






ORIGINAL ARTICLE

Association between *APOE* polymorphisms and lipid profile in Mexican Amerindian population

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Abstract

Background: Apolipoprotein E (ApoE) is a glycoprotein that plays an important role in lipid homeostasis at both cerebral and systemic levels. Moreover, the differential distribution of *APOE* gene alleles among different populations, means that ApoE isoforms could have different effects on lipids metabolism. The present study aims to evaluate the relationship between *APOE* gene alleles and the lipid profile in a Mexican Amerindian (MA) population.

Methods: This study included 1997 MA individuals of different ethnicities distributed throughout different states of Mexico. All individuals underwent anthropometric measurements as well as laboratory tests including fasting glucose (FG), total cholesterol (TC), triglycerides, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C). TaqMan[®] probe genotyping assays were used to genotype *APOE*. The Kruskal–Wallis test was performed to determine the correlation between *APOE* gene alleles and genotypes and the biochemical variables measured.

Results: Among the biochemical variables analyzed, only the HDL-C and LDL-C levels showed statistical differences (p -value < .05) between individuals carrying different *APOE* alleles. For HDL-C, individuals carrying the E2 allele had higher HDL-C levels, followed by individuals carrying the E3 allele and carriers of the E4 allele presented the lowest levels of HDL-C (E2 > E3 > E4). This relationship was inverted for LDL-C levels (E2 < E3 < E4). Nevertheless, the difference of HDL-C levels between *APOE-E3* and *APOE-E4* carriers remained only in obese individuals.

Conclusions: Our results suggest that *APOE* gene genotypes play an important role in the differential modulation of lipid profiles in the MA population with obesity.

KEYWORDS

APOE gene, body mass index, cholesterol, Mexican population, triglyceride

1 | INTRODUCTION

Apolipoprotein E (ApoE) is a 34-kDa glycoprotein with 299 amino acid residues that plays a key role in lipid metabolism (Mahley, 1988; Smelt & de Beer, 2004). ApoE is involved in the reverse transport of cholesterol and clearance of very low-density lipoprotein (LDL) remnants (Greenow, Pearce, & Ramji, 2005; Phillips, 2014). ApoE in humans is encoded by a 3647-bp gene found in the 19q13.32 region (Nguyen, Dhanasekaran, Phillips, & Lund-Katz, 2009). The three primary ApoE protein isoforms are originated from two non-synonymous single nucleotide polymorphisms (SNPs) which are located in the coding region of the LDL receptor binding domain of the protein (rs429358 and rs7412); the two SNPs are in high linkage disequilibrium (Saito et al., 2003; Takei et al.,). The rs429358 polymorphism promotes a shift of a cysteine residue (C) to an arginine residue (R) at position 112 of the protein (p.C112R), whereas the rs7412 promotes a change of an R residue to a C residue at position 158 of the protein (p.R158C) (Saito et al., 2003). Three different gene alleles and three protein isoforms arise from the combination of the two SNPs and are commonly referred to as E2, E3, and E4 (Nguyen et al., 2009; Suarez & Schonfeld, 1981).

The *APOE* E2 allele encodes a protein with a Cys residue at both positions of the protein, the E3 allele encodes a Cys residue at position 112 and an Arg residue at position 158 and the E4 allele encodes an Arg protein at both positions (Nguyen et al., 2010; Suarez & Schonfeld, 1981). The three ApoE isoforms are originated from the substitution of these amino acid residues and lead to differential functions in lipid metabolism (Boerwinkle, Brown, Sharrett, Heiss, & Patsch, 1994; Boerwinkle & Utermann, 1988; Gregg & Brewer, 1988; Gregg et al., 1986; Hauser, Narayanaswami, & Ryan, 2011; Villeneuve, Brisson, & Gaudet, 2015). Additionally, each isoform of ApoE conveys a different risk of some diseases, such as Alzheimer's disease (AD) (Chen, Baum, Ng, Chan, & Pang, 1999) schizophrenia (Vila-Rodriguez, Honer, Innis, Wellington, & Beasley, 2011), osteoporosis (Singh, Singh, Singh, Juneja, & Kaur, 2010), or arteriosclerosis, which could be due the different functions and structures of the ApoE isoforms (Mahley, Weisgraber, & Huang, 2009; Ray, Ahalawat, & Mondal, 2017).

Due to a different distribution of *APOE* alleles among different ethnic populations, ApoE isoforms may also have a differential lipid metabolism which results in different lipid profiles among populations. For instance, it is well known that LDL cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and total cholesterol (TC) levels in individuals with a higher indigenous component differ significantly compared with the levels observed in individuals of African (AFR) origin, and it seems that a differential lipid modulation could be influenced by population-specific genetic and epigenetic factors, such as differential *APOE* alleles distribution

(Huebbe & Rimbach, 2017; Rodriguez et al., 2002). The current Mexican population is considered mestizo (MM) which comes from a mixture of three main populations: Mexican Amerindian (MA), Caucasian and AFR. Thus, the MM genome is a conjunction of regions of the genome derived from these different origins (Silva-Zolezzi et al., 2009). There the importance of understanding how the *APOE* alleles differentially modulate lipid profile in the main populations that originated the MM, in order to better understand the relationship between *APOE* and lipid profile. Hence, the present study aims to evaluate the relationship between biochemical variables (FG, TC, triglycerides [TGs], LDL-C, and HDL-C) and *APOE* alleles in a sample of MA individuals.

2 | MATERIALS AND METHODS

2.1 | Ethical compliance

This protocol was approved by the ethics and research committees of the National Institute of Genomic Medicine (Approval number: INMG/DI/149/2014). All individuals signed a letter of informed consent.

2.2 | Study population

The study included a total of 1997 individuals of Mexican native descent from different regions of Mexico. Recruited individuals belonged to the Mexican indigenous cohort of a metabolic study (MAIS). Considerations for the inclusion of individuals had been previously reported (Contreras-Cubas et al., 2016).

2.3 | Sociodemographic and biochemical variables

Information regarding age, gender, and education of every individual was collected through a structured questionnaire. Height in metres and weight in kilograms were measured using the Tanita[®] digital scale (Tanita Corporation, Clearbrook) with the stadiometer adjusted to 1-mm pressure. The body mass index (BMI) was calculated by dividing the weight in kilograms by the square of the height in metres. Biochemical tests, such as FG, TGs, HDL-C, LDL-C, and TC, were determined using the Cholestec LDX system[®] (Bio-Rad).

2.4 | Genotyping

Genotyping of rs7412 and rs429358 polymorphisms on *APOE* (NC_000019.9) was performed with allelic discrimination assays using Taqman[®] probes (C_3084793_20 and C_904973_10, respectively, Applied Biosystems). The thermocycling conditions used for each test were established by

the supplier. The thermocycling and allelic discrimination were performed using the 7900 real-time equipment with the SDS v2.1 software (Applied Biosystems). As a quality control for genotyping, 20% of the samples were genotyped in duplicate.

2.5 | Statistical analysis

Data are presented as numbers with frequencies and percentages for categorical variables. The demographic description (years of age, years of school), anthropometric (BMI) and clinic characteristics (glucose, cholesterol, high-density lipoprotein, LDL, and TG) are presented by means and standard deviations as continuous variables.

Because different ApoE isoforms have non-identical functions in relation to lipid metabolism (Mahley et al., 2009), we performed two different analyses. First, MA individuals were divided into two groups according with the *APOE* alleles carried (i.e., carrying E2+, E3/E3 homozygotes, and carrying E4+). Next, we divided the population into five groups according with the *APOE* genotypes, the groups were as follows: (a) individuals with E2/E4 genotype, (b) individuals with E2/E3 genotype, (c) individuals homozygous for E3 allele, (d) individuals with E3/E4 genotype (e) individuals homozygous for E4 allele. For continuous variables we tested for normality in all the variables using Shapiro–Wilk normality test and all the variables had a non-normal distribution (p -value < .0001). The continuous variables are presented as medians and interquartile distance, while categorical variables are presented as total individuals and percentages. Next, in order to explore differences between the groups we performed the Kruskal–Wallis test. A p -value lower than .05 was considered significant. All statistical analyses were performed using the free R software.

3 | RESULTS

3.1 | Sociodemographic variables

The majority of MA individuals were women (68.5%) with a mean age of 51.19 years. Regarding their educational level, 23.79% ($N = 470$) did not have any formal education, and 76.21% ($N = 1679$) had only 3 years of education. In relation to the BMI, 32.65% ($n = 652$) of the total sample presented normal weight 798 individuals (39.96%) were overweight and 547 individuals (27.39%) were obese. The summary of sociodemographic and biochemical variables of the MA population is shown in Table 1.

3.2 | Association of APOE polymorphisms with lipid and glucose profiles

The analysis of *APOE* alleles distribution showed that *APOE-E3* was the most frequent (88.81%), followed by *APOE-E4*

TABLE 1 Sociodemographic and biochemical characteristics of 1997 Mexican Amerindian (MA) individuals

Sociodemographic	
Gender ^a	
Men	630 (31.5%)
Women	1,367 (68.5%)
Age (years)	50 (39–63)
Total public education (years)	1.0 (0.0–2.0)
Body mass index (BMI, kg/m ²)	27.1 (24.2–30.4)
Normal weight	652 (32.65%)
Overweight	798 (39.96%)
Obese	547 (27.39%)
Biochemical	
Fasting glucose (FG, mg/dL) ^b	92.0 (82.0–105.0)
Total cholesterol (TC, mg/dL)	178.0 (154.0–205.0)
Triglycerides (TG, mg/dL)	168.5 (121.0–239.2)
High-density cholesterol (HDL-C, mg/dL)	38.00 (31.0–46.0)
Low-density cholesterol (LDL-C, mg/dL)	101.00 (82.0–122.0)
APOE	
Genotype frequencies	
E2/E4	6 (0.30%)
E2/E3	15 (0.75%)
E3/E3	1,589 (79.57%)
E3/E4	354 (17.73%)
E4/E4	33 (1.65%)
Allelic frequencies	
E2	21 (0.53%)
E3	3,547 (88.81%)
E4	426 (10.67%)

^aResults by gender, normal weight, overweight, obese, and genotype frequencies are of the total individuals (percentages in parentheses).

^bFor the BMI and biochemical variables, the results are reported as medians (interquartile range in parentheses).

(10.67%) and the *APOE-E2* allele was the least frequent (0.53%). The most frequent genotype was *E3* homozygote (79.57%). With regards of *APOE-E2* allele, no *E2* homozygote was found, only as heterozygote E2/E4 and E2/E3 (*APOE-E2+*). For individuals carrying the *APOE-E4* allele, the most frequent form was heterozygote E3/E4 (17.73%); homozygote E4 represented 1.65%, and overall, individuals carrying *APOE-E4* allele represented 19.38% in this MA sample (Table 1).

First, we analyzed differences observed on biochemical tests in correlation to different *APOE* allele carriers (i.e. comparing E2+, E3/E3, and E4+) (Table 2). Individuals with E2+ presented significantly higher HDL-C values (median:

TABLE 2 Summary of the biochemical characteristics of the MA population stratified by *APOE* alleles

	E2+ (<i>n</i> = 21)	E3/E3 (<i>n</i> = 1,589)	E4+ (<i>n</i> = 387)	<i>p</i> -value
BMI ^a	26.8 (25.5–31.1)	27.1 (24.1–30.5)	27.1 (24.3–30.3)	.74
Normal weight	4 (19.05)	527 (33.17)	121 (31.27)	.61
Overweight	10 (47.62)	626 (39.40)	162 (41.86)	
Obese	7 (33.33)	436 (27.44)	104 (26.87)	
TG	160.0 (120.0–240.0)	166.0 (120.0–234.5)	179.5 (125.8–258.8)	.05
TC	171.0 (160.0–212.0)	177.0 (151.8–204.0)	181.0 (159.0–208.8)	.06
HDL-C	41.0 (38.3–51.8)	38.0 (31.6–46.0)	36.0 (30.0–44.0)	.001
LDL-C	89.0 (79.2–111.3)	101.0 (82.0–121.0)	105.0 (85.3–126.8)	.02
FG	92.0 (85.0–169.0)	92.0 (82.0–105.0)	91.5 (82.0–104.8)	.71

Note: In bold, biochemical variables that show statistically significant differences.

Abbreviations: BMI, body mass index; FG, fasting glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

^aFor the biochemical variables, the results are reported as medians (interquartile range in parentheses).

TABLE 3 Summary of the biochemical characteristics of the MA population stratified by *APOE* genotypes

	<i>APOE</i> genotype					<i>p</i> -value
	E2/E4	E2/E3	E3/E3	E3/E4	E4/E4	
BMI ^a	25.8 (25.2–27.3)	27.2 (26.4–30.7)	27.1 (24.1–30.4)	27.0 (24.2–30.2)	27.4 (24.7–30.8)	.80
TG	132.5 (97.75–480.0)	160.0 (132.0–231.0)	166.0 (120.0–234.5)	183.5 (125.0–261.0)	173.5 (131.8–257.2)	.21
TC	204.5 (165.0–271.8)	171.0 (158.5–196.5)	177.0 (151.8–204.0)	179.0 (158.0–210.0)	185.0 (160.0–206.0)	.18
HDL-C	39.5 (30.9–47.0)	41.0 (39.3–51.8)	38.0 (31.6–46.0)	36.0 (30.0–44.0)	37.0 (30.0–45.0)	.006
LDL-C	96.5 (81.1–127.3)	89.0 (77.5–111.1)	101.0 (82.0–121.0)	105.0 (85.5–126.5)	107.0 (85.0–127.5)	.09
FG	120.0 (95.0–205.0)	89.0 (76.5–134.0)	92.0 (82.0–105.0)	92.0 (82.0–105.0)	89.0 (78.0–102.0)	.23

Note: In bold, biochemical variables that show statistically significant differences.

Abbreviations: BMI, body mass index; FG, fasting glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

^aFor the BMI and biochemical variables, the results are reported as medians (interquartile range in parentheses).

41.0 [38.3–51.8]) than individuals with E3/E3 genotype (median: 38.0 [31.6–46.0]), and individuals carrying the E4 allele (median: 36.0 [30.0–44.0]). Levels of LDL-C in individuals carrying E2+ were significantly lower (median: 89.0 [79.2–111.3]) than in individuals with E3/E3 genotype (median: 101.0 [82.0–121.0]), and also lower than individuals with E4+ (median: 105.0 [85.3–126.8]). In the analysis by genotypes (dividing individuals in five groups) only the HDL-C levels showed statistically significant differences (Table 3), with HDL-C levels: E3/E4 < E4/E4 < E3/E3 < E2/E4 < E2/E3.

Second, we analyzed the biochemical characteristics after stratifying the population based on the BMI (normal with BMI <25, overweight with BMI ≥25 or <30 and obese with BMI ≥30). As the number of individuals carrying E2+ allele was very low, we only stratified and analysed individuals homozygous for E3 allele and individuals carrying E4+ (*n* = 1,976 individuals). In normal weight and overweight individuals, *APOE* alleles or genotypes did not show

differences in any of the biochemical variables (Table 4). Also, the BMI in the individuals did not differ between the different *APOE* allele or genotype carriers (Tables 2 and 3). Meanwhile, obese individuals carrying E4+ allele had higher TC, TG, and LDL-C values than individuals homozygous for E3 allele. In contrast, obese individuals carrying E4 allele (median: 34.0 [29.0–40.5]) had reduced HDL-C levels when compared with obese individuals homozygous for E3 allele (median: 37.0 [31.0–44.8]). In the analysis by genotype (i.e. comparing E3/E3, E3/E4, and E4/E4), only HDL-C levels remain with statistically significant.

Next, we performed an analysis of LDL-C and HDL-C, in the individuals with different grades of obesity (obesity grade 1 with BMI ≥30 or <35, obesity grade 2 with BMI ≥35 or <40 and obesity grade 3 with BMI ≥40). In this analysis, differences in LDL-C remain significant only in the individuals with obesity grade 1, between individuals homozygous for E3 allele (median: 101.0 [83.5–119.5]) and individuals carriers of the E4 allele (median: 110.5

TABLE 4 Summary of the biochemical characteristics of the MA population stratified by *APOE* genotypes

	All	E3/E3	E3/E4	E4/E4	E4+	p-value ^a	p-value ^b
Normal weight (BMI < 25.0 kg/m ²)							
<i>n</i>	648 (32.79)	527 (81.33)	110 (16.98)	11 (1.70)	121 (18.67)	—	—
TG	146.0 (103.0–200.0)	143 (102.5–196.5)	156.0 (120.0–221.0)	133.0 (120.0–221.0)	155.0 (106.0–212.2)	.21	.46
TC	172.0 (147.0–199.0)	172.5 (147.0–198.0)	172.0 (145.0–202.0)	164.0 (158.0–199.0)	171.5 (146.0–201.8)	.85	.96
HDL-C	40.0 (33.0–50.38)	40.0 (33.0–51.0)	39.0 (31.8–50.0)	38.3 (36.0–45.0)	39.0 (32.0–48.0)	.10	.24
LDL-C	98.0 (80.0–116.5)	98.0 (80.0–116.0)	103.0 (82.0–117.0)	98.0 (89.0–137.0)	102.0 (82.5–118.2)	.40	.66
FG	90.0 (81.0–101.0)	90.0 (82.0–101.0)	90.0 (81.0–105.0)	89.0 (78.0–91.0)	90.0 (80.3–105.0)	.82	.69
Overweight (BMI ≥ 25.0 kg/m ² and <30.0 kg/m ²)							
<i>n</i>	788 (39.88)	626 (79.44)	147 (18.65)	15 (1.90)	162 (20.56)	.40	.66
TG	182.0 (131.5–260.0)	182.0 (133.0–258.0)	188.0 (129.5–273.0)	200.5 (123.5–264.8)	188.0 (128.5–271.5)	.60	.85
TC	180.5 (157.0–207.0)	180.0 (155.0–206.0)	180.0 (162.0–210.0)	200.0 (173.5–225.0)	181.0 (162.0–210.0)	.27	.31
HDL-C	36.9 (30.0–44.0)	37.0 (30.2–44.0)	35.9 (30.0–42.0)	36.8 (28.5–46.5)	36.0 (29.8–43.3)	.25	.4
LDL-C	103.0 (85.0–124.0)	103.0 (85.0–122.3)	104.0 (85.0–132.0)	111.0 (99.8–134.0)	104.0 (85.0–132.0)	.23	.43
FG	92.0 (83.0–105.0)	92.0 (83.0–106.0)	92.0 (83.0–104.0)	88.0 (76.5–101.0)	92.0 (82.5–104.0)	.53	.50
Obese (BMI ≥ 30.0 kg/m ²)							
<i>n</i>	540 (27.33)	436 (80.74)	95 (17.59)	9 (1.66)	104 (19.26)	.85	.96
TG	186.0 (134.0–247.0)	181.0 (132.0–241.0)	203.0 (141.0–292.0)	173.0 (150.0–223.0)	199.5 (146.0–289.5)	.02	.08
TC	181.5 (156.0–207.0)	180.0 (154.0–207.0)	186.0 (164.8–213.0)	184.0 (167.0–191.0)	186.0 (165.0–213.0)	.03	.06
HDL-C	36.0 (30.0–44.0)	37.0 (31.0–44.8)	33.5 (28.3–39.5)	34.0 (33.0–42.0)	34.0 (29.0–40.5)	.003	.01
LDL-C	104.0 (83.3–123.1)	101.0 (82.0–122.0)	113.0 (96.0–126.0)	99.5 (77.8–120.8)	112.0 (92.0–126.0)	.03	.05
FG	93.5 (83.0–106.8)	93.0 (83.0–107.0)	94.0 (82.8–104.3)	90.0 (78.0–102.0)	94.0 (82.0–104.0)	.93	.97

Note: In bold, variables that show statistically significant differences.

Abbreviations: BMI, body mass index; FG, fasting glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

^ap-value reported for analysis by allele.

^bp-value reported for analysis by genotype.

[92.75–126.0]) (p -value = .04). Also, differences in HDL-C remain significant only in individuals with obesity grade 2, both by alleles and by genotype of carriers of the E4 allele (median: 110.5 [92.75–126.0]) (p -value = .04). Also, differences in HDL-C remain significant only in individuals with obesity grade 2, both by alleles and by genotype of *APOE*.

4 | DISCUSSION

The association of *APOE* alleles with lipid and glucose metabolism has been replicated in different populations worldwide (Baila-Rueda et al., 2016; Breitling et al., 2015; Ward et al., 2009; Yasuno et al., 2012). Several studies have proposed that individuals have metabolic differences in lipid regulation depending on the expressed *APOE* alleles, and that some of pathological processes promoted by ApoE may correlate with isoform-dependent changes at the structural level of the protein (Mahley et al., 2009). Also, these differences in the modulation of lipid profile depending on the ApoE isoform could be influenced by the variation in *APOE* alleles based on the ethnic background of the population analyzed. Therefore, in this study, we performed an analysis of the relationship between the *APOE* alleles and the biochemical profile in the MA population.

We compared the *APOE* allele frequency in our population with frequencies reported by Eichner et al. in a meta-analysis of allelic and genotypic *APOE* frequencies, and we found that our MA population has some of the lowest E2 and E4 allele frequencies of the populations included in the meta-analysis (Eichner et al., 2002). These differences of *APOE* allele frequency in the MA population could indicate different disease risks; for instance, the E4 allele that confers a higher risk of coronary artery disease (CAD) or AD, in the MA populations is less frequent and could be important in the modulation of lower risk for CAD or AD that has been previously reported for Hispanic populations (Fujiyoshi et al., 2017; Maestre et al., 1996).

Regarding the modulation of lipid profile by *APOE* in MA individuals, we found that MA carriers of E4+ allele had lower HDL-C and higher LDL-C levels than homozygotes for E3 allele, and then E2+ carriers. In agreement with our observations, differential modulation of lipid profile (HDL-C, LDL-C, and TC) dependent on the ApoE isoform has been reported previously in other populations (Bennet et al., 2007; Boulenouar et al., 2013; Volcik et al., 2006; Wu et al., 2007). The association between *APOE* alleles and lipid profile has been one of the most studied worldwide, and even these results have been validated in an animal model (Hopkins, Huang, McGuire, & Pitas, 2002).

It has been reported that the effects of *APOE* alleles on differential lipid profile modulation depend on both genetic and environmental factors (Bernstein et al., 2002; Nicklas et al., 2002). One factor that may modulate the interaction

of lipid levels with ApoE is the BMI (Cronk, Johnson, & Burns, 2010; Gamboa et al., 2008; Romas, Tang, Berglund, & Mayeux, 1999). In the present study, obese individuals carrying the E4 allele had lower HDL-C levels and higher TC and TG levels than obese individuals homozygous for E3 allele. A decrease of HDL-C levels has been consistently associated with an increased risk of CAD, increased mortality, atherosclerosis and decreased cognitive function (Christiansen et al., 2017; Gillum & Obisesan, 2011; Larifla et al., 2017). The CAD risk is inversely dependent on HDL-C plasma levels (DeFaria Yeh, Freeman, Meigs, & Grant, 2007; Mahdy Ali, Wonnerth, Huber, & Wojta, 2012). Based on the relationship found in our analysis in which the E4 allele promoted low HDL-C levels, this effect was potentiated in obese MA individuals. In the MA population it has been reported a higher prevalence of obesity (Hu, Huff, Yamamura, Wu, & Strom, 2015; Schulz & Chaudhari, 2015) compared to other populations; thus, the high incidence of obesity in the MA population places the MA population at a high risk for the development of CAD.

The MA population has been neglected throughout history in terms of being exposed to factors that affect their health. Therefore, the present work is one of the first analyses of possible factors that can modulate lipid profiles in the MA population. In another study, where only 146 MA individuals were included, it was found an association between the E2/E3 genotype and low levels of LDL-C (Aguilar et al., 1999). On the other hand, although one of the strengths of the present study is the moderate sample size of MA individuals included, we consider as a limitation the lack of endophenotype data that may help to understand the association between *APOE* polymorphism and other biochemical markers in this population (Bojar et al., 2015; Smalinskiene et al., 2013). Nevertheless, the results are interesting and further investigations could lead to new knowledge in the way genetic variants affect the modulation of lipid profile in MA populations.

5 | CONCLUSIONS

The analysis of this cohort of MA ancestry individuals support findings observed in other populations, showing that individuals with *APOE-E4* polymorphism present lower HDL-C and higher LDL-C, TG and TC levels. Additionally, the effect of the E4 allele decreasing HDL-C levels, is enhanced in obese MA individuals.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All procedures performed in this study were carried out in accordance with the Helsinki declaration. The protocol was submitted and approved by the ethical and research

committees of the National Institute of Genomic Medicine (number INMG/DI/149/2014). Written informed consent was obtained from all subjects included in the protocol.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

JJMM, ADGM, CATZ, TBGC, and YHD contributed to the writing of this manuscript/ equally to this research. AMH, HGO, and LO conducted the laboratory and data analyses. IJR, MLLN, and HN interpreted the data and drafted the initial manuscript. All authors revised the initial manuscript. All authors approved the final draft.

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REFERENCES

- Aguilar, C. A., Talavera, G., Ordovas, J. M., Barriguete, J. A., Guillén, L. E., Leco, M. E., ... Rull, J. A. (1999). The apolipoprotein E4 allele is not associated with an abnormal lipid profile in a Native American population following its traditional lifestyle. *Atherosclerosis*, *142*(2), 409–414. [https://doi.org/10.1016/S0021-9150\(98\)00251-2](https://doi.org/10.1016/S0021-9150(98)00251-2)
- Baila-Rueda, L., Pérez-Ruiz, M. R., Jarauta, E., Tejedor, M. T., Mateo-Gallego, R., Lamiquiz-Moneo, I., ... Civeira, F. (2016). Cosegregation of serum cholesterol with cholesterol intestinal absorption markers in families with primary hypercholesterolemia without mutations in LDLR, APOB, PCSK9 and APOE genes. *Atherosclerosis*, *246*, 202–207. <https://doi.org/10.1016/j.atherosclerosis.2016.01.005>
- Bennet, A. M., Di Angelantonio, E., Ye, Z., Wensley, F., Dahlin, A., Ahlbom, A., ... Danesh, J. (2007). Association of apolipoprotein E genotypes with lipid levels and coronary risk. *JAMA*, *298*(11), 1300–1311. <https://doi.org/10.1001/jama.298.11.1300>
- Bernstein, M. S., Costanza, M. C., James, R. W., Morris, M. A., Cambien, F., Raoux, S., & Morabia, A. (2002). Physical activity may modulate effects of ApoE genotype on lipid profile. *Arteriosclerosis, Thrombosis, and Vascular Biology*, *22*(1), 133–140. <https://doi.org/10.1161/hq0102.101819>
- Boerwinkle, E., Brown, S., Sharrett, A. R., Heiss, G., & Patsch, W. (1994). Apolipoprotein E polymorphism influences postprandial retinyl palmitate but not triglyceride concentrations. *American Journal of Human Genetics*, *54*(2), 341–360.
- Boerwinkle, E., & Utermann, G. (1988). Simultaneous effects of the apolipoprotein E polymorphism on apolipoprotein E, apolipoprotein B, and cholesterol metabolism. *American Journal of Human Genetics*, *42*(1), 104–112.
- Bojar, I., Owoc, J., Wojcik-Fatla, A., Raszewski, G., Stanciak, J., & Raczkiwicz, D. (2015). Cognitive functions, lipid profile, and Apolipoprotein E gene polymorphism in postmenopausal women. *Annals of Agricultural and Environmental Medicine*, *22*(2), 313–319. <https://doi.org/10.5604/12321966.1152086>
- Boulouar, H., Benchechor, S., Meroufel, D., Hetraf, S. A., Djellouli, H., Hermant, X., ... Goumidi, L. (2013). Impact of APOE gene polymorphisms on the lipid profile in an Algerian population. *Lipids in Health and Disease*, *12*, 155. <https://doi.org/10.1186/1476-511x-12-155>
- Breitling, C., Gross, A., Büttner, P., Weise, S., Schleinitz, D., Kiess, W., ... Körner, A. (2015). Genetic contribution of variants near SORT1 and APOE on LDL cholesterol independent of obesity in children. *PLoS ONE*, *10*(9), e0138064. <https://doi.org/10.1371/journal.pone.0138064>
- Chen, L., Baum, L., Ng, H. K., Chan, L. Y., & Pang, C. P. (1999). Apolipoprotein E genotype and its pathological correlation in Chinese Alzheimer's disease with late onset. *Human Pathology*, *30*(10), 1172–1177. [https://doi.org/10.1016/S0046-8177\(99\)90034-5](https://doi.org/10.1016/S0046-8177(99)90034-5)
- Christiansen, M. K., Larsen, S. B., Nyegaard, M., Neergaard-Petersen, S., Ajjan, R., Würtz, M., ... Kristensen, S. D. (2017). Coronary artery disease-associated genetic variants and biomarkers of inflammation. *PLoS ONE*, *12*(7), e0180365. <https://doi.org/10.1371/journal.pone.0180365>
- Contreras-Cubas, C., Sánchez-Hernández, B. E., García-Ortiz, H., Martínez-Hernández, A., Barajas-Olmos, F., Cid, M., ... Orozco, L. (2016). Heterogenous distribution of MTHFR Gene variants among Mestizos and diverse Amerindian Groups from Mexico. *PLoS ONE*, *11*(9), e0163248. <https://doi.org/10.1371/journal.pone.0163248>
- Cronk, B. B., Johnson, D. K., & Burns, J. M. (2010). Body mass index and cognitive decline in mild cognitive impairment. *Alzheimer Disease and Associated Disorders*, *24*(2), 126–130. <https://doi.org/10.1097/WAD.0b013e3181a6bf3f>
- DeFaria Yeh, D., Freeman, M. W., Meigs, J. B., & Grant, R. W. (2007). Risk factors for coronary artery disease in patients with elevated high-density lipoprotein cholesterol. *American Journal of Cardiology*, *99*(1), 1–4. <https://doi.org/10.1016/j.amjcard.2006.07.053>
- Eichner, J. E., Dunn, S. T., Perveen, G., Thompson, D. M., Stewart, K. E., & Stroehla, B. C. (2002). Apolipoprotein E polymorphism and cardiovascular disease: A HuGE review. *American Journal of Epidemiology*, *155*(6), 487–495. <https://doi.org/10.1093/aje/155.6.487>
- Fujiyoshi, A., Jacobs, D. R., Fitzpatrick, A. L., Alonso, A., Duprez, D. A., Sharrett, A. R., ... Rapp, S. R. (2017). Coronary artery calcium and risk of dementia in MESA (multi-ethnic study of atherosclerosis). *Circulation: Cardiovascular Imaging*, *10*(5), e005349. <https://doi.org/10.1161/CIRCIMAGING.116.005349>

- Gamboa, R., Huesca-Gómez, C., Pérez-Méndez, O., Cruz-Robles, D., Fragoso, J. M., Juárez-Cedillo, T., ... Vargas-Alarcón, G. (2008). Apolipoprotein E polymorphisms in Mexican patients with coronary artery disease. *Clinical Chemistry and Laboratory Medicine*, 46(4), 481–485. <https://doi.org/10.1515/ccml.2008.077>
- Gillum, R. F., & Obisesan, T. O. (2011). High-density lipoprotein cholesterol, cognitive function and mortality in a U.S. national cohort. *Lipids in Health and Disease*, 10, 26. <https://doi.org/10.1186/1476-511x-10-26>
- Greenow, K., Pearce, N. J., & Ramji, D. P. (2005). The key role of apolipoprotein E in atherosclerosis. *Journal of Molecular Medicine (Berlin)*, 83(5), 329–342. <https://doi.org/10.1007/s00109-004-0631-3>
- Gregg, R. E., & Brewer, H. B., Jr. (1988). The role of apolipoprotein E and lipoprotein receptors in modulating the in vivo metabolism of apolipoprotein B-containing lipoproteins in humans. *Clinical Chemistry*, 34(8b), B28–32.
- Gregg, R. E., Zech, L. A., Schaefer, E. J., Stark, D., Wilson, D., & Brewer, H. B., Jr. (1986). Abnormal in vivo metabolism of apolipoprotein E4 in humans. *Journal of Clinical Investigation*, 78(3), 815–821. <https://doi.org/10.1172/jci.112645>
- Hauser, P. S., Narayanaswami, V., & Ryan, R. O. (2011). Apolipoprotein E: From lipid transport to neurobiology. *Progress in Lipid Research*, 50(1), 62–74. <https://doi.org/10.1016/j.plipres.2010.09.001>
- Hopkins, P. C., Huang, Y., McGuire, J. G., & Pitas, R. E. (2002). Evidence for differential effects of apoE3 and apoE4 on HDL metabolism. *Journal of Lipid Research*, 43(11), 1881–1889. <https://doi.org/10.1194/jlr.M200172-JLR200>
- Hu, H., Huff, C. D., Yamamura, Y., Wu, X., & Strom, S. S. (2015). The relationship between Native American Ancestry, body mass index and diabetes risk among Mexican-Americans. *PLoS ONE*, 10(10), e0141260. <https://doi.org/10.1371/journal.pone.0141260>
- Huebbe, P., & Rimbach, G. (2017). Evolution of human apolipoprotein E (APOE) isoforms: Gene structure, protein function and interaction with dietary factors. *Ageing Research Reviews*, 37, 146–161. <https://doi.org/10.1016/j.arr.2017.06.002>
- Larifla, L., Armand, C., Bangou, J., Blanchet-Deverly, A., Numeric, P., Fonteau, C., ... Vélayoudom-Céphise, F.-L. (2017). Association of APOE gene polymorphism with lipid profile and coronary artery disease in Afro-Caribbeans. *PLoS ONE*, 12(7), e0181620. <https://doi.org/10.1371/journal.pone.0181620>
- Maestre, G., Schofield, P., Chun, M., Tang, M.-X., Tycko, B., & Mayeux, R. (1996). *Ethnic variation in the association between APOE-ε4 and Alzheimer's disease: A follow-up study*. Berlin, Heidelberg: Springer. ISBN: 978-3-642-80109-9.
- Mahdy Ali, K., Wonnert, A., Huber, K., & Wojta, J. (2012). Cardiovascular disease risk reduction by raising HDL cholesterol—current therapies and future opportunities. *British Journal of Pharmacology*, 167(6), 1177–1194. <https://doi.org/10.1111/j.1476-5381.2012.02081.x>
- Mahley, R. W. (1988). Apolipoprotein E: Cholesterol transport protein with expanding role in cell biology. *Science*, 240(4852), 622–630.
- Mahley, R. W., Weisgraber, K. H., & Huang, Y. (2009). Apolipoprotein E: Structure determines function, from atherosclerosis to Alzheimer's disease to AIDS. *Journal of Lipid Research*, 50(Suppl), S183–188. <https://doi.org/10.1194/jlr.R800069-JLR200>
- Nguyen, D., Dhanasekaran, P., Nickel, M., Nakatani, R., Saito, H., Phillips, M. C., & Lund-Katz, S. (2010). Molecular basis for the differences in lipid and lipoprotein binding properties of human apolipoproteins E3 and E4. *Biochemistry*, 49(51), 10881–10889. <https://doi.org/10.1021/bi1017655>
- Nguyen, D., Dhanasekaran, P., Phillips, M. C., & Lund-Katz, S. (2009). Molecular mechanism of apolipoprotein E binding to lipoprotein particles. *Biochemistry*, 48(13), 3025–3032. <https://doi.org/10.1021/bi9000694>
- Nicklas, B. J., Ferrell, R. E., Bunyard, L. B., Berman, D. M., Dennis, K. E., & Goldberg, A. P. (2002). Effects of apolipoprotein E genotype on dietary-induced changes in high-density lipoprotein cholesterol in obese postmenopausal women. *Metabolism*, 51(7), 853–858. <https://doi.org/10.1053/meta.2002.33337>
- Phillips, M. C. (2014). Apolipoprotein E isoforms and lipoprotein metabolism. *IUBMB Life*, 66(9), 616–623. <https://doi.org/10.1002/iub.1314>
- Ray, A., Ahalawat, N., & Mondal, J. (2017). Atomistic insights into structural differences between E3 and E4 isoforms of apolipoprotein E. *Biophysical Journal*, 113(12), 2682–2694. <https://doi.org/10.1016/j.bpj.2017.10.006>
- Rodriguez, C., Pablos-Mendez, A., Palmas, W., Lantigua, R., Mayeux, R., & Berglund, L. (2002). Comparison of modifiable determinants of lipids and lipoprotein levels among African-Americans, Hispanics, and Non-Hispanic Caucasians > or =65 years of age living in New York City. *American Journal of Cardiology*, 89(2), 178–183.
- Romas, S. N., Tang, M. X., Berglund, L., & Mayeux, R. (1999). APOE genotype, plasma lipids, lipoproteins, and AD in community elderly. *Neurology*, 53(3), 517–521. <https://doi.org/10.1212/WNL.53.3.517>
- Saito, H., Dhanasekaran, P., Baldwin, F., Weisgraber, K. H., Phillips, M. C., & Lund-Katz, S. (2003). Effects of polymorphism on the lipid interaction of human apolipoprotein E. *Journal of Biological Chemistry*, 278(42), 40723–40729. <https://doi.org/10.1074/jbc.M304814200>
- Schulz, L. O., & Chaudhari, L. S. (2015). High-risk populations: The Pimas of Arizona and Mexico. *Curr Obes Rep*, 4(1), 92–98. <https://doi.org/10.1007/s13679-014-0132-9>
- Silva-Zolezzi, I., Hidalgo-Miranda, A., Estrada-Gil, J., Fernandez-Lopez, J. C., Uribe-Figueroa, L., Contreras, A., ... Jimenez-Sanchez, G. (2009). Analysis of genomic diversity in Mexican Mestizo populations to develop genomic medicine in Mexico. *Proceedings of the National Academy of Sciences*, 106(21), 8611–8616. <https://doi.org/10.1073/pnas.0903045106>
- Singh, M., Singh, P., Singh, S., Juneja, P. K., & Kaur, T. (2010). A susceptible haplotype within APOE gene influences BMD and intensifies the osteoporosis risk in postmenopausal women of Northwest India. *Maturitas*, 67(3), 239–244. <https://doi.org/10.1016/j.maturitas.2010.06.017>
- Smalinskiene, A., Petkeviciene, J., Luksiene, D., Jureniene, K., Klumbiene, J., & Lesauskaite, V. (2013). Association between APOE, SCARB1, PPARalpha polymorphisms and serum lipids in a population of Lithuanian adults. *Lipids in Health and Disease*, 12, 120. <https://doi.org/10.1186/1476-511x-12-120>
- Smelt, A. H., & de Beer, F. (2004). Apolipoprotein E and familial dysbetalipoproteinemia: Clinical, biochemical, and genetic aspects. *Seminars in Vascular Medicine*, 4(3), 249–257. <https://doi.org/10.1055/s-2004-861492>
- Suarez, B. K., & Schonfeld, G. (1981). Characterization of apolipoprotein E (ApoE) apoprotein levels in the various ApoE phenotypes. *Journal of Clinical Endocrinology and Metabolism*, 53(2), 435–438. <https://doi.org/10.1210/jcem-53-2-435>
- Takei, N., Miyashita, A., Tsukie, T., Arai, H., Asada, T., Imagawa, M., ... Kuwano, R. Genetic association study on in and around

- the APOE in late-onset Alzheimer disease in Japanese. *Genomics*, 93(5), 441–448. <https://doi.org/10.1016/j.ygeno.2009.01.003>
- Vila-Rodriguez, F., Honer, W. G., Innis, S. M., Wellington, C. L., & Beasley, C. L. (2011). ApoE and cholesterol in schizophrenia and bipolar disorder: Comparison of grey and white matter and relation with APOE genotype. *Journal of Psychiatry and Neuroscience*, 36(1), 47–55. <https://doi.org/10.1503/jpn.090116>
- Villeneuve, S., Brisson, D., & Gaudet, D. (2015). Influence of abdominal obesity on the lipid-lipoprotein profile in apoprotein E2/4 carriers: The effect of an apparent duality. *Journal of Lipids*, 2015, 742408. <https://doi.org/10.1155/2015/742408>
- Volcik, K. A., Barkley, R. A., Hutchinson, R. G., Mosley, T. H., Heiss, G., Sharrett, A. R., ... Boerwinkle, E. (2006). Apolipoprotein E polymorphisms predict low density lipoprotein cholesterol levels and carotid artery wall thickness but not incident coronary heart disease in 12,491 ARIC study participants. *American Journal of Epidemiology*, 164(4), 342–348. <https://doi.org/10.1093/aje/kwj202>
- Ward, H., Mitrou, P. N., Bowman, R., Luben, R., Wareham, N. J., Khaw, K. T., & Bingham, S. (2009). APOE genotype, lipids, and coronary heart disease risk: A prospective population study. *Archives of Internal Medicine*, 169(15), 1424–1429. <https://doi.org/10.1001/archinternmed.2009.234>
- Wu, K., Bowman, R., Welch, A. A., Luben, R. N., Wareham, N., Khaw, K. T., & Bingham, S. A. (2007). Apolipoprotein E polymorphisms, dietary fat and fibre, and serum lipids: The EPIC Norfolk study. *European Heart Journal*, 28(23), 2930–2936. <https://doi.org/10.1093/eurheartj/ehm482>
- Yasuno, F., Tanimukai, S., Sasaki, M., Ikejima, C., Yamashita, F., Kodama, C., ... Asada, T. (2012). Effect of plasma lipids, hypertension and APOE genotype on cognitive decline. *Neurobiology of Aging*, 33(11), 2633–2640. <https://doi.org/10.1016/j.neurobiolaging.2011.12.028>

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