instead adjusted using: a) both linear and quadratic terms; b) 10 year categories; or c) two age categories (<60 years old, ≥ 60 years old)(data not shown). Conversely, a significant, direct relationship was found between non-sIgE (i.e., tIgE minus sum[sIgE]) and MI, although this relationship was somewhat attenuated upon full adjustment (Table E11). Finally, given the reduced prevalence of current hay fever among MI subjects (Table I), we also analyzed the relationship 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 due to 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 that these clusters associate independently with allergic disease.²² In order to determine whether specific allergen classifications account for (i.e., underlie) the overall relationship between sIgE and MI, we tested the relationship between seven prespecified allergen clusters²² and MI. As shown in Table V, upon adjustment for coronary risk factors, house dust mite (HDM, i.e., *Der p* and *Der f*) 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 relationship between mite-specific IgE and MI persisted after adjustment for all other allergen clusters (Table V), indicating its independence from

other allergens. The relationship 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 Th1/Th2 paradigm and its application to human disease, good evidence exists that Th1 and Th2 immune programs are mutually suppressive. Moreover, the potential for Th2 responses to exogenous antigens to reprogram Th1 disease responses to endogenous antigens has been clearly demonstrated. For example, Th2-biased pre-immunization to keyhole limpet hemocyanin ameliorates experimental autoimmune encephalomyelitis through reprogramming autoreactive T cells from Th1 to Th2.²⁷ In support of mutual Th1/Th2 antagonism in human disease, reduced rates of sIgE and allergic disease have been reported in rheumatoid arthritis and multiple sclerosis.^{28–30} Th1-biased diseases. Experimental data derived from rodents indicate that ASCVD is also Th1-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 U.S. 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 Th1-predominant^{2–10} and yet positively associated with tIgE.^{11–14} We find that sIgE (inverse) and non-sIgE (direct) have opposite relationships to MI, with tIgE (their sum) concordant with the latter fraction. This may be viewed as analogous to the relationships of HDL-C (inverse), non-HDL-C (direct), and TC (direct) to MI. We speculate that the direct relationship of tIgE to MI stems from the well-described capacity of IgE itself to promote vascular injury through actions on cell types displaying its receptor, FcεR (e.g., 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 anti-atherogenic. Rather, we posit that sIgE may be a quantitative biomarker of atheroprotective Th2 programming. That is, sIgE may track quantitatively with more 'proximal' master regulators of the Th2 program (e.g., IL-4) that are atheroprotective (to a degree that outstrips possible FcεR-dependent pro-atherogenic effects of sIgE protein) through antagonizing Th1 immunity. Indeed, we found that tIgE predicts MI only among non-atopic subjects. Conversely, the inverse relationship 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, INTERHEART 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 as 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 house dust mite, as opposed to more generalized across 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 *Der f*, but not some other antigens inhibited Th1-biased collagen-induced arthritis, and did so in a dose-responsive fashion.²⁴ Rheumatoid arthritis patients have lower HDM-specific IgE than controls.²⁸ As HDM

allergens are homologous to host cholesterol transport proteins,^{34, 35} it is also intriguing to speculate that HDM-specific antibodies might also impact atheroprotective cholesterol trafficking through cross-reactivity.

The inverse relationship between sIgE was limited to females. This finding should also be interpreted with caution as males displayed a relationship between sum[sIgE] and MI that fell just short of statistical significance (Table III). Nonetheless, fairly extensive published data indicate that females have enhanced Th2 responses,^{36–39} perhaps explaining how atopy in females could be quantitatively or even qualitatively different in its relationship to MI. Indeed, transfer of female bone marrow cells, compared to male counterparts, confers enhanced repair of atherosclerotic lesions in mice likely due to enhanced Th2 function.⁴⁰ Female-specific gene-IgE and gene-atopy associations have been reported,^{41–43} suggesting distinct molecular pathways to atopy in females. Male and female CD4⁺ T cells display non-overlapping genomic correlations to IgE,⁴⁴ and distinct genomic signatures upon allergen exposure.⁴⁵ A growing literature also suggests that ASCVD is itself pathophysiologically different in females.⁴⁶ As 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. As our analysis was cross-sectional, the temporality, causality, and directionality of the sIgE-MI relationship are uncertain. We cannot exclude the possibility of reverse causation, which could hypothetically occur, for example, if post-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 due to missing data had higher CRP 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 (i.e., nonfatal) MI. We did not adjust our primary finding (sIgE-MI relationship) for multiple testing as our analyses were performed in stages, and the sIgE-MI relationship 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 (e.g., exertional angina) as well as subjects who may have suffered an MI if not for revascularization. While self-report also carries 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 Th17 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. As the Th2 cytokine IL-5 ameliorates ASCVD in part through induction of anti-oxidized LDL 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 anti-allergy 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 relationship of sIgE to past MI. In the U.S. population, sIgE is inversely and independently related to past MI. Future studies in rodent

models are warranted to determine whether Th2-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.

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Abbreviations

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
sIgE	allergen-specific immunoglobulin E
Th	T helper
tIgE	total immunoglobulin E

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Clinical Implications

We report an inverse relationship between atopy, as defined by allergen-specific IgE, and past myocardial infarction in the U.S. population. Atopy may be an independent protective factor against myocardial infarction.

Table I

Characteristics of the study population *

Characteristic	Total Population	MI Yes	MI No	P-value [‡]
Population (N)	4002	159	3843	
Age (years)	46.5 (0.8)	65.1 (1.0)	45.9 (0.8)	<.001
Age category (%)				<.001
20–39	37.5 (1.6)	3.5 (2.0)	38.7 (1.5)	
40	62.5 (1.6)	96.5 (2.0)	61.3 (1.5)	
Gender (%)				0.05
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	11.3 (1.3)	20.9 (4.4)	11.0 (1.3)	
High School - 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	15.5 (0.8)	25.4 (4.0)	15.2 (0.9)	0.03
Body Mass Index (kg/m ²)	28.5 (0.3)	29.6 (0.5)	28.5 (0.2)	0.04
Smoking Status (%)				0.001
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)	
C-Reactive Protein [†] (mg/dL)	0.18 (0.01)	0.26 (0.02)	0.18 (0.01)	<.001
Total Cholesterol (mg/dL)	199.3 (0.8)	179.6 (3.4)	199.9 (0.9)	<.001
HDL Cholesterol (mg/dL)	54.8 (0.4)	51.2 (2.0)	54.9 (0.4)	0.08
Total IgE [*] (kU/L)	40.93 (1.51)	55.13 (7.27)	40.51 (1.56)	0.05
Allergen-specific IgE: 1 positive (%)	44.2 (1.1)	29.9 (4.8)	44.6 (1.1)	0.02
Allergen -specific IgE: # 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 allergen-specific IgE [*] (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)	0.002

* Parenthetical values are standard errors.

[†] Geometric mean reported as log-transformed value is used as a covariate in adjusted logistic regression models.[‡] P-value result from Chi-square test of homogeneity or t-test of main effect for cardiovascular outcomes.

Unadjusted and adjusted odds ratios for the association between the number of positive allergen-specific IgE tests and MI*

Table II

	N	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				0.48		0.40
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)	
Gender				0.01		0.01
Males	1914	4.1 (0.6)	0.87 (0.81–0.94)		0.97 (0.90–1.05)	
Females	2088	2.6 (0.4)	0.66 (0.54–0.80)		0.73 (0.61–0.87)	

* Odds Ratio (OR) and 95% confidence interval (CI) for myocardial infarction (MI) for each positive allergen-specific IgE detected from a panel of 19 allergens.

[†] Adjusted for age, sex, ethnicity/race (non-Hispanic white, non-Hispanic Black, Mexican American, Others), education of household reference person (< 9th grade, 9–12 and no diploma, high school graduate or GED, some college, college degree), diagnosis of diabetes mellitus, diagnosis of hypertension, family history of MI before age 50 years, smoking status (never, past, current), body mass index (continuous raw score), TC/HDL (continuous), CRP (continuous log10 transformed).

Table III

Unadjusted and adjusted odds ratios for the association between the sum of allergen-specific IgE values and MI*

	N	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				0.35		0.25
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)	
Gender				0.14		0.06
Males	1914	4.1 (0.6)	0.59 (0.48–0.71)		0.82 (0.65–1.02)	
Females	2088	2.6 (0.4)	0.35 (0.18–0.67)		0.44 (0.26–0.77)	

* Odds Ratio (OR) and 95% confidence interval (CI) for myocardial infarction (MI) per log₂ change in sum of the allergen-specific IgE values from a panel of 19 allergens.

[†] Adjusted for age, sex, ethnicity/race (non-Hispanic white, non-Hispanic Black, Mexican American, Others), education of household reference person (< 9th grade, 9–12 and no diploma, high school graduate or GED, some college, college degree), diagnosis of diabetes mellitus, diagnosis of hypertension, family history of MI before age 50 years, smoking status (never, past, current), body mass index (continuous raw score), TC/HDL (continuous), CRP (continuous log₁₀ transformed).

Table IV
Unadjusted and adjusted odds ratios for the association between (sum [sIgE]/tIgE) and MI*

	N	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				0.93		0.75
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)	
Gender				0.82		0.69
Males	1914	4.1 (0.6)	0.73 (0.51–1.07)		0.86 (0.70–1.04)	
Females	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 odds ratios (ORs) and 95% confidence interval (CI) for myocardial infarction (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, 9–12 and no diploma, high school graduate or GED, some college, college degree), diabetes mellitus, hypertension, family history of MI before age 50 years, smoking status (never, past, current), body mass index (continuous raw score), TC/HDL-C ratio (continuous), CRP (continuous log10 transformed).

Table V

Unadjusted and adjusted odds ratios for the association between allergen-specific IgE 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>Der p</i> , <i>Der f</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)

^{*} Odds Ratios (OR) and 95% confidence interval (CI) for myocardial infarction (MI) for a positive allergen-specific IgE 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, 9–12 and no diploma, high school graduate or GED, some college, college degree), diagnosis of diabetes mellitus, diagnosis of hypertension, family history of MI before age 50 years, smoking status (never, past, current), body mass index (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.

^{//} Rye Grass, Bermuda Grass, Oak, Birch, Ragweed, Peanut, Thistle.