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The *APOA1/C3/A4/A5* cluster and markers of allostatic load in the Boston Puerto Rican Health Study

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Abstract

Background and Aims—The *APOA1/C3/A4/A5* cluster encodes key regulators of plasma lipids. Interactions between dietary factors and single nucleotide polymorphisms (SNPs) in the cluster have been reported. Allostatic load, or physiological dysregulation in response to stress, has been implicated in shaping health disparities in ethnic groups. We aimed to determine the association between polymorphisms in the *APOA1/C3/A4/A5* cluster with allostatic load parameters, alone, and in interaction with dietary fat intake in Puerto Ricans adults.

Methods and Results—Data on demographic and anthropometric measures, lifestyle behaviors, and medication use, as well as blood and urine samples for biomarker analysis, were obtained from participants of the Boston Puerto Rican Health Study ($n=821$, ages 45–75 y). The twelve polymorphisms analyzed were not associated with allostatic load parameters. Significant interactions were observed between dietary fat intake and *APOA1* -75 in association with waist circumference (WC), ($P=0.005$), *APOC3* -640 with diastolic blood pressure (DBP), ($P=0.003$), and *APOA4* N147S and *APOA5* S19W with systolic blood pressure (SBP), ($P=0.001$ and $P=0.002$, respectively). Puerto Ricans homozygous for the common allele of *APOA1* -75, *APOA4* N147S and *APOA5* S19W had lower WC and SBP when consuming <31% of total fat from energy, than participants with the minor allele. Participants heterozygous for *APOC3* -640 had lower DBP at total fat intake $\geq 31\%$ from energy.

Conclusion—SNPs in *APOA1/C3/A4/A5*, as modulated by dietary fat intake, appear to influence allostatic load parameters in Puerto Ricans.

Keywords

allostatic load; *APOA1/C3/A4/A5* cluster; gene-diet interaction; Puerto Ricans; single nucleotide polymorphism

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Introduction

A cluster of four apolipoprotein genes (*APOA1/C3/A4/A5*) on chromosome 11q23 has been well recognized as a key regulator of plasma lipids in various populations (1). The four genes that comprise the cluster (*APOA1*, *APOC3*, *APOA4*, *APOA5*) are involved in several steps of lipid metabolism, and have implications in the development of metabolic and chronic disease (2). There are numerous examples of associations between single nucleotide polymorphisms (SNPs) in this cluster and lipid measures (1), (3). Several interactions with dietary factors have been reported with gene variants in the cluster, particularly in response to fat intake. For example, interactions have been reported for the *APOA1* -75 variant and polyunsaturated fatty acid (PUFA) intake in association with plasma high density lipoprotein (HDL-C), *APOC3* -455 and saturated fat intake with lipid profile, and several *APOA5* variants that modulate TG in response to an oral fat tolerance test (4), (5).

We have previously observed that chromosome 11 may be a candidate for environmental pressure in Puerto Ricans, as suggested by exceptional population differentiation values in that locus (6). This was also observed for intronic, non-synonymous and promoter region SNPs. In addition, we showed that Puerto Ricans had significantly different minor allele frequency (MAF) for several SNPs of this cluster compared to non-Hispanic whites (6), and other studies show that Puerto Ricans living in the United States present multiple health disparities for chronic diseases (7), (8). Differences by ethnic group in MAF in disease-associated genetic loci play a role in the genetic contribution to health outcomes (9), and may account for some of the observed health disparities in Puerto Ricans. Interactions of such genetic candidates with environmental factors may also provide a key to the observed differences in genetic risk for disease in diverse populations (10).

Allostatic load has been explored in studies of health disparities in minority ethnic groups (11), (12). Allostatic load refers to the cumulative burden or dysregulation in physiological responses due to constant and/or prolonged exposure to stressors (13). This wear and tear of the system can cause physiological parameters to exceed normal operating ranges, and may lead to disease (14). Although no consensus has been attained regarding an operational definition of allostatic load, a set of validated physiological markers spanning several body systems is commonly used to define this cumulative measure (12), (15). We have recently shown that 10 parameters of biological functions across a range of regulatory systems are associated with chronic disease in Puerto Ricans, including markers of neuroendocrine function, blood pressure, adipose tissue deposition, and lipid and glucose metabolism (16). Some of these parameters have been implicated with the function of apolipoproteins and with genetic polymorphisms in the *APOA1/C3/A4/A5* cluster. As several markers of allostatic load have documented associations with nutritional factors, particularly dietary fat intake, it is likely that fat may be a modifier in the relationship between the *APOA1/C3/A4/A5* cluster SNPs and allostatic load parameters.

Genetic variations have been proposed as modulators of allostatic load markers (17), (18), yet no studies on the genetic contribution to physiological dysregulation have been reported in Puerto Ricans. Thus, we aimed to determine the association between polymorphisms in the *APOA1/C3/A4/A5* cluster with 10 parameters of allostatic load, alone, and in interaction with dietary fat intake in a cohort of Puerto Rican older adults.

Methods

Study Population

The sample consisted of 1020 unrelated individuals at the time of analysis who participated in the Boston Puerto Rican Health Study, a longitudinal study on stress, nutrition, health and

aging (11). Eligible participants had to be able to answer interview questions in either English or Spanish, be of Puerto Rican descent, between the ages of 45–75 years, and living in the Boston, MA area at the time of the study. Ethnicity was self-reported. The Institutional Review Board for Human Research at Tufts Medical Center approved the protocol and consent forms of the study. All participants signed consent forms. Baseline data obtained during 2004 to 2006 was used for this analysis.

Measurements

Detailed data collection and laboratory protocols have been described previously (16). Briefly, data were obtained during a home-based interview by trained staff. A comprehensive questionnaire was used to obtain demographic and socio-economic information, medical diagnoses and medication use. Questions about drinking and smoking behaviors were used to determine smoking status and alcohol intake (never, past, current).

Physical activity was measured with a modified version of the Paffenbarger questionnaire of the Harvard Alumni Activity Survey. A physical activity score was calculated based on hours spent on typical 24-hour activities. The interviewer administered a 126-item, semi-quantitative food frequency questionnaire (FFQ), specially designed for this population and adapted, originally, from the National Cancer Institute-Block FFQ format, but revised to include appropriate foods, recipes and portion sizes (19). FFQs were scanned using the OPSCAN program and linked with a portion size entry program. Data were then linked with the Minnesota Nutrient Data System (NDS, version 5.0_35) for nutrient analyses.

Blood pressure and anthropometric measures were taken following standard protocol, in duplicate, during the home visit. Blood pressure was taken after short rests at three time points during the interview; the average of the second and third readings was used for this analysis. The average of the two readings for height, weight, and waist circumference (WC) was used for analysis. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2).

After the interview, participants were instructed to fast and to collect urine for 12 hours prior to the next visit. On the following morning, a certified phlebotomist obtained 12-hour fasting blood samples for biochemical analyses and 12-hour urine collection samples for measures for cortisol, epinephrine and norepinephrine. Standard laboratory protocols were followed as described previously (16).

Gene variants and genotyping

The *APOA1/C3/A4/A5* cluster polymorphisms used in this analysis were selected based on their MAF (>5%), potential functionality, and representation of the haplotype block, as well as being subject to selection in this population (6). A total of 12 SNPs were included for analysis. Genotyping has been previously described in detail elsewhere (6). Briefly, genomic DNA was purified using the QIAamp® DNA Blood Mini kits (*Qiagen, Hilden, Germany*) from buffy coats of nucleated cells obtained from blood samples. Genotyping was carried using TaqMan® SNP genotyping assays (*Applied Biosystems, Foster City, CA*). Quality control estimated the genotyping error as less than 1%.

Population admixture

Calculation for population admixture in this sample has been described previously (20). Briefly, individual ancestry was calculated based on the genotypes of 100 ancestry informative markers with reference to three ancestral populations: West African, European, and Native American. We controlled for population admixture in this analysis by including African and European ancestries as covariates in the models. Those components were the

two major ancestries in this Puerto Rican sample, and more likely to be confounders in models for association with chronic conditions, than adjusting for Native-American ancestry (20).

Statistical Analysis

A total of 821 participants with available genotype information, energy intake between 600 and 4,800 kcals, and BMI ≥ 18 were included in this analysis. Initial exploratory analysis was done to check for normality of distribution of continuous variables. The variables for serum dehydroepiandrosterone sulfate (DHEA-S), urinary cortisol, epinephrine and norepinephrine were log-transformed to normalize the distribution of the data. Pearson's chi-square statistic was used to test Hardy-Weinberg Equilibrium (HWE) for each SNP. Pairwise linkage disequilibrium (LD) between SNPs in the *APOA1/C3/A4/A5* cluster were estimated with the correlation coefficient R^2 using PowerMarker software (21).

The relationship between each SNP and ten continuous parameters of allostatic load (systolic and diastolic blood pressure (SBP and DBP), plasma cholesterol, plasma HDL-C, WC, glycosylated hemoglobin (HbA1c), DHEA-S, cortisol, epinephrine and norepinephrine) were evaluated using analysis of covariance (ANCOVA), and the adjusted means were estimated after controlling for potential confounders, including age, sex, alcohol intake, smoking, medications (diabetes, hypertension or lipid-lowering), BMI or physical activity, and population admixture. The interactions between total dietary fat intake (as a categorical variable defined as two groups divided by the median intake of the population) and polymorphisms were also tested in multivariate interaction models, after adjusting for the same covariates and total energy intake.

For SNPs with low frequency of the minor allele homozygotes, the carriers of the minor allele were grouped and compared against common allele homozygotes. Standard regression diagnostic procedures were used to ensure the appropriateness of the models. Statistical analyses were performed using SPSS version 15.0. All reported probability tests were two-sided. Results with $P < 0.007$ were deemed statistically significant, after Bonferroni correction for multiple tests.

Results

The pairwise LD coefficient R^2 between the *APOA1/C3/A4/A5* cluster SNPs in the Puerto Rican sample indicates several SNP pairs that are in linkage (Table 1). SNPs within a gene show stronger LD than between genes; namely *APOA1* -2803 with *APOA1* -2630; *APOA1* -3012 with *APOA1* -75; and the four *APOC3* SNPs with each other. *APOA4* and *APOA5* polymorphisms do not show strong linkage to others in the cluster. All SNPs were in HWE. The majority of the participants were women (73%) (Table 2). Similar results for the tested models were obtained for men and women, and thus, data were combined for all participants to ensure adequate statistical power to test associations.

Association between *APOA1/C3/A4/A5* gene variants and parameters of allostatic load were analyzed adjusting for potential confounders (Table 3). No statistically significant associations were observed at $P < 0.007$. However, there were several associations at the $P < 0.05$ level. Participants homozygotes for the common allele of *APOA1* -75 and *APOA1* -3012 had significantly lower DHEA-S than minor allele carriers ($P = 0.044$ for both SNPs). On the other hand, common homozygotes for *APOA5* -1131 showed significantly higher DHEA-S than carriers of the minor allele ($P = 0.044$). Three SNPs in the *APOA1* gene (-2630, -2803 and -3012) were significantly associated with urinary epinephrine at the $P < 0.05$ level ($P = 0.023$, $P = 0.037$ and $P = 0.010$, respectively). Carriers of the minor alleles for *APOA1* -2630 and -3012 had lower epinephrine than participants with the common

allele, while the opposite was observed for the -2803 polymorphism. Finally, minor allele carriers of the *APOA5* S19W showed significantly lower HDL-C concentration than did those common homozygous ($P=0.041$).

Modulation by total dietary fat intake on the association between these gene variants and the same markers was explored, adjusting for the same covariates and total energy intake. Total fat intake was categorized using the median of total fat as percent from energy (31%). Several interactions were deemed significant at the $P<0.007$ level (Figure 1). Participants homozygous for the common allele of *APOA1* -75 had significantly lower WC in the lower total fat intake group than minor allele carriers ($P=0.005$), while there was no difference by variant with total fat intake $\geq 31\%$ of energy ($P=0.235$), (Figure 1A). For the *APOC3* -640 polymorphism, a significant interaction with total fat intake was observed in association with DBP ($P=0.003$), (Figure 1B). Heterozygous (GT) participants had significantly lower DBP than common GG participants ($P=0.030$), but not lower than minor TT homozygous ($P=0.304$) when consuming more than 31% of total fat from energy. There were no significant differences by genotype at the lower total fat intake category.

APOA4 N147S and *APOA5* S19W showed significant interaction with total fat intake in association with SBP ($P=0.001$ and $P=0.002$, respectively). Carriers of the G minor allele of *APOA4* N147S had higher SBP ($P=0.052$) with lower total fat intake, and lower SBP ($P=0.010$) with high total fat intake, in comparison to participants with the common AA genotype (Figure 1C). Carriers of the *APOA5* S19W minor allele had significantly higher SBP when consuming less than 31% of total fat from energy ($P=0.025$) and lower SBP at higher dietary fat intake category ($P=0.038$), in comparison to participants with the CC genotype (Figure 1D). No other significant interactions with total fat intake were observed at $P<0.007$ (data not shown).

Discussion

Twelve polymorphisms in the *APOA1/C3/A4/A5* cluster were not associated with parameters of allostatic load in Puerto Ricans. However, several interactions between SNPs in the cluster and dietary fat intake were observed. Puerto Ricans carrying the common allele of *APOA1* -75 had more favorable measure of WC, while *APOA4* N147S and *APOA5* S19W had more favorable measure of SBP, when consuming $<31\%$ of total fat from energy. This protective effect disappeared on a high fat intake, as those carriers appear to be more susceptible to high WC and SBP. The opposite was observed for participants carrying the minor allele of these SNPs. Heterozygous participants for *APOC3* -640 showed significantly lower DBP at the high fat intake category.

Pairwise LD analysis in this population showed that only SNPs within a gene (*APOA1* or *APOC3*) were in strong LD. This suggests that each of the significant gene-diet interactions observed for individual genes may be independent contributions, rather than a consequence of linkage with SNPs mapping to other cluster genes tested analyzed. Several gene variants in the *APOA1/C3/A4/A5* cluster have been previously associated with some of the parameters tested in this analysis, namely total cholesterol, HDL-C and blood pressure (1), (10), (22). We did not observe any individual associations between the SNPs and allostatic load parameters at the designated P -value after the Bonferroni correction. However, as this adjustment has been deemed conservative for this type of study (23), some of the associations with marginal P -values could be indicative of true associations in this population. At the $P<0.05$ level, we observed an association for *APOA5* S19W with HDL-C, and for several variants in *APOA1* and *APOA5* with epinephrine and DHEA-S, a catecholamine and a hormone produced in the adrenal gland. Low levels of DHEA-S can indicate critical illness as this biomarker affects general well-being and the immune

response (24), while high epinephrine could mark high stress levels and serious disorders (18). Associations with such neuroendocrine biomarkers have not been reported for variants in the *APOA1/C3/A4/A5* cluster.

Apolipoprotein AI plays a role in adrenal function through its interaction with scavenger receptor class B, member 1 (SCARB1). SCARB1 is responsible for accumulation of cholesteryl ester (CE) obtained from HDL-C by the adrenal cells, which is then used for steroid production (25). A more direct and essential role of ApoA1 in adrenal function has been suggested by studies in knockout mice showing that ApoA1 deficiency causes an almost complete failure to accumulate CE in steroidogenic cells, as well as diminished basal corticosteroid production, a blunted steroidogenic response to stress, and increased expression of compensatory pathways to provide cholesterol substrate for steroid production (26). Functional characterization of the promoter SNPs in *APOA1* could help determine if they have any regulatory influence on gene expression that may explain our observations on DHEA-S and epinephrine levels.

A role of apolipoprotein A-V on adrenal gland function has not been established. It is possible that the interconnection of *APOA5* with other components of HDL-C metabolism may play a role in its effect on adrenal function. Potential association between SNPs in the cluster and adrenal hormones and neurotransmitters surely deserves further exploration.

We observed interactions between gene variants and dietary fat intake for *APOA1* -75 with WC, *APOC3* -640 with DBP, and *APOA4* N147S and *APOA5* S19W with SBP. Although the mechanisms of effect for the *APOA1/C3/A4/A5* cluster polymorphisms are not yet clear and are likely complex, possible mechanisms include differential response to circulating apolipoproteins (27), impaired ribosomal translation efficiency (28), or regulation through PPAR or thyroid hormones (29,30).

An interaction of fat consumption with *APOA1* -75 has been reported in modulation of HDL-C concentration in women, with those carrying the minor allele showing an increase in HDL-C with increased intake of PUFA, while the opposite was true for those homozygous for the common allele (31). The same beneficial effect was observed here for those with the common allele homozygous, who showed lower WC when consuming <31% of total fat from energy. Studies showing interactions between SNPs and dietary fat to modulate blood pressure are scarce. Individual associations of cluster SNPs with blood pressure have been reported for *APOA1* -75, with lowest pressure associated with the most common genotype (32); for *APOA5* S19W, with minor allele carriers showing higher SBP and DBP (33); and for the *APOC3* 3206 T/G variant (not tested in this study) with higher DBP (34). Here, we observed higher DBP for participants with the common homozygous *APOC3* -640 genotype, as well as higher SBP for participants with the common homozygous genotype of *APOA4* N147S and *APOA5* S19W, when consuming higher fat. Given that close to 70% of this Puerto Rican sample carry each of these common risk alleles, observing a diet low in fat may be valuable in maintaining lower blood pressure and WC in this population. These results may partly explain some of the health disparities observed in Puerto Ricans living in the United States, who present high prevalence of abdominal obesity and hypertension, and who may be consuming high amounts of fat as they adapt to a typical American diet.

Several factors could have influenced the results observed in this study. First, it is possible that other functional SNPs within or near the *APOA1/C3/A4/A5* cluster not included in our study could be associated with allostatic load parameters and be driving the associations seen here. Our SNP selection was partially based on LD analysis performed in other populations, which may differ from the current population (22). Future studies should focus on the identification of unique haplotype structure in this population and the analysis of

additional SNPs in the cluster. Secondly, it has been shown that some individual SNPs in the *APOA1/C3/A4/A5* cluster do not have significant effects on lipid parameters, but rather interact with yet other SNPs within the cluster to define two-SNP genotypes that do have a significant effect (35). It is possible that some of the non-significant results obtained here are due to this type of gene-gene interaction within the cluster, as well as with other genes outside the cluster that have shown joint effects with cluster polymorphisms, such as the LDL-receptor gene (35). Similarly, interactions with other environmental factors, such as smoking or PUFA intake, have been reported for SNPs in this cluster in other populations and should be explored in Puerto Ricans (4), (36).

In conclusion, polymorphisms in the *APOA1/C3/A4/A5* cluster, as modulated by dietary fat intake, may influence physiological markers of allostatic load in Puerto Ricans living in the United States, in a way that may explain some of the health disparities present in this community. Results also suggest that some of the polymorphisms in the cluster may be associated with neuroendocrine markers from the allostatic load response, a novel observation that requires further exploration.

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Abbreviations

ANCOVA	analysis of covariance
BMI	body mass index
CE	cholesteryl ester
DHEA-S	dehydroepiandrosterone sulfate
DBP	diastolic blood pressure
FFQ	food frequency questionnaire
HbA1c	glycosylated hemoglobin
HWE	Hardy-Weinberg Equilibrium
HDL-C	high density lipoprotein
LD	linkage disequilibria
MAF	minor allele frequency
PUFA	polyunsaturated fatty acid
SCARB1	scavenger receptor class B, member 1
SNP	single nucleotide polymorphism
SBP	systolic blood pressure
WC	waist circumference

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Figure 1.

Parameters of allostatic load by polymorphisms in the *APOA1/C3/A4/A5* cluster and total fat intake category in participants of the Boston Puerto Rican Health Study. Total fat intake category is defined as below or above the population median. *P* for interaction between total fat intake and polymorphism for panel A (*APOA1* -75) =0.005, panel B (*APOC3* -640) =0.003, panel C (*APOA4* N147S) =0.001, and panel D (*APOA5* S19W) =0.002.

Values indicate estimated means (error bars are standard error), adjusted for age, sex, smoking, alcohol intake, medication use (lipid-lowering, diabetes and hypertension), population admixture, BMI or physical activity, and total energy intake.

P-values indicate the difference between means by SNP genotype within each fat category for Panels A, C, and D; and between major or minor homozygous in comparison to heterozygous genotype for Panel B.

Pairwise linkage disequilibria R² coefficient between polymorphisms in the *APOA1/C3/A4/A5* cluster in the Boston Puerto Rican Health Study

Table 1

	<i>APOA1</i> -2803	<i>APOA1</i> -3012	<i>APOA1</i> -75	<i>APOA1</i> N147S	<i>APOA4</i> S367T	<i>APOC3</i> -2886	<i>APOC3</i> -455	<i>APOC3</i> -482	<i>APOC3</i> -640	<i>APOA5</i> -1131	<i>APOA5</i> S19W
<i>APOA1</i> -2630 (rs613808)	0.916	0.190	0.195	0.107	0.100	0.094	0.140	0.204	0.132	0.097	0.063
<i>APOA1</i> -2803 (rs2727784)		0.173	0.177	0.104	0.052	0.131	0.177	0.261	0.171	0.086	0.052
<i>APOA1</i> -3012 (rs11216158)			0.652	0.016	0.029	0.044	0.040	0.027	0.052	0.000	0.068
<i>APOA1</i> -75 (rs670)				0.001	0.029	0.039	0.055	0.027	0.034	0.003	0.066
<i>APOA4</i> N147S (rs5104)					0.021	0.244	0.158	0.190	0.203	0.130	0.000
<i>APOA4</i> S367T (rs675)						0.190	0.076	0.001	0.080	0.019	0.015
<i>APOC3</i> -2886 (rs2542051)							0.613	0.469	0.634	0.057	0.001
<i>APOC3</i> -455 (rs2854116)								0.728	0.872	0.100	0.001
<i>APOC3</i> -482 (rs2854117)									0.725	0.107	0.000
<i>APOC3</i> -640 (rs2542052)										0.084	0.001
<i>APOA5</i> -1131 (rs662799)											0.016
<i>APOA5</i> S19W (rs3135506)											

Table 2

Baseline anthropometric and biological characteristics for 821 participants of the Boston Puerto Rican Health Study

Characteristic	Men (n=221)	Women (n=600)	All participants (n=821)
Age (years)	57.8 (7.6)	57.9 (7.1)	57.9 (7.2)
Cortisol (µg/g creatinine)	30.3 (18.9)	28.7 (26.0)	29.1 (24.3)
DHEA-S (ng/mL)	1144.2 (936.2)	654.8 (490.5)*	787.0 (67.7)
Epinephrine (µg/g creatinine)	4.4 (4.0)	3.8 (3.5)	4.0 (3.6)
Norepinephrine (µg/g creatinine)	35.0 (25.7)	41.4 (26.8)*	39.1 (26.7)
Systolic blood pressure (mmHg)	139.7 (18.8)	134.9 (18.4)*	136.2 (18.6)
Diastolic blood pressure (mmHg)	83.0 (11.7)	80.4 (10.1)*	81.1 (10.6)
HDL-C (mg/dL)	39.6 (12.2)	47.0 (12.6)*	45.0 (12.9)
Total cholesterol (mg/dL)	170.6 (42.5)	188.6 (41.2)*	183.7 (42.3)
Waist circumference (cm)	101.3 (13.5)	101.8 (15.4)	101.7 (14.9)
Glycosylated Hemoglobin (%)	7.1 (2.0)	7.1 (1.7)	7.1 (7.8)
Physical activity score	32.3 (5.5)	31.3 (4.0)*	31.6 (4.5)
BMI (kg/m ²)	29.6 (5.2)	33.1 (7.0)*	32.2 (6.7)
Energy intake (kcal/day)	2415.2 (856.2)	2052.3 (858.6)*	2150.0 (872.4)
Total fat (% from total energy)	31.9 (5.2)	30.6 (5.2)*	31.0 (5.2)
Carbohydrate (% from total energy)	50.4 (7.5)	52.6 (7.5)*	52.0 (7.6)
Protein (% from total energy)	17.1 (3.0)	17.3 (3.6)	17.3 (3.5)
European Ancestry ^a (%)	57.9 (15.2)	56.7 (15.4)	57.0 (15.3)
African Ancestry ^a (%)	26.5 (15.5)	27.9 (15.9)	27.5 (15.8)
Native American Ancestry ^a (%)	15.6 (6.9)	15.3 (6.5)	15.4 (6.6)
Current smoker (%)	32.7	19.3*	22.9
Current drinker (%)	53.2	34.5*	39.5
Diabetes medication use (%)	33.8	33.6	33.6
Hypertension medication use (%)	56.6	56.3	56.4
Lipid-lowering medication use (%)	41.1	40.4	40.6

Values are mean (standard deviation) or percent.

^aExpressed as the percent that each ancestral population contributes to total composition.

* Significantly different by sex, $P < 0.05$

Table 3

Estimated means for association of *APOA1/C3/A4/A5* cluster gene variants with allostatic load parameters in participants of the Boston Puerto Rican Health Study

SNP	Genotype, % of participants	Cortisol	DHEA-S	Epinephrine	Norepinephrine	SBP
<i>APOA1</i> -2630	GG	22.9 (20.5–25.5)	547.3 (491.3–609.1)	3.6 (3.3–4.0) ^a	33.2 (30.2–36.6)	137.6 (1.2)
	GA	21.8 (20.0–23.7)	598.8 (551.7–649.4)	3.3 (3.0–3.5)	31.8 (29.6–34.2)	134.8 (0.9)
	AA	22.2 (19.8–24.8)	552.8 (495.2–617.1)	3.0 (2.7–3.3)	31.3 (28.4–34.5)	136.6 (1.3)
<i>APOA1</i> -2803	GG	22.0 (19.8–24.6)	565.7 (508.8–623.3)	3.0 (2.7–3.3) ^a	31.2 (28.5–34.4)	136.7 (1.3)
	GA	22.0 (20.2–23.9)	600.0 (552.8–650.7)	3.3 (3.0–3.5)	32.3 (30.1–34.8)	134.9 (0.9)
<i>APOA1</i> -3012	AA	22.6 (20.2–25.4)	561.2 (500.7–628.3)	3.6 (3.2–4.0)	32.0 (28.9–35.4)	137.4 (1.3)
	GG	22.2 (20.7–23.7)	553.9 (518.0–590.0) ^a	3.4 (3.2–3.6) ^a	31.2 (29.4–33.0)	135.5 (0.8)
<i>APOA1</i> -75	GA+AA	22.0 (19.7–24.5)	626.4 (566.8–699.2)	3.0 (2.7–3.3)	34.8 (31.8–38.9)	137.8 (1.2)
	CC	22.4 (20.9–23.9)	550.0 (514.9–588.2) ^a	3.4 (3.2–3.6)	31.2 (29.4–33.1)	135.7 (0.8)
<i>APOC3</i> -2886	CT+TT	21.4 (19.3–23.7)	620.2 (561.2–685.4)	3.1 (2.8–3.4)	34.1 (31.2–37.3)	137.3 (1.2)
	TT	22.6 (20.2–25.2)	606.1 (545.1–673.8)	3.4 (3.0–3.7)	32.9 (29.9–36.2)	137.6 (1.2)
<i>APOC3</i> -455	TG	22.4 (20.8–22.3)	585.5 (541.9–631.4)	3.3 (3.1–3.6)	32.3 (30.2–34.5)	135.4 (0.9)
	GG	20.7 (18.2–23.6)	520.1 (458.5–590.5)	3.1 (2.7–3.5)	30.5 (27.3–34.2)	136.0 (1.5)
<i>APOC3</i> -482	TT	21.6 (19.4–24.2)	610.3 (548.9–678.6)	3.4 (3.1–3.8)	33.5 (30.4–36.9)	137.0 (1.2)
	TC	22.6 (20.9–24.5)	584.6 (540.8–631.4)	3.3 (3.0–3.5)	32.2 (30.1–34.5)	136.3 (0.9)
<i>APOC3</i> -640	CC	21.3 (18.9–24.1)	510.3 (453.5–573.6)	3.2 (2.8–3.5)	30.0 (27.0–33.4)	134.7 (1.4)
	GG	22.4 (20.4–24.9)	572.5 (520.1–632.1)	3.4 (3.2–3.8)	34.8 (31.8–37.7)	137.3 (1.1)
<i>APOA4</i> N147S	GA	22.4 (20.1–24.2)	565.1 (544.0–636.5)	3.3 (3.0–3.5)	31.4 (29.4–33.6)	135.7 (0.9)
	AA	21.2 (18.5–24.3)	539.2 (473.4–614.0)	3.1 (2.7–3.5)	30.4 (27.0–34.1)	135.4 (1.5)
<i>APOA4</i> S367T	GG	22.0 (19.6–24.6)	591.7 (530.6–659.8)	3.4 (3.0–3.7)	33.4 (30.3–36.9)	137.2 (1.2)
	GT	21.9 (20.2–23.7)	585.8 (541.9–633.3)	3.3 (3.1–3.6)	32.2 (30.1–34.5)	135.9 (0.9)
<i>APOA5</i> -1131	TT	22.2 (19.6–25.1)	523.2 (464.1–589.3)	3.2 (2.8–3.5)	30.5 (27.4–34.0)	135.9 (1.4)
	AA	21.5 (20.1–23.0)	583.5 (545.7–623.9)	3.3 (3.1–3.5)	33.2 (31.3–35.2)	136.5 (0.8)
<i>APOA5</i> -1131	AG+GG	23.7 (21.4–26.2)	553.9 (502.2–610.9)	3.3 (3.0–3.6)	30.1 (27.6–32.8)	135.8 (1.1)
	AA	22.6 (21.2–24.2)	586.4 (549.5–625.8)	3.3 (3.1–3.4)	31.6 (29.8–33.4)	136.3 (0.8)
<i>APOA5</i> -1131	AT+TT	21.4 (19.2–23.9)	558.4 (502.2–620.8)	3.3 (3.0–3.7)	33.5 (30.5–36.9)	135.6 (1.2)
	AA	22.2 (20.8–23.6)	593.5 (557.2–631.4) ^a	3.3 (3.2–3.5)	32.9 (31.1–34.8)	136.2 (0.7)

SNP	Genotype, % of participants	Cortisol	DHEA-S	Epinephrine	Norepinephrine	SBP
APOA5 S19W	AG+GG	22.8	518.0 (461.3–581.7)	3.1 (2.8–3.4)	29.6 (26.8–32.8)	135.6 (1.3)
	CC	79.7	560.0 (526.4–595.9)	3.3 (3.1–3.5)	31.3 (29.7–33.1)	136.0 (0.7)
	CG+GG	20.3	639.1 (561.2–724.9)	3.3 (2.9–3.7)	35.3 (31.6–39.4)	136.1 (1.5)

Values are estimated mean (standard error), or geometric mean (95% confidence interval) for anti-log transformed measures for DHEA-S, urinary cortisol, epinephrine and norepinephrine. ANCOVA model were run for each polymorphism as main predictor, after adjustment for age, sex, smoking, alcohol intake, medication use (lipid-lowering, diabetes and hypertension), population admixture, and BMI or physical activity.

Units: cortisol (µg/g creatinine), DHEA-S (ng/mL), epinephrine (µg/g creatinine), norepinephrine (µg/g creatinine), SBP (mmHg), DBP (mmHg), HDL-C (mg/dL), total cholesterol (mg/dL), WC (cm), HbA1c (%)

^a $P < 0.05$ for difference between means

Table 3

Estimated means for association of *APOA1/C3/A4/A5* cluster gene variants with allostatic load parameters in participants of the Boston Puerto Rican Health Study, continued

SNP	Genotype	DBP	HDL-C	Total cholesterol	WC	HbA1C
<i>APOA1</i> -2630	GG	81.8 (0.7)	45.4 (0.8)	185.9 (2.9)	101.5 (1.0)	7.1 (0.1)
	GA	80.8 (0.5)	45.5 (0.6)	183.6 (2.2)	101.7 (0.8)	7.1 (0.1)
	AA	80.7 (0.7)	44.8 (0.9)	183.9 (2.9)	101.8 (1.0)	7.2 (0.1)
<i>APOA1</i> -2803	GG	80.9 (0.7)	44.8 (0.8)	184.2 (2.8)	102.2 (1.0)	7.1 (0.1)
	GA	80.7 (0.5)	45.2 (0.6)	183.7 (2.2)	101.2 (0.8)	7.1 (0.1)
	AA	81.7 (0.7)	45.8 (0.9)	186.2 (3.0)	102.4 (1.1)	7.2 (0.1)
<i>APOA1</i> -3012	GG	81.1 (0.4)	45.3 (0.5)	184.6 (1.7)	101.2 (0.6)	7.1 (0.1)
	GA+AA	81.2 (0.7)	45.1 (0.8)	183.6 (2.7)	102.7 (1.0)	7.2 (0.1)
	CC	81.2 (0.4)	45.4 (0.5)	184.9 (1.8)	101.3 (0.6)	7.1 (0.1)
<i>APOC3</i> -2886	CT+TT	80.9 (0.7)	44.8 (0.8)	182.8 (2.6)	102.6 (0.9)	7.2 (0.1)
	TT	81.7 (0.7)	45.9 (0.8)	183.4 (2.8)	101.8 (1.0)	7.2 (0.1)
	TG	81.1 (0.5)	44.6 (0.6)	184.4 (2.0)	101.9 (0.7)	7.1 (0.1)
<i>APOC3</i> -455	GG	80.8 (0.8)	46.0 (1.0)	185.8 (3.4)	101.0 (1.2)	7.0 (0.1)
	TT	81.5 (0.7)	45.9 (0.8)	184.7 (2.8)	102.3 (1.0)	7.2 (0.1)
	TC	81.3 (0.5)	44.8 (0.6)	184.2 (2.1)	101.5 (0.7)	7.1 (0.1)
<i>APOC3</i> -482	CC	80.6 (0.8)	45.7 (0.9)	185.1 (3.1)	101.0 (1.1)	7.0 (0.1)
	GG	81.7 (0.6)	46.4 (0.8)	185.7 (2.6)	102.7 (0.9)	7.2 (0.1)
	GA	81.0 (0.5)	44.8 (0.6)	183.3 (2.1)	101.1 (0.7)	7.1 (0.1)
<i>APOC3</i> -640	AA	80.8 (0.9)	44.4 (1.0)	184.7 (3.4)	101.1 (1.2)	7.0 (0.1)
	GG	81.4 (0.7)	46.4 (0.9)	185.2 (2.9)	103.1 (1.0)	7.2 (0.1)
	GT	81.1 (0.5)	44.4 (0.6)	183.5 (2.1)	101.5 (0.7)	7.1 (0.1)
<i>APOA4</i> N147S	TT	81.3 (0.8)	45.5 (0.9)	186.6 (3.2)	101.4 (1.1)	7.0 (0.1)
	AA	81.2 (0.4)	45.8 (0.5)	184.6 (1.8)	102.0 (0.6)	7.2 (0.1)
	AG+GG	81.3 (0.7)	44.1 (0.8)	183.3 (2.6)	100.9 (0.9)	7.0 (0.1)
<i>APOA4</i> S367T	AA	81.1 (0.4)	44.7 (0.5)	183.3 (1.7)	102.2 (0.6)	7.1 (0.1)
	AT+TT	81.3 (0.7)	46.4 (0.8)	187.9 (2.8)	100.7 (1.0)	7.1 (0.1)
	AA	81.3 (0.4)	45.2 (0.5)	184.2 (1.7)	101.6 (0.6)	7.1 (0.1)
<i>APOA5</i> -1131	AA	81.3 (0.4)	45.2 (0.5)	184.2 (1.7)	101.6 (0.6)	7.1 (0.1)
	AG+GG	80.9 (0.7)	44.9 (0.9)	183.5 (3.1)	102.0 (1.1)	7.1 (0.1)

SNP	Genotype	DBP	HDL-C	Total cholesterol	WC	HbA1c
APOA5 S19W	CC	81.0 (0.4)	45.6 (0.5) ^a	185.5 (1.6)	101.2 (0.6)	7.1 (0.1)
	CG+GG	81.5 (0.8)	43.4 (1.0)	180.4 (3.3)	103.7 (1.2)	7.2 (0.1)

Values are estimated mean (standard error), or geometric mean (95% confidence interval) for anti-log transformed measures for DHEA-S, urinary cortisol, epinephrine and norepinephrine. ANCOVA model were run for each polymorphism as main predictor, after adjustment for age, sex, smoking, alcohol intake, medication use (lipid-lowering, diabetes and hypertension), population admixture, and BMI or physical activity.

Units: cortisol (µg/g creatinine), DHEA-S (ng/mL), epinephrine (µg/g creatinine), norepinephrine (µg/g creatinine), SBP (mmHg), DBP (mmHg), HDL-C (mg/dL), total cholesterol (mg/dL), WC (cm), HbA1c (%)

^a $P < 0.05$ for difference between means