

RESEARCH ARTICLE

# Association of *APOE* gene polymorphism with lipid profile and coronary artery disease in Afro-Caribbeans

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## Abstract

### Objectives

Apolipoprotein E gene (*APOE*) polymorphism is associated with the lipid profile and cardiovascular disease. However, these relationships vary between ethnic groups.

We evaluated, for the first time in an Afro-Caribbean population, the distribution of *APOE* polymorphisms and their associations with coronary artery disease (CAD), the lipid profile and other cardio-metabolic risk factors.

### Methods

We studied 712 Afro-Caribbean subjects including 220 with documented CAD and 492 healthy subjects. TaqMan assays were performed to genotype rs7412 and rs429358, the two variants that determine the *APOE* alleles  $\epsilon 2$ ,  $\epsilon 3$  and  $\epsilon 4$ . The association between *APOE* genotype and the lipid profile was analysed by comparing  $\epsilon 2$  carriers,  $\epsilon 3$  homozygotes and  $\epsilon 4$  carriers.

### Results

The frequencies of  $\epsilon 2$ ,  $\epsilon 3$  and  $\epsilon 4$  in the overall sample were 8%, 70% and 22%, respectively. CAD was not associated with *APOE* polymorphism. The total cholesterol level was higher in  $\epsilon 4$  carriers compared with  $\epsilon 2$  carriers: 5.07 vs 4.59 mmol/L ( $P = 0.016$ ). The LDL-cholesterol level was lower in *APOE*  $\epsilon 2$  carriers compared with  $\epsilon 3$  homozygotes and  $\epsilon 4$  carriers: 2.65 vs 3.03 and 3.17 mmol/L, respectively ( $p = 0.002$ ). The total cholesterol/HDL-cholesterol and LDL-cholesterol/HDL-cholesterol ratios were similar in the three allelic groups. *APOE*

polymorphism was not associated with diabetes, hypertension, waist circumference or body mass index.

## Conclusions

Our results indicate that *APOE* gene polymorphism is associated with the lipid profile but not with CAD in Afro-Caribbean people. This lack of association with CAD may be explained by the low atherogenic profile observed in  $\epsilon 4$  carriers, which may warrant further investigation.

## Introduction

Apolipoprotein E (ApoE) is a polymorphic glycoprotein that plays a multifunctional role in lipid metabolism. ApoE is essential in the formation of chylomicrons, very low-density and high-density lipoproteins (HDL), and is involved in the transport of cholesterol from the peripheral tissues to the liver [1]. The *APOE* gene is located on chromosome 19 and encodes three alleles,  $\epsilon 2$ ,  $\epsilon 3$  and  $\epsilon 4$ , which have been shown to affect the lipid profile and the development of coronary artery disease (CAD) [2, 3]. The distribution of these alleles varies between ethnic groups: Europeans and African-Americans have a high frequency of  $\epsilon 4$ ; Asians have a low frequency of  $\epsilon 2$  and  $\epsilon 4$  [2].

In the multi-ethnic population of Guadeloupe, a French Caribbean island, about 80% of the population are of African descent, about 8% of Indian descent and about 4% of Caucasian descent. Despite the high prevalence of several cardio-vascular risk factors such as type 2 diabetes (8.1%), hypertension (29.2%) and obesity (22.9%) in the general population [4, 5], data from the regional health observatory indicate a lower mortality rate from ischaemic heart disease (by 50% in men and 40% in women) compared with mainland France [6]. This finding has also been reported in Afro-Caribbean people living in the United Kingdom [7, 8] and may reflect, in part, a more favourable lipid profile in Afro-Caribbean people even in the context of insulin resistance or diabetes [9].

In a study of a sample of the general population of Guadeloupe, Foucan et al. reported a low frequency of hypercholesterolaemia (total cholesterol concentration  $\geq 5.2$  mmol/L in 38.7% and  $\geq 6.2$  mmol/L in 11.7% of the sample population) compared with mainland France and other industrialized countries [10]. However, the influence of genetic variants of *APOE* on the metabolic profile and CAD occurrence has never been reported in the Afro-Caribbean population.

The aim of this study was to evaluate the distribution of *APOE* polymorphisms and their association with CAD, lipid parameters and other cardio-metabolic risk factors in Afro-Caribbeans.

## Materials and methods

### Study population

We performed a prospective study that included 754 Afro-Caribbeans (234 CAD patients and 520 non-CAD patients) living on French West Indies islands. The CAD group included patients hospitalized for CAD or those with a documented history of acute coronary syndrome, coronary stenosis, coronary angioplasty or coronary artery by-pass surgery. Non-CAD controls were selected from two units of medicine at the university hospitals of Guadeloupe and Martinique (a neighbouring French island) and a medical health centre in Guadeloupe.

Both islands share the same history, have, approximately 420 000 inhabitants, similar socio-economic status, and ethnic distribution with a majority of Afro-Caribbeans. Controls were deemed free of cardio-vascular disease including myocardial infarction, acute coronary syndrome, peripheral artery disease and stroke. The ethnic origin was determined when the patient defined him/herself and his/her two first-degree relatives as Afro-Caribbean. The study was approved by the regional ethics committee (Sud-Ouest/Outre-Mer III, France). All patients gave their written informed consent to participate in this study.

## Data collection

Data on age, sex, height, weight and use of antihypertensive and/or hypolipidaemic treatment were collected during the enrollment visit. Body mass index (BMI) was calculated as weight divided by height squared ( $\text{kg}/\text{m}^2$ ). Waist circumference (WC) was measured at the midpoint between the lowest rib margin and the top of the iliac crest at minimal respiration with the participant standing. Systolic and diastolic blood pressure was assessed using an automated monitor after the subject had rested for at least 5 min. The recorded values were the average of two measurements in each arm.

## Biochemical analyses

Collection of blood samples was done within a week (generally less than 24h) after the formal enrollment. Blood samples were collected after an overnight fast of  $> 10$  h. The concentrations of glucose, total cholesterol, HDL and triglycerides were measured using an automatic multi-channel chemical analyser (Cobas Integra 800, Roche Diagnostic, France). Low-density lipoprotein (LDL) cholesterol concentration was calculated using the Friedewald formula in subjects with triglyceride level  $< 3.9$  mmol/L (340 mg/dL) and the Planella formula based on apolipoprotein B when the triglyceride level was  $\geq 3.9$  mmol/L.

## Determination of APOE isoforms

Genomic DNA was extracted from whole blood cells using a QIAamp<sup>®</sup> DNA purification kit (Qiagen, France), and DNA content was quantified using NanoVue Plus<sup>™</sup> (GE Healthcare Life Sciences, France). Genotyping was performed using published TaqMan methods (Applied Biosciences). Genotypes were assigned according to the combinations of the two single-nucleotide polymorphism allelic forms (rs7412 and rs429358) of the APOE gene, known as  $\epsilon 2$ ,  $\epsilon 3$  and  $\epsilon 4$ .

## Definition of clinical factors

Obesity was defined as a BMI  $\geq 30$   $\text{kg}/\text{m}^2$ . Dyslipidaemia was defined as a history of blood lipid abnormality and/or receiving lipid-lowering treatment. Hypertension was defined as a systolic blood pressure  $\geq 140$  mmHg or a diastolic blood pressure  $\geq 90$  mm Hg, or current use of antihypertensive medication.

## Statistical analyses

The data are presented as mean  $\pm$  standard deviation for continuous variables and as numbers (percentages) for categorical variables. Student's *t* test or one-way analysis of variance (ANOVA) were used to compare means and F-test and Levene's test were used for variance equality. T-test and ANOVA assumptions were satisfied for all variables.

The chi-squared test or Fisher's exact test was used to compare proportions. Triglyceride values were  $\log_{10}$  transformed to approach a normal distribution before statistical analysis.

Only participants with complete genotype (712 of 754) were included in the study. The proportion of successful APOE genotyping was similar in the subjects with CAD (0.95) and the subjects without CAD (0.94).

Subjects were divided into three groups according to their genotype: ε2+ (ε2/ε2, ε2/ε3), ε3 homozygotes (ε3/ε3) and ε4+ (ε3/ε4, ε4/ε4). One-way analysis of variance (ANOVA) and the Bonferroni post hoc test were used to compare the lipid profile and cardio-vascular risk factors between the groups. All tests were two-sided and a p value < 0.05 was considered significant. IBM SPSS Statistics for Windows, Version 19.0 (IBM Corp., Armonk, NY) was used to analyse the data.

## Results

### Characteristics of CAD and non-CAD patients

Table 1 shows the characteristics of the participants according to CAD status. Diabetes, hypertension and dyslipidaemia were significantly more prevalent in the CAD group compared with the control group. Patients with CAD were also older and had a larger WC. The proportion of obese subjects did not differ between the two groups.

The proportion of successful APOE genotyping was similar in subjects with or without CAD (0.95 and 0.94 respectively). The distribution of the APOE polymorphism genotypic

**Table 1. Characteristics of the participants according to CAD status.**

	Non-CAD N = 492	CAD N = 220	P
Male (%)	205 (41.7%)	141 (64.1%)	<0.001
Age (years)	51.11(±13.43)	63.51(±10.46)	0.004
Diabetes mellitus (%)	61 (12.4%)	110 (50%)	<0.001
Hypertension (%)	140 (28.5%)	175 (79.5%)	<0.001
Dyslipidemia (%)	78 (15.9%)	112 (50.9%)	<0.001
Smoking	70 (14.3%)	59 (26.8%)	<0.001
Lipid-lowering medication (%)	39 (8%)	166 (77.9%)	<0.001
<b>Anthropometric</b>			
Waist circumference	90.4 (±13.8)	98.54 (±11.8)	<0.001
BMI (kg/m <sup>2</sup> )	27.3 (±5.9)	27.4 (± 4.7)	0.831
Obesity (BMI ≥ 30 kg/m <sup>2</sup> )	143 (29.4%)	50 (22.9%)	0.077
<b>Genotype (%)</b>			0.762
ε <sub>2</sub> /ε <sub>2</sub>	5 (1%)	2 (0.9%)	
ε <sub>2</sub> /ε <sub>3</sub>	53 (10.8%)	27 (12.3%)	
ε <sub>2</sub> /ε <sub>4</sub>	19 (3.9%)	5 (2.3%)	
ε <sub>3</sub> /ε <sub>3</sub>	241 (49%)	100 (45.4%)	
ε <sub>3</sub> /ε <sub>4</sub>	150 (30.5%)	76 (34.6%)	
ε <sub>4</sub> /ε <sub>4</sub>	24 (4.9%)	10 (4.5%)	
<b>Allele frequency</b>			0.972
ε <sub>2</sub>	8.3	8.2	
ε <sub>3</sub>	69.6	68.9	
ε <sub>4</sub>	22.1	22.9	

Data are presented as means ± SD or number (percentage)

The Fisher's exact test was used to compare genotype distribution and the chi-squared test to compare allele frequencies and other proportions, among CAD and non-CAD groups.

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**Table 2. Association between APOE genotype, cardiovascular risk factors, and CAD.**

	Multivariate logistic regression		
	OR	95% CI	P
Age	1.06	(1.04–1.08)	<0.001
Male gender	3.48	(2.18–5.56)	<0.001
Hypertension	5.19	(3.23–8.36)	<0.001
Diabetes	2.16	(1.32–3.53)	0.002
Hypercholesterolemia	3.49	(2.22–5.51)	<0.001
Smoking	3.03	(1.72–5.34)	<0.001
APOE-ε4 carrier	1.11	(0.71–1.73)	0.648

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frequencies was within the Hardy–Weinberg equilibrium in both groups. In the total sample, the frequencies of the ε2, ε3 and ε4 alleles were 8%, 70% and 22%, respectively. Most subjects were ε3/ε3 homozygotes (n = 341; 48%), 284 subjects (40%) were ε4 carriers (carrying at least one ε4 allele) and 111 (16%) were ε2 carriers (carrying at least one ε2 allele). The APOE genotype distribution did not differ significantly between the CAD and the non-CAD groups (Tables 1 and 2). Individuals with the ε2/ε4 genotype (n = 24) were excluded from the subsequent analysis.

### Lipid profile and APOE polymorphism in non-CAD patients

For non-CAD patients who were not receiving a lipid-lowering treatment (n = 425), the concentrations of total cholesterol, LDL-cholesterol and triglycerides differed significantly between the three genotype groups (Table 3, S1 Fig). APOE-ε4 carriers had a higher total cholesterol level compared with ε2 carriers: 5.07 vs 4.59 mmol/L (P = 0.016). LDL levels were significantly different in APOE-ε2 carriers, ε3 homozygotes and ε4 carriers: 2.65 vs 3.03 and 3.17 mmol/L, respectively (P = 0.002). APOE-ε2 carriers had a higher triglyceride level compared with ε3 homozygotes and APOE-ε4 carriers: 1.38 vs 1.08 and 1.07 mmol/L, respectively (P = 0.012 and P = 0.015). The mean HDL-cholesterol level was non-significantly higher in APOE-ε4 carriers compared with ε3 homozygotes and ε2 carriers: 3.17 vs 3.03 and 2.65

**Table 3. Association between lipid levels and APOE genotypes in non-CAD subjects.**

	All N = 425	ε2+ N = 56	ε3/ε3 N = 215	ε4+ N = 154	P
Total-C (mmol/L)	4.90 (±1.08)	4.59 (±1.19)	4.87 (±1.06)	5.07 (±1.05) <sup>a</sup>	0.015
LDL-C (mmol/L)	3.03 (±0.96)	2.65 (±0.88)	3.03 (±0.93) <sup>b</sup>	3.17 (±0.98) <sup>c</sup>	0.002
HDL-C (mmol/L)	1.42 (±0.63)	1.33 (±0.62)	1.39 (±0.58)	1.49 (±0.70)	0.171
Total-C/HDL-C	3.89 (±1.88)	4.12 (±3.63)	3.91 (±1.49)	3.79 (±1.36)	0.520
LDL-C/HDL-C	2.46 (±1.33)	2.44 (±2.37)	2.47 (±1.10)	2.44 (±1.08)	0.973
Triglycerides (mmol/L)	1.12 (±0.68)	1.38 (±0.88)	1.08 (±0.60) <sup>d</sup>	1.07 (±0.70) <sup>e</sup>	0.008

Data are presented as means ± SD and were compared between groups using one-way ANOVA and the Bonferroni post hoc test. Only data from non-CAD patients who were not receiving lipid-lowering medication were considered in the analysis.

<sup>a</sup> P = 0.016 for ε4+ vs ε2+;

<sup>b</sup> P = 0.019 for ε3/ε3 vs ε2+;

<sup>c</sup> P = 0.001 for ε4+ vs ε2+;

<sup>d</sup> P = 0.012 for ε3/ε3 vs ε2+;

<sup>e</sup> P = 0.015 for ε4+ vs ε2+

Total-C: total cholesterol; HDL-C: HDL-cholesterol; LDL-C: LDL-cholesterol

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**Table 4. Association between APOE genotypes and other cardio-metabolic risk factors.**

	Carrier Group			P
	ε2+ N = 87	ε3/ε3 N = 341	ε4+ N = 260	
Male gender %	57.5	50.4	42.7	0.033
Age (SD)	54.7 (±12.4)	55.1 (±14.1)	55.3 (±14.2)	0.944
Hypertension %	36.8	44.0	46.9	0.255
Diabetes %	23.0	24.0	25.8	0.831
BMI (SD)	27.4 (±5.6)	27.1 (±5.4)	27.6 (±5.9)	0.484
BMI>30%	24.4	26.8	30.0	0.537
Waist circumference (SD)	94.5 (±13.1)	92.3 (±13.7)	92.9 (±14.3)	0.439

BMI: Body mass index

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mmol/L, respectively (P = 0.171). The ratios of total cholesterol/HDL and LDL/HDL did not differ significantly between the three allelic groups.

### Association between other cardio-metabolic risk factors and APOE allele

No significant associations were observed between APOE polymorphism and diabetes, hypertension, WC or BMI (Table 4).

## Discussion

### Allelic distribution of APOE in Afro-Caribbeans

The wide variation in the distribution of the APOE phenotype and APOE alleles between ethnic groups is well established [1]. This study is the first to assess the frequency of APOE alleles and to analyse its association with the lipid profile, cardio-vascular risk factors and CAD in Afro-Caribbeans. We found higher frequencies of the ε4 allele (22%) and lower frequencies of the ε3 allele (70%) in the studied sample compared with most other populations described in the literature. Higher frequencies of the non-ε3 allele form and especially the ε4 allele have been reported in African-Americans compared with Asians and Caucasians and in Africans compared with African-Americans [11–14]. Our results indicate that the APOE allelic distribution in Afro-Caribbeans is close to that in the African-American population.

### Association of APOE polymorphism with the lipid profile

APOE-ε4 carriers had the highest total cholesterol concentration whereas APOE-ε2 carriers had the lowest LDL and the highest triglyceride concentrations. These findings are consistent with previous studies in different populations [15, 16], some of which suggested that the relationship between the ε2 allele and LDL or total cholesterol concentration might be stronger in people of African descent compared with Caucasians [17, 18].

Most studies and meta-analyses have indicated that ε4 carriers have a lower HDL level compared with ε3 homozygotes and ε2 carriers [16]. In our study, the mean HDL concentration was higher in ε4 carriers compared with other allelic groups, although the difference was not significant. Although the ε2 allele was associated with a lower LDL concentration compared with the ε3 and ε4 alleles, the relative and absolute differences between the three allelic groups were low. As a consequence, the LDL/HDL and total cholesterol/HDL ratios, which reflect the atherogenicity of the lipid profile, were similar in the ε2+, ε3/ε3 and ε4+ participants in this study. This finding is unusual but is consistent with the observation that the effect



of *APOE* polymorphism on the blood lipid profile may vary with ethnic, genetic and environmental factors [1, 19–21]. In a study including 207 healthy volunteers, Loktionov et al. reported lower, total cholesterol, LDL cholesterol and total cholesterol/HDL ratio in black South Africans compared to United Kingdom Caucasians with similar *APOE* genotypes [22].

### Association of *APOE* polymorphism with CAD

We found no association between *APOE* gene variants and CAD. Previous epidemiological studies have investigated the relationship between *APOE* polymorphism, plasma concentrations of total cholesterol, LDL and apolipoprotein B, and CAD risk. Most of these studies have reported a significant association of between the *APOE*- $\epsilon$ 2/ $\epsilon$ 3/ $\epsilon$ 4 genotype and susceptibility to CAD. The *APOE*- $\epsilon$ 2 allele seems to be associated with a lipid profile that confers a lower coronary risk and that may be driven by compensatory upregulation of LDL receptors [16]. In contrast to *APOE*- $\epsilon$ 2, *APOE*- $\epsilon$ 4 is usually associated with high risk of cardio-vascular disease and CAD [2]. This association could be explained, at least partially, by the atherogenic lipid profile reported in  $\epsilon$ 4 allele carriers. Although we found significant differences in lipid concentrations according to the *APOE* allele, no allelic form appeared to be associated with a particularly adverse profile in our sample. The  $\epsilon$ 4 allele was associated with a high HDL concentration and low total cholesterol/HDL and LDL/HDL ratios. These variables did not differ according to *APOE* allele. The total cholesterol/HDL and LDL/HDL ratios are strong predictors of the risk of coronary heart disease, even stronger than LDL or HDL levels alone [23–25]. Thus, the association of *APOE* polymorphisms with CAD could be weak or non-existent in the absence of differences in the total cholesterol/HDL and LDL/HDL ratios between allelic groups. This hypothesis is supported by the results of a large prospective cohort study that reported that the association of *APOE* genotype with CAD was no longer significant after adjustment for various cardio-vascular risk factors and especially for the LDL/HDL ratio [26]. The absence of an unfavourable influence of the ApoE genetic variants on the lipid profile combined with the relatively low LDL concentration in Afro-Caribbeans may explain the lack of association between *APOE* polymorphism and CAD.

The low prevalence of smoking in the study sample as well as in our general population is another characteristic that might explain the lack of association between *APOE* polymorphism and CAD. Some studies, have reported a significant interactive effect between *APOE* genotype and smoking on CAD and that the presence of the  $\epsilon$ 4 allele is associated with an increased risk of CAD exclusively or mainly in smokers [27–30]. This interaction may be attributable to the reduced antioxidant capacity of apoE4 and/or higher levels of LDL and small dense LDL in *APOE*- $\epsilon$ 4 carriers, which make them vulnerable to the effects of reactive oxygen species produced by smoking [28, 31]. However, such an interaction between smoking and the *APOE*- $\epsilon$ 4 allele has not been observed in other studies or meta-analysis [26, 32].

### Association of *APOE* polymorphism with other cardio-metabolic risk factors

The association between *APOE* gene variants and other cardio-vascular risk factors, such as obesity, diabetes and the metabolic syndrome has also been studied in different ethnic groups. A meta-analysis of 45 studies including 13 940 cases and 16 364 controls by Stoumpos et al. indicated an increased risk of hypertension associated with the  $\epsilon$ 4 allele compared with the  $\epsilon$ 2 and  $\epsilon$ 3 alleles [33]. This association was stronger in populations of Asian descent, with an odds ratio (OR) of 1.49 (95% confidence interval (CI): 1.05–2.13) vs an OR of 1.39 (95% CI: 1.12–1.72) for the overall population (mostly of European descent). However, none of the studies

included in this meta-analysis was conducted in an African population or of African descent and few included black subjects.

Although several studies have reported an association between *APOE* polymorphism and obesity, insulin resistance and the metabolic syndrome, the results are inconsistent [34–36]. We found no association between *APOE* polymorphism and any of the traditional cardio-vascular risk factors (except lipid levels) including hypertension, diabetes, smoking, BMI, obesity, waist, age and sex. This lack of association of *APOE* alleles with the cardio-metabolic risk factors measured in our study might reflect the specific effects of these alleles on blood lipid levels and environmental factors such as diet in Afro-Caribbeans. Several studies have indicated that ApoE isoforms may be associated with obesity and its related disorders through direct and indirect effects on lipid metabolism and that obesity and dyslipidaemia play a pivotal role in the development of the metabolic syndrome [35, 37, 38]. The exact role of ApoE isoforms and *APOE* polymorphism in the development of these cardio-metabolic abnormalities remains unclear.

Our study had some limitations. Because of the limited sample size, we cannot rule out that a weak association between *APOE* and CAD may have been undetected because of a lack of statistical power. Moreover, because most of the CAD patients were receiving lipid-lowering treatment at the time of inclusion, the analysis of the lipid profile in relation to the allele distribution focused only on non-CAD subjects.

## Conclusions

This study provides new data about the metabolic and cardio-vascular profile associated with *APOE* polymorphism in Afro-Caribbeans. Unlike numerous studies in other populations, we found no association between *APOE* polymorphism and CAD. Although blood lipid levels were influenced by *APOE* genotype, no allelic form was associated with an atherogenic lipid profile. These findings support the idea that the link between *APOE* polymorphism and CAD varies between different populations and may depend on the effects of *APOE* polymorphism on blood lipid levels.

## Supporting information

**S1 Fig. Distribution of lipids concentration according to apolipoprotein E genotypes.** (DOCX)

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## Author Contributions

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