

Relationship of serum cholesterol levels to atopy in the US population

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Abstract

Background: Cholesterol promotes Th2 immunity and allergic inflammation in rodents; whether this occurs in humans is unclear. Reports of both direct and inverse associations between serum cholesterol and atopy in different populations suggest that race and/or other demographic variables may modify these relationships.

Aims of the study: To determine the relationships between levels of three serum cholesterol measures [total cholesterol (TC), high density lipoprotein-cholesterol (HDL-C), and non-HDL-C] and atopy in a sample representative of the US population.

Methods: Cross-sectional study of 6854 participants aged ≥ 6 years from the 2005–2006 National Health and Nutrition Examination Survey.

Results: In the overall population, adjusted odds ratios (AORs) per two-standard deviation increase in TC and non-HDL-C for biochemical atopy (defined as ≥ 1 allergen-specific IgE to 19 allergens) were 1.17 [95% confidence interval (CI), 1.00–1.38] and 1.19 (95% CI, 1.03–1.39), respectively. Interactions by race were noted for the two relationships (interaction $P = 0.004$ and $P = 0.009$, respectively) with non-Hispanic Whites (NHWs) having direct relationships [TC: AOR 1.27 (95% CI, 1.03–1.57); non-HDL-C: AOR 1.27 (95% CI, 1.03–1.56)] and non-Hispanic Blacks (NHBs) inverse relationships [TC: AOR 0.77 (95% CI, 0.62–0.95); non-HDL-C: AOR 0.86 (95% CI, 0.69–1.08)]. The adjusted HDL-C–atopy relationship was non-significant for NHWs and inverse for NHBs [AOR 0.77 (95% CI, 0.61–0.96)]. Relationships were independent of body mass index and serum C-reactive protein and unmodified by corticosteroid or statin usage. Results were similar using current hay fever/allergy as the atopy outcome.

Conclusions: There are marked inter-racial differences in the relationship between serum cholesterol and atopy in the US population.

Atopic sensitization and disease appear to have increased in the United States in recent decades, suggesting a possible interaction of allergy with prevalent environmental factor(s) that have evolved over the same timeframe (1). Dyslipidemia [i.e., high serum low density lipoprotein-cholesterol (LDL-C)] has declined since 1960 (2) and is known to potentially impact the development of atopy (3–6), but reports differ on the direction of the effect. Dyslipidemia promotes pro-atopic Th2 immunity and allergic inflammation in rodents (6), and cholesterol enhances latex-specific IgE and Th2 cytokine production by mononuclear cells of patients

with atopy (3). Allergic sensitization is also related directly to LDL-C, and inversely to high density lipoprotein-cholesterol (HDL-C) in Chinese men (7). On the other hand, serum total cholesterol (TC) is inversely related to atopy in Finnish children (4) and in German adults, no independent relationship with atopic disease was found for LDL-C, and a direct relationship was observed for HDL-C (5). These few human studies addressing the association between serum cholesterol and atopy have each been limited to demographically narrow populations. Collectively, their divergent results raise the interesting possibility of important interactions of the

cholesterol-atopy relationship with genetic and/or demographic background.

We are unaware of any prior report of the relationship between serum cholesterol and atopy in the racially and ethnically diverse US population. The National Health and Nutrition Examination Survey (NHANES) 2005–2006 measured serum cholesterol and allergen-specific IgE and characterized allergic symptoms in a sample of subjects representative of the US population. We hypothesized that there would be differences in the relationship between serum cholesterol and atopy among US racial/ethnic groups. Our primary goal was thus to test for independent relationships between serum cholesterol levels and atopy prevalence within US racial/ethnic strata using national survey data from the NHANES 2005–2006.

Methods

Study population

Data were obtained from the NHANES 2005–2006, which was designed to assess the health and nutrition of the civilian, noninstitutionalized US population under the approval of the NCHS Research Ethics Review Board (see <http://www.cdc.gov/nchs/>). The NHANES classifies participants into five racial/ethnic groups: non-Hispanic White (NHW), non-Hispanic Black (NHB), Mexican American, other Hispanic, and other/Multi-race. Due to the heterogeneity of the latter two categories (non-Mexican Hispanics, Asians, Native Americans, Multiracial), we included them in the analysis of the overall population but did not analyse them individually. Low density lipoprotein-cholesterol was measured only in participants who were asked to fast for ≥ 8.5 h ($n = 3026$), of whom $n = 250$ did not meet the fasting requirements. By contrast, TC and HDL-C were measured in fasting and non-fasting participants ($n = 7360$). Fasting duration was recorded in this combined population, permitting assignment to individual cholesterol measurements. Non-HDL-C (i.e., TC minus HDL-C) has comparable or better predictive value than LDL-C for cardiovascular disease (8), and both fasting and nonfasting non-HDL-C are predictive (9). Thus, all analyses were based upon TC and HDL-C measured in a combined fasting and nonfasting study population.

Outcomes

Biochemical atopy was defined as ≥ 1 detectable (≥ 0.35 kU/l) serum allergen-specific IgE to a panel of 19 allergens (10). Subjects were defined as having current clinical atopy if they affirmed ≥ 1 of the following two items: (i) current hay fever (affirmative answer to both 'Has a doctor ever told you that you have hay fever?' and 'During the past 12 months, have you had an episode of hay fever?'); (ii) current allergy (affirmative answer to both 'Has a doctor ever told you that you have allergies?' and 'During the past 12 months, have you had any allergy symptoms or an allergy attack?').

Serum cholesterol measurement

Serum TC and HDL-C were measured using a Roche Hitachi 717 or 912. We derived serum non-HDL-C by subtracting HDL-C from TC.

Covariates

Covariates were obtained from questionnaire, lab analyses, and physical examination. IgE was measured using the Pharmacia Diagnostics ImmunoCAP 1000 System (Kalamazoo, MI, USA). Cotinine was measured by isotope dilution-high performance liquid chromatography/tandem mass spectrometry, and C-reactive protein (CRP) by latex-enhanced nephelometry. Body mass index (BMI) is a weight divided by height squared (kg/m^2).

Statistical analyses

Relationships between serum cholesterol and atopy (dependent variable) were examined in stratified logistic regression analyses, and odds ratios (ORs) estimated per two-standard deviation (SD) increase for each cholesterol subtype (11). Analyses within racial/ethnic, corticosteroid use, and statin use strata were prespecified as the primary analysis, based on the a priori hypothesis that these variables would modify the cholesterol-biochemical atopy relationship [nine comparisons (three variables $\times$ three cholesterol measures)]. Subsequent exploratory analyses (age, gender, BMI) were conducted after the primary analyses were completed. The weighted SDs for TC (39.1 mg/dl), non-HDL-C (39.3 mg/dl), and HDL-C (14.4 mg/dl) were determined for the overall NHANES 2005–2006 population for which values were available ($n = 7360$). Covariates in adjusted models included age, sex, race/ethnicity (total population), householder education, BMI, log-transformed cotinine, CRP, and time fasting. Analyses were adjusted for the NHANES complex sampling design using SAS statistical software (version 9.1.3; SAS, Cary, NC, USA) survey procedures according to NHANES analysis specifications. Statistical significance was defined as $P \leq 0.05$ (main effects) or ≤ 0.10 (interactions).

Results

Table 1 and Fig. 1 show the features of 6854 subjects aged ≥ 6 years in the NHANES 2005–2006 for whom data were available for serum allergen-specific IgE, TC, HDL-C, and other covariates as shown. Among racial/ethnic groups, NHBs had the lowest non-HDL-C and the highest HDL-C. NHBs had the highest prevalence of biochemical atopy yet lower prevalence of current clinical atopy than NHWs. Table S1 shows the degree of concordance between atopy outcomes.

As given in Table 2, after adjustment, there was a borderline significant, direct TC-biochemical atopy relationship and significant, direct non-HDL-C-biochemical atopy relationship in the overall population. A highly significant interaction by

Table 1 Characteristics of study population by race/ethnicity*

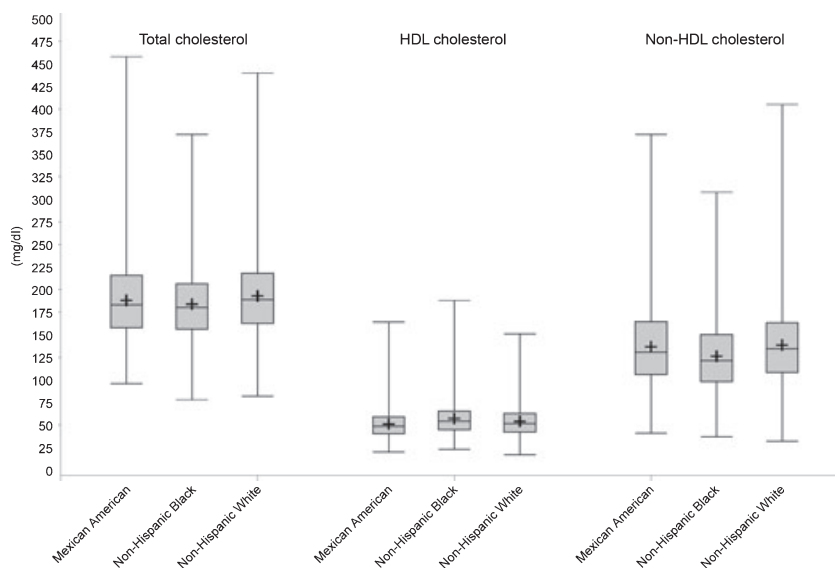
Characteristic	Total population	Mexican American	Non-Hispanic Black	Non-Hispanic White	P-value†
Population (N)	6854	1722	1791	2825	
Age (years)	40.0 (0.8)	31.6 (0.6)	36.5 (0.9)	42.3 (0.9)	<0.001
Age (years) (%)					
6–17	17.1 (0.7)	24.5 (0.2)	19.9 (0.4)	15.0 (0.7)	<0.001
≥18	82.9 (0.7)	75.5 (0.8)	80.1 (1.6)	85.0 (2.4)	
Gender (%)					
Male	48.9 (0.5)	52.7 (0.5)	46.2 (0.9)	49.4 (1.6)	0.07
Female	51.1 (0.5)	47.3 (0.5)	53.8 (1.1)	50.6 (1.4)	
Education (%)					
<9th grade	6.4 (0.7)	34.2 (0.5)	4.4 (0.1)	2.8 (0.4)	<0.001
9th to <12th	11.6 (1.2)	19.2 (0.2)	19.5 (0.4)	9.3 (1.1)	
High school – GED	25.1 (1.2)	20.6 (0.3)	25.1 (0.6)	26.1 (1.5)	
Some college	31.1 (1.1)	19.7 (0.3)	35.1 (0.7)	32.3 (1.3)	
College graduate	25.8 (2.2)	6.3 (0.1)	15.9 (0.4)	29.6 (2.1)	
Body mass index (kg/m ²)	27.2 (0.2)	26.9 (0.2)	28.8 (0.3)	27.2 (0.3)	<0.001
Serum cotinine‡ (ng/ml)	0.37 (0.04)	0.13 (0.02)	0.69 (0.17)	0.40 (0.06)	<0.001
C-reactive protein (mg/dl)	0.37 (0.02)	0.43 (0.04)	0.44 (0.02)	0.37 (0.02)	0.02
Fasting time (hours)	7.0 (0.1)	7.9 (0.2)	7.5 (0.2)	6.8 (0.1)	<0.001
Total cholesterol (mg/dl)	191.8 (0.6)	188.4 (1.5)	184.4 (0.7)	193.3 (0.7)	<0.001
HDL-cholesterol (mg/dl)	54.5 (0.3)	51.4 (0.7)	57.7 (0.3)	54.4 (0.4)	<0.001
non-HDL-cholesterol (mg/dl)	137.4 (0.8)	137.1 (1.6)	126.7 (0.8)	138.9 (0.9)	<0.001
Subjects with ≥1 positive allergen-specific IgE (%)	44.6 (1.2)	46.7 (1.6)	57.9 (1.6)	41.5 (1.3)	<0.001
Subjects with current clinical atopy (%)§	25.0 (1.0)	12.7 (1.4)	20.2 (0.9)	27.6 (1.4)	<0.001
Subjects using statins in the last 30 days (%)	10.7 (0.7)	3.1 (0.5)	8.7 (0.7)	12.3 (0.8)	<0.001

*Mean value or percent reported with standard error.

†P-value from Chi-square test of homogeneity or ANOVA test of main effect for three race/ethnicity groups.

‡Geometric mean reported because log (cotinine) is used as a covariate in the adjusted logistic regression models.

§Current clinical atopy was defined as physician-diagnosed current hay fever or current allergies or both.

**Figure 1** Serum cholesterol values by race/ethnicity. Box plots of serum cholesterol depicting the 25th, 50th, and 75th percentiles

(horizontal lines on box), minimum and maximum values (whiskers), and the mean (plus symbol).

Table 2 Associations between biochemical atopy and serum cholesterol from logistic regression analysis

Characteristic	Total cholesterol (TC)*		HDL-C*		Non-HDL-C*	
	Unadjusted OR (95% CI)	Adjusted OR† (95% CI)	Unadjusted OR (95% CI)	Adjusted OR† (95% CI)	Unadjusted OR (95% CI)	Adjusted OR† (95% CI)
Total population‡	0.97 (0.85–1.12)	1.17 (1.00–1.38)	0.86 (0.79–0.94)	0.96 (0.86–1.06)	1.03 (0.90–1.17)	1.19 (1.03–1.39)
Mexican American§	1.03 (0.83–1.28)	1.13 (0.87–1.45)	0.97 (0.71–1.31)	1.17 (0.90–1.52)	1.04 (0.81–1.33)	1.07 (0.81–1.42)
Non-Hispanic Black§	0.65 (0.53–0.81)	0.77 (0.62–0.95)	0.73 (0.57–0.93)	0.77 (0.61–0.96)	0.76 (0.62–0.93)	0.86 (0.69–1.08)
Non-Hispanic White§	1.07 (0.89–1.28)	1.27 (1.03–1.57)	0.87 (0.78–0.97)	1.01 (0.88–1.16)	1.12 (0.95–1.32)	1.27 (1.03–1.56)

Biochemical atopy was defined as having ≥ 1 positive allergen-specific IgE.

HDL-C, high density lipoprotein-cholesterol.

*Odds ratio (OR) and 95% confidence interval (CI) per two-standard deviation (SD) increase in each cholesterol subtype. SDs (TC = 39.1 mg/dl, non-HDL-C = 39.3 mg/dl, HDL-C = 14.4 mg/dl).

†Adjusted racial/ethnic interaction $P = 0.004$ for TC, $P = 0.38$ for HDL-C, and $P = 0.009$ for non-HDL-C.

‡From unadjusted model (atopy = cholesterol) and fully adjusted model including age, race/ethnicity, gender, householder education, body mass index, serum CRP, log-transformed serum cotinine, and hours fasting.

§Fully adjusted model does not include race/ethnicity.

race/ethnicity was, however, noted for both cholesterol measures, with NHWs having direct TC- and non-HDL-C-biochemical atopy relationships, and NHBs having an inverse TC-biochemical atopy relationship. Whereas NHWs had no significant relationship between HDL-C and atopy in the fully adjusted model, a significant inverse relationship was noted for NHBs. No significant relationships were observed in Mexican Americans. No significant interactions were found by age (6–17, 18–39, ≥ 40 years), gender, or BMI (<85th, 85–94th, ≥ 95 th percentile) in the cholesterol-atopy relationships in the overall population (Table S2). As statins are prescribed for dyslipidemia and also modulate immunity, and corticosteroids are prescribed for allergy and may impact serum lipids, we also explored the effect of these two medication classes. No significant interactions were noted for either statins or (combined oral and inhaled) corticosteroids (Table S2), indicating that neither drug class modifies the cholesterol-atopy relationships. With a few exceptions, race/ethnicity-stratified results using current clinical atopy as an outcome were gener-

ally consistent with those for the biochemical atopy outcome (Table 3).

Discussion

It is well established that cholesterol promotes allergic inflammation in rodents, but few reports have addressed the relationship between serum cholesterol and atopy in humans. Individually, these reports have analysed demographically narrow study populations; collectively, they have yielded a variety of results on whether the LDL-C-atopy and HDL-C-atopy relationships are direct or inverse. Herein, in the first such analysis, to our knowledge, using national survey data in a racially and ethnically diverse study population, we have uncovered novel, marked inter-racial differences in the relationship between serum cholesterol levels and atopy.

Although the TC- and non-HDL-C-atopy ORs we report for NHWs are of modest magnitude, they are in fact comparable to reported ORs of serum cholesterol for myocardial

Table 3 Associations between current clinical atopy and serum cholesterol from logistic regression analysis

Characteristic	Total-cholesterol (TC)*		HDL-C*		Non-HDL-C*	
	Unadjusted OR (95% CI)	Adjusted OR† (95% CI)	Unadjusted OR (95% CI)	Adjusted OR† (95% CI)	Unadjusted OR (95% CI)	Adjusted OR† (95% CI)
Total population‡	1.18 (1.04–1.34)	1.08 (0.93–1.26)	1.09 (1.02–1.17)	1.00 (0.88–1.12)	1.14 (1.01–1.29)	1.08 (0.95–1.24)
Mexican American§	1.14 (0.85–1.53)	1.02 (0.74–1.42)	1.28 (0.91–1.80)	1.22 (0.84–1.78)	1.06 (0.80–1.40)	0.95 (0.69–1.30)
Non-Hispanic Black§	0.85 (0.69–1.04)	0.81 (0.67–0.97)	0.85 (0.74–0.98)	0.87 (0.69–1.10)	0.91 (0.75–1.11)	0.85 (0.70–1.03)
Non-Hispanic White§	1.23 (1.09–1.40)	1.16 (0.99–1.36)	1.06 (0.97–1.17)	0.97 (0.83–1.14)	1.21 (1.08–1.35)	1.17 (1.03–1.34)

Current clinical atopy was defined as currently having diagnosis of either hay fever or allergies or both.

HDL-C, high density lipoprotein-cholesterol.

*Odds ratio (OR) and 95% confidence interval (CI) per two-standard deviation (SD) increase in each cholesterol subtype. SDs (TC = 39.1 mg/dl, non-HDL-C = 39.3 mg/dl, HDL-C = 14.4 mg/dl).

†Adjusted racial/ethnic interaction $P = 0.02$ for TC, $P = 0.09$ for HDL-C, and $P = 0.04$ for non-HDL-C.

‡From unadjusted model (atopy = cholesterol) and fully adjusted model including age, race/ethnicity, gender, householder education, body mass index, serum CRP, log-transformed serum cotinine, and hours fasting.

§Fully adjusted model does not include race/ethnicity.

infarction (12), the disease with perhaps the best-established causal relationship with cholesterol. The cholesterol-atopy relationships also appear robust as they are generally consistent between two very different atopy outcomes: a biochemical measure of sensitization and a clinical measure of current disease. Perhaps most striking is the qualitative difference in the relationship between races we report, with the TC-atopy relationship inverse for NHBs and direct for NHWs. While widely used clinically, lipoprotein cholesterol levels may oversimplify and obscure underlying biologically important qualitative features of lipoproteins. For example, NHBs have increased levels of oxidized LDL (13). To what degree qualitative differences in lipoproteins can explain the marked racial/ethnic differences in our data is uncertain. The concordant directionality of the non-HDL-C- and HDL-C-atopy relationships among NHBs may suggest, however, that 'dyslipidemia' per se as a unifying process is not related to atopy in NHBs. A separate process that modulates atopy and also concordantly impacts HDL-C and LDL-C, such as inflammation (14), may explain the relationship in NHBs, although persistence of the relationships after the adjustment for CRP argues against a role for inflammation. The lack of relationship modification by statins may suggest that statins do not modulate a biological pathway between cholesterol and atopy; indeed, statins do not affect Th1/Th2 balance in human T cells (15). Nevertheless, future investigations of statin $\times$ race interactions in atopy are warranted.

Our study had limitations. The cross-sectional design of the NHANES precludes the determinations of causality. Despite the multiple adjustments made, the possibility of unmeasured confounders also remains. For example, nutritional factors (antioxidants, fatty acids) may differ among racial/ethnic groups and possibly impact the cholesterol-atopy relationship. Finally, we performed our analyses with combined 'fasting' and 'nonfasting' cholesterol values; this notwithstanding, the fasting time in our study population had tight variation, was close to the ≥ 8 h fast traditionally imposed for fasting serum lipid measurement and was adjusted for in the regressions.

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It would be premature to translate our findings to practical clinical situations. If independently confirmed, however, the data do raise the interesting possibility that hypercholesterolemia and its treatment may affect risk for atopy differentially among races, and that, in inflammatory diseases involving dyslipidemia (e.g., atherosclerosis), cholesterol may modulate pathogenesis differentially among races through effects on Th1/Th2 balance. The present findings also complement a recent report of inter-racial/ethnic differences in the relationship between serum cholesterol and asthma (16), and previous reports identifying opposite gene-HDL-C associations between blacks and whites (17). Given the high prevalence of dyslipidemia and atopy in modern society, future studies exploring interactions between these two disease entities in greater detail may yield insights of great public health significance.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Prevalence of biochemical atopy vs current clinical atopy.

Table S2. Stratified analyses of the cholesterol-biochemical atopy relationship by logistic regression.

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Table S1. Prevalence of biochemical atopy vs. current clinical atopy

Frequency Percent	Current clinical atopy		
	Yes	No	Total
Biochemical atopy			
Yes	870 12.69	2452 35.77	3322 48.47
No	497 7.25	3035 44.28	3532 51.53
Total	1367 19.94	5487 80.06	6854 100.00

In the study population, 57% (12.69% + 44.28%) are concordant for the definitions of biochemical atopy and current clinical atopy.

Table S2. Stratified analyses of the cholesterol-biochemical atopy relationship by logistic regression

Characteristic	Total Cholesterol*			HDL Cholesterol*			Non-HDL Cholesterol*		
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Adj. Inter. P-val [†]	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Adj. Inter. P-val [†]	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Adj. Inter. P-val [†]
Gender			0.76			0.86			0.92
Male	1.05 (0.86-1.27)	1.18 (0.96-1.44)		0.99 (0.83-1.19)	1.00 (0.81-1.23)		1.05 (0.88-1.25)	1.18 (0.98-1.42)	
Female	0.96 (0.82-1.11)	1.18 (0.98-1.42)		0.92 (0.79-1.09)	0.92 (0.78-1.09)		0.98 (0.87-1.11)	1.23 (1.03-1.47)	
Age (yrs)			0.89			0.32			0.75
6-17	1.04 (0.72-1.51)	1.05 (0.71-1.56)		1.07 (0.85-1.34)	1.09 (0.82-1.44)		1.01 (0.70-1.45)	1.02 (0.68-1.53)	
18-39	1.11 (0.80-1.53)	1.10 (0.79-1.54)		0.74 (0.58-0.94)	0.85 (0.65-1.10)		1.23 (0.91-1.65)	1.16 (0.84-1.60)	
>= 40	1.09 (0.88-1.34)	1.12 (0.92-1.37)		0.93 (0.80-1.09)	0.97 (0.80-1.17)		1.12 (0.94-1.34)	1.14 (0.97-1.33)	
BMI (%ile)			0.22			0.39			0.41
<85	0.96 (0.83-1.12)	1.16 (0.98-1.37)		0.89 (0.79-1.01)	0.98 (0.84-1.13)		1.01 (0.87-1.18)	1.18 (1.00-1.40)	
85-94	1.08 (0.82-1.41)	1.20 (0.88-1.63)		0.88 (0.66-1.18)	1.08 (0.85-1.38)		1.12 (0.84-1.51)	1.18 (0.85-1.64)	
≥95	0.90 (0.75-1.09)	1.07 (0.87-1.31)		0.75 (0.58-0.97)	0.85 (0.61-1.18)		0.97 (0.80-1.17)	1.11 (0.93-1.32)	
Statin Use			0.99			0.80			0.96
Yes	1.18 (0.83-1.68)	1.04 (0.71-1.50)		0.82 (0.57-1.20)	0.93 (0.54-1.60)		1.26 (0.89-1.79)	1.06 (0.75-1.50)	

Characteristic	Total Cholesterol*			HDL Cholesterol*			Non-HDL Cholesterol*		
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Adj. Inter. P-val [†]	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Adj. Inter. P-val [†]	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Adj. Inter. P-val [†]
No	0.94 (0.80-1.10)	1.17 (0.96-1.42)		0.86 (0.79-0.94)	0.95 (0.86-1.05)		0.99 (0.85-1.16)	1.19 (0.98-1.44)	
Steroid Use			0.63			0.86			0.49
Yes	1.04 (0.70-1.55)	1.48 (0.87-2.53)		0.78 (0.43-1.42)	0.76 (0.46-1.26)		1.20 (0.74-1.94)	1.79 (0.96-3.34)	
No	0.97 (0.84-1.13)	1.17 (0.99-1.39)		0.86 (0.79-0.94)	0.97 (0.87-1.08)		1.02 (0.89-1.17)	1.19 (1.01-1.39)	

Biochemical atopy was defined as having ≥ 1 positive allergen-specific IgE.

*Odds ratio (OR) and 95% confidence interval (CI) per 2-standard deviation (SD) increase in each cholesterol subtype from unadjusted model (atopy = cholesterol) and fully adjusted model including age, race/ethnicity, gender, householder education, BMI, serum CRP, log-transformed serum cotinine, and hours fasting.

[†]Adjusted interaction P-value

SDs (TC = 39.1 mg/dL, non-HDL-C = 39.3 mg/dL, HDL-C = 14.4 mg/dL).

HDL; high density lipoprotein.