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Association of Apolipoprotein E (ApoE) Polymorphism with the Prevalence of Metabolic Syndrome: The National Heart, Lung and Blood Institute Family Heart Study

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Abstract

Objective—Metabolic syndrome (MetS), characterized by abdominal obesity, atherogenic dyslipidemia, elevated blood pressure, and insulin resistance is a major public health concern in the United States. The effects of Apolipoprotein E (Apo E) polymorphism on MetS are not well established.

Methods—We conducted a cross-sectional study consisting of 1,551 participants from the National Heart, Lung, and Blood Institute (NHLBI) Family Heart Study to assess the relation of

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Apo E polymorphism with the prevalence of MetS. MetS was defined according to the AHA-NHLBI-IDF-WHO Harmonized Criteria. We used generalized estimating equations to estimate adjusted odds ratios for prevalent MetS and the Bonferroni correction to account for multiple testing in the secondary analysis.

Results—Our study population had a mean age (SD) of 56.5 (11.0) years and 49.7% had MetS. There was no association between the Apo E genotypes and MetS. The multivariable adjusted ORs (95% CI) were 1.00 (reference), 1.26 (0.31-5.21), 0.89 (0.62-1.29), 1.13 (0.61-2.10), 1.13 (0.88-1.47), and 1.87 (0.91-3.85) for the $\epsilon 3/\epsilon 3$, $\epsilon 2/\epsilon 2$, $\epsilon 2/\epsilon 3$, $\epsilon 2/\epsilon 4$, $\epsilon 3/\epsilon 4$, and $\epsilon 4/\epsilon 4$ genotypes, respectively. In a secondary analysis, $\epsilon 2/\epsilon 3$ genotype was associated with 41% lower prevalence odds of low HDL [multivariable adjusted ORs (95% CI) = 0.59 (0.36-0.95)] compared to $\epsilon 3/\epsilon 3$ genotype.

Conclusions—Our findings do not support an association between Apo E polymorphism and MetS in a multi-center population based study of predominantly white US men and women.

Keywords

Apolipoprotein E (Apo E) polymorphism; metabolic syndrome; blood pressure; glucose; dyslipidemia; high-density lipoprotein cholesterol

Introduction

Metabolic syndrome (MetS) has been a major public health concern in the United States for the past few decades and its prevalence has been increasing due to higher rates of obesity. The US National Health Statistics Report showed that 34% of adults over 20 years of age from the National Health and Nutrition Examination Survey (NHANES) (2003-2006) had MetS [1]. Various diagnostic criteria have been proposed by different organizations over the past decade. However, the International Diabetes Federation (IDF), National Heart, Lung, and Blood Institute (NHLBI), American Heart Association (AHA), World Health Organization (WHO) came up with a joint scientific statement in 2009, identifying metabolic syndrome as a cluster of risk factors for cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM), which include raised blood pressure, dyslipidemia (raised triglycerides and lowered high-density lipoprotein cholesterol), raised fasting glucose, and central obesity [2].

The Apolipoprotein E (Apo E) gene, located on chromosome 19, provides instructions for making Apo E, a multifunctional protein that plays a key role in the metabolism of cholesterol and triglycerides by binding to receptors on the liver to help mediate clearance of chylomicrons and very low-density lipoproteins (VLDLs) from the bloodstream [3]. It is polymorphic with three common alleles, $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$, producing three isoforms of the protein; E2, E3 and E4. The six most common genotypes ranking from most to least common are $\epsilon 3/\epsilon 3$, $\epsilon 4/\epsilon 3$, $\epsilon 3/\epsilon 2$, $\epsilon 4/\epsilon 4$, $\epsilon 4/\epsilon 2$ and $\epsilon 2/\epsilon 2$ [4]. The $\epsilon 3$ is the most common allele, and approximately 60% of North Americans are homozygous for this genetic variant [5]. The prevalence of $\epsilon 4$ allele was about 13% in a predominantly white Caucasian population in the Framingham Heart Study [6].

Several genome-wide association studies (GWAS) have identified a number of novel genes and loci associated with the components of MetS [7-9]. However, most of these studies analyzed one component each time and did not treat MetS as an entity in itself. Using a multivariate approach, Avery et al.[10] identified genome-wide significant SNPs that were associated with MetS in European Americans and African Americans. However, many of these loci were associated with only one trait domain and none that encompassed all MetS traits were identified.

Epidemiological studies have investigated the direct impact of Apo E on CVD, as well as its influence on cholesterol levels. One study of middle-aged men from nine populations estimated an approximately 40 percent increased risk for CVD mortality for $\epsilon 4$ carriers compared with $\epsilon 3/\epsilon 3$ genotype or $\epsilon 2$ carriers [11]. Other studies have reported that $\epsilon 4$ carriers are more prone to develop disseminated coronary lesions and have an increased risk of death from CHD [12-15]. Results from the Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) study showed that the CHD mortality rate increased by 24.5/100,000 for an increase of 0.01 in the relative frequency of the $\epsilon 4$ allele [16]. Apo E polymorphism was also investigated in T2DM. A meta-analysis conducted by Anthopoulos et al reported that Apo E2 was a moderate risk factor for T2DM (OR=1.18; 95% CI=1.02, 1.35) [17].

The significant impact of Apo E polymorphism in T2DM, total cholesterol, TG and LDL metabolism implies that determination of the Apo E genotypes may be a useful adjunct to the assessment of the MetS profile of an individual. However, the association between Apo E polymorphism and MetS as an outcome has not been established. The current paper presents the association between ApoE polymorphisms and MetS in a predominantly Caucasian population.

Materials and Methods

In our cross-sectional study, we analyzed data from 1,551 participants. Of the 5975 original participants, only 1,750 subjects were genotyped. We excluded subjects with missing data on metabolic syndrome criteria and covariates (n=199). MetS was defined using the AHA-NHLBI-IDF-WHO Harmonized Criteria (2009), noted as having 3 or more of the following conditions: systolic blood pressure ≥ 130 mmHg and / or diastolic blood pressure ≥ 85 mmHg or on antihypertensive therapy; fasting triglycerides (TG) ≥ 150 mg/dL or on triglyceride-lowering therapy; high-density lipoprotein (HDL) cholesterol of less than 40 mg/dL for men and 50 mg/dL for women or on drug therapy for low HDL cholesterol; fasting glucose of ≥ 100 mg/dL or on antidiabetic therapy; and waist circumference of ≥ 102 cm in men or ≥ 88 cm in women. A detailed description on the study population has been described in previous studies [18, 19]. Apo E genotypes were determined during the parent study. Information on cigarette smoking and alcohol consumption was obtained by interview during clinic visits. The amount of exercise was obtained through self-reports.

We categorized Apo E according to the Apo E genotypes and used the most common group, $\epsilon 3/\epsilon 3$ as the reference. Baseline characteristics were presented according to Apo E genotypes and compared using ANOVA.

To correct for familial clustering, we used generalized estimating equations (GEE) to calculate the prevalence odds ratios and 95% confidence intervals (CIs) for the presence of metabolic syndrome across the different Apo E genotypes. GEE accounts for correlation matrix among related individuals. We assessed confounding by age, gender (male/female), race (Caucasian/African American/other), current drinker (yes/no), current smoker (yes/no), exercise (continuous), and field center (Forsyth, NC/ Minneapolis, MN/ Framingham, MA/ Salt Lake, UT).

In a secondary analysis, we repeated the above analyses for individual components of MetS according to the AHA-NHLBI-IDF-WHO Harmonized Criteria definition [4]. All p-values are two-tailed and significance was set at an alpha of 0.05 (0.01 with Bonferroni correction for 5 exposures in secondary analysis). We also did the analysis of variance (ANOVA) test to determine the absolute differences in mean HDL between genotypes, followed by the Kruskal-Wallis test as the groups were of unequal size. All analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, NC).

Results

Table 1 represents baseline characteristics of our study participants according to MetS status. The mean age (SD) of our sample was 56.5 (11.0) years and the prevalence of MetS was 49.7%.

The most frequent genotype in our sample was $\epsilon 3/\epsilon 3$ (58.0%), followed by $\epsilon 3/\epsilon 4$ (25.5%), $\epsilon 2/\epsilon 3$ (10.8%), $\epsilon 4/\epsilon 4$ (2.7%), $\epsilon 2/\epsilon 4$ (2.5%), and $\epsilon 2/\epsilon 2$ (0.5%). Prevalences of MetS among the respective genotypes were $\epsilon 3/\epsilon 3$ (48.9%), $\epsilon 3/\epsilon 4$ (50.4%), $\epsilon 2/\epsilon 3$ (47.0%), $\epsilon 4/\epsilon 4$ (61.9%), $\epsilon 2/\epsilon 4$ (55.3%), and $\epsilon 2/\epsilon 2$ (62.5%).

There was no significant association between ApoE genotypes and prevalence of MetS. Adjustment for age, gender, field center, alcohol consumption, smoking and exercise did not alter our results. (Figure 1). We did an additional analysis comparing $\epsilon 2$ carriers and non- $\epsilon 2$ carriers and did not find any significant association between these groups and MetS (OR=1.12; 95% CI: 0.82-1.53, p-value=0.48). Repeating analyses using the IDF 2005 and NCEP ATP III 2004 did not alter our results (data not presented).

Using the multivariable adjusted generalized estimating equations and Bonferroni correction, we did not find any significant associations between Apo E genotypes and blood pressure, glucose, triglycerides, or waist circumference. When compared to subjects with $\epsilon 3/\epsilon 3$ genotype, the risk of having a low HDL level was less for subjects with the $\epsilon 2/\epsilon 3$ genotype (OR=0.59; 99% CI=0.36-0.95, p-value=0.005). All the genotypes; with the exception of $\epsilon 2/\epsilon 3$, had a lower mean HDL when compared to $\epsilon 3/\epsilon 3$. With $\epsilon 3/\epsilon 3$ (49.1 mg/dL (± 15.9 mg/dL)) as the reference group, the differences in mean HDL were as follows: 4.3mg/dL (± 4.3 mg/dL) for $\epsilon 2/\epsilon 2$, 2.2mg/dL (± 1.2 mg/dL) for $\epsilon 2/\epsilon 4$, 2.8mg/dL (± 1.9 mg/dL) for $\epsilon 3/\epsilon 4$, and 3.5mg/dL (± 4.0 mg/dL) for $\epsilon 4/\epsilon 4$. Only the $\epsilon 2/\epsilon 3$ genotype had a higher mean difference of 2.9mg/dL (± 0.2 mg/dL). There was a significant difference in HDL levels at the $p < 0.01$ level for the genotypes [$F(5) = 4.11$, $p = 0.001$]. Using Kruskal Wallis test, we found

a significant difference across genotypes on median difference in HDL levels: $\chi^2=19.92$, $p=0.0013$.

Discussion

In our cross-sectional study, we did not find an association between Apo E polymorphism and prevalent MetS. To our knowledge, this study is the first in a predominantly Caucasian population. In a recent study of young Asian Indian patients with acute myocardial infarction, none of the Apo E alleles was associated with a higher prevalence of MetS [20]. In contrast, Tao MH et al. reported that the $\epsilon 4$ allele was associated with a significantly increased risk of MetS in an elderly Chinese male population [21]. The $\epsilon 4$ allele was also reported to be associated with a significantly increased risk of MetS in an Italian population who were non-diabetics, not on lipid-lowering therapy but presented with a medical history of cardiovascular disease [22]. In a Romanian study, the investigators reported that the frequency of the $\epsilon 4$ allele was higher in the MetS group compared to those without MetS [23]. However, the $\epsilon 4$ allele was inversely associated with prevalent MetS in an extremely obese Brazilian population [24].

All the studies above used either the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) or IDF definition. However, we used the new AHA-NHLBI-IDF-WHO Harmonized Criteria (2009). This new criteria is more stringent than the ATP III or IDF definition because drug therapy (anti-hypertensives, lipid-lowering therapy and anti-diabetics) were taken into consideration. We repeated our analyses using the IDF and NCEP ATP III definitions for MetS but that did not alter our findings. It is difficult to compare the association of ApoE polymorphism with MetS across these studies, given the small sample sizes, heterogeneity among these ethnic populations and possibly the influence of epigenetic modifications [25].

In a secondary analysis, subjects with $\epsilon 2/\epsilon 3$ genotype had higher HDL levels compared to the $\epsilon 3/\epsilon 3$ genotype. Our result was consistent with a meta-analysis that also showed a slight increase of HDL levels in the $\epsilon 2/\epsilon 3$ genotype [26], indicating a potential cardioprotective effect [27, 28]; although a recent Mendelian randomization study implied that raised HDL cholesterol did not seem to lower the risk of myocardial infarction [29].

Based on Table 1, the $\epsilon 2/\epsilon 2$ genotype had a higher mean TG level, higher BMI, larger waist circumference and a higher prevalence of hypertension and diabetes. It is however associated with lower LDL levels and a lower prevalence of coronary heart disease. Despite the small sample size, the results of our study are consistent with the findings of a large meta-analysis, showing that the $\epsilon 2/\epsilon 2$ genotype was associated with a 21% higher mean TG levels than to the $\epsilon 3/\epsilon 3$ genotype and a 31% lower mean LDL compared to the $\epsilon 4/\epsilon 4$ genotype. Compared to the $\epsilon 3/\epsilon 3$ genotype, the $\epsilon 2/\epsilon 2$ genotype carriers had a 17% lower risk of CHD [26]. In another meta-analysis, Anthopoulos et al. reported that the $\epsilon 2$ allele carriers were at an 18% increased risk of developing type 2 diabetes mellitus. In addition, they also reported elevated TG levels in patients with diabetes [17], which was also proven in another study [30].

These differing effects in lipid profile and disease phenotypes might be influenced by the complexity of the disease pathophysiology and variations in other lipidomic profile, i.e. Apolipoprotein A1, Apolipoprotein B, intermediate density lipoprotein, very low density lipoprotein [31] and adiponectin [32]. In addition, other factors such as circulating C-reactive protein [33, 34], nitric oxide and other cellular immunity [35] may also mediate these effects through various regulation pathways, therefore making it challenging to determine an association between the individual phenotypes and metabolic syndrome.

The prevalence of MetS in this study was 49.7%, approximately 16% higher than the 2009 US National Health Statistics Report. The US National Health Statistics Report used the NECP ATP III revised guidelines, of which only anti-hypertensives and anti-diabetics were accounted for. However, we used the AHA-NHLBI-IDF-WHO Harmonized Criteria, of which lipid-lowering therapy was also accounted for, and this could have possibly led to the higher prevalence of MetS observed.

Study Limitations & Strengths

One of the study limitations was the inability to determine causal relation between Apo E polymorphism and MetS because of the cross-sectional study design. Although the causal relation could not be determined, the genetic makeup of each individual does not change over time, therefore the estimates of no association was expected to be relatively reliable. However, with the small sample size, it is also possible that we did not find an association because of inadequate statistical power to detect the small effect size. According to the AHA-NHLBI-IDF-WHO Harmonized Criteria, the most commonly used drugs for elevated triglycerides and reduced HDL-C were fibrates and nicotinic acid; patients taking one of these drugs were presumed to have high TG and low HDL-C. However, in this study the specific type of lipid lowering therapy our participants were prescribed with was not available for analysis. One further concern was the single measurement of fasting glucose, TG and HDL levels, which might have led to random errors. However, all these measurements were fasting levels, which is a good predictor of the actual state of condition.

To date, this is the largest and the only multi-center, population-based study assessing the relationship between Apo E polymorphism with prevalent MetS in a predominantly Caucasian population. We also adjusted for environmental and behavioral factors that might affect the phenotype independently of the genes of interest.

Conclusion

Our findings do not support an association between Apo E polymorphism and MetS in this multi-center population-based study of predominantly white US men and women.

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Figure 1. Prevalence odds ratios (95% confidence intervals) of metabolic syndrome according to Apolipoprotein E genotypes

Adjusted for age, gender, race, field center (Forsyth/ Minneapolis/ Framingham/ Salt Lake), alcohol intake (yes/no), smoking (yes/no), exercise (quartiles) using generalized estimating equations (GEE)

Table 1
Baseline characteristics of 1,551 subjects in the NHLBI Family Heart Study by Apolipoprotein E genotypes

Variables	Apolipoprotein E Genotypes					
	*e3/e3 (n=900)	*e2/e2 (n=8)	*e2/e3 (n=168)	*e2/e4 (n=38)	*e3/e4 (n=395)	*e4/e4 (n=42)
Age (y)	56.8±11.1	65.3±6.1	57.8±11.1	59.6±8.2	54.9±10.7	53.8±12.0
Body mass index (kg/m ²)	28.4±5.7	30.0±4.6	28.6±5.8	28.9±3.4	28.3±5.4	29.1±5.7
Waist Circumference (cm)	100.1±14.7	107.0±12.6	100.2±16.1	101.6±9.9	99.2±15.1	100.0±14.2
TG (mg/dL)	161.9±106.3	241.1±164.6	168.6±122.5	188.6±135.7	172.4±101.0	181.8±84.4
LDL (mg/dL)	131.6±34.7	83.3±34.9	114.0±31.3	116.1±31.2	132.4±36.1	136.7±38.9
HDL (mg/dL)	49.1±15.9	44.8±11.6	52.0±16.1	46.9±14.9	46.3±14.0	45.6±11.9
Exercise (min/day)	28.4±34.5	14.5±20.0	27.2±33.7	20.8±23.2	26.5±42.9	35.7±63.3
Males (%)	47.0	50.0	45.2	57.9	48.1	50.0
Race & Ethnicity (%)						
Non-Hispanic	98.0	100.0	95.2	100.0	93.2	92.9
White						
African American	1.6	0.0	3.6	0.0	5.6	7.1
Others	0.4	0.0	1.2	0.0	1.3	0.0
Hypertension (%)	37.4	50.0	33.3	47.4	30.1	40.5
Diabetes (%)	9.6	25.0	11.3	7.9	8.6	2.4
Coronary Heart Disease (%)	19.0	12.5	14.9	21.1	19.0	21.4
Current Smoker (%)	13.8	12.5	14.9	10.5	13.2	21.4
Current Drinker (%)	48.9	62.5	48.2	60.5	48.6	50.0
Prevalence of MetS (%)	48.9	62.5	47.0	55.3	50.4	61.9

Data are presented as means (±) SD or percentages