rfm
Revista *de la* Facultad *de* Medicina

ORIGINAL RESEARCH

Genotypic frequency of the *APOE* gene polymorphism and its association with lipid profile and inflammatory markers in students from a university in Pereira, Colombia

Frecuencia genotípica del polimorfismo del gen APOE y su relación con el perfil lipídico y marcadores inflamatorios en estudiantes universitarios de Pereira, Colombia

Jorge Alberto Bravo-Pérez[1] Laura Castaño-Vargas[1] Nicolás David Covaleda-Martínez[1] Josué Montes-Ángel[1] Andrés Gaviria-Mendoza[1,2] Sandra Catalina Garzón-Castaño[1]

[1] Institución Universitaria Visión de las Américas - Pereira Campus - Faculty of Medicine - Grupo de Investigación de Biomedicina - Pereira - Colombia.
[2] Universidad Tecnológica de Pereira - Pereira Campus - Faculty of Medicine - Grupo de Investigación en Farmacoepidemiología y Farmacovigilancia - Audifarma S.A. - Pereira - Colombia.

Open access
Received: 18/08/2023
Accepted: 03/07/2024

Corresponding author: Sandra Catalina Garzón-Castaño. Grupo de Investigación de Biomedicina, Facultad de Medicina, Institución Universitaria Visión de las Américas. Pereira. Colombia. E-mail: sandra.garzon@uam.edu.co.

Keywords: Apolipoproteins E; Mutation; Lipids; Inflammation Mediators; Students (MeSH).

Palabras clave: Apolipoproteínas E; Mutación; Lípidos; Mediadores de inflamación; Estudiantes (DeCS).

How to cite: Bravo-Pérez JA, Castaño-Vargas L, Covaleda-Martínez ND, Montes-Ángel J, Gaviria-Mendoza A, Garzón-Castaño SC. Genotypic frequency of the *APOE* gene polymorphism and its association with lipid profile and inflammatory markers in students from a university in Pereira, Colombia. Rev. Fac. Med. 2024;72(2):e111289. English. doi: https://doi.org/10.15446/revfacmed.v72n2.111289.

Cómo citar: Bravo-Pérez JA, Castaño-Vargas L, Covaleda-Martínez ND, Montes-Ángel J, Gaviria-Mendoza A, Garzón-Castaño SC. [Frecuencia genotípica del polimorfismo del gen *APOE* y su relación con el perfil lipídico y marcadores inflamatorios en estudiantes universitarios de Pereira, Colombia]. Rev. Fac. Med. 2024;72(2):e111289. English. doi: https://doi.org/10.15446/revfacmed.v72n2.111289.

Abstract

Introduction: Apolipoprotein E (ApoE) enables serum lipid clearance. Its polymorphism has been associated with dyslipidemia which, if persistent, leads to a proinflammatory state and the subsequent development of atherosclerosis.
Objective: To determine the genotypic frequency of the *APOE* gene polymorphism and to evaluate its association with lipid profile and inflammatory markers in university students from Pereira (Risaralda, Colombia).
Materials and methods: A descriptive cross-sectional study was carried out in 77 university students. Sociodemographic and anthropometric variables, ApoE polymorphism, lipid profile, and inflammatory markers were analyzed by means of questionnaires, body measurements, and blood samples. A bivariate analysis was performed to evaluate the association between the presence of dyslipidemia and the levels of inflammatory markers, sex, weekly physical activity level, and dietary pattern.
Results: The mean age of the participants was 19 years and 62.34% were women. The most frequent polymorphism was ApoE rs429358 C/T (100%), followed by ApoE rs7412 C/C (97.40%), and ApoE rs7412 C/T (2.60%). All parameters assessed in the lipid profile, as well as IL-1β and IL-6, were higher in ApoE rs7412 C/C genotype carriers than in ApoE rs7412 C/T carriers. Furthermore, 70.13% had dyslipidemia. Levels of IL-1β, IL-6, and TNFα were higher in participants with dyslipidemia than in individuals without this condition, but the differences were not statistically significant.
Conclusion: The ApoE rs429358 C/T polymorphism was expressed in all participants, suggesting a genetic predisposition to dementia and cardiovascular and cerebrovascular diseases according to the literature. ApoE rs7412 C/C carriers showed higher levels in all lipid profile parameters, IL-1β, and IL-6, demonstrating that lipid profile and inflammation markers are linked to the specific expression of *APOE* gene genotypes.

Resumen

Introducción. La apolipoproteína E (ApoE) permite el aclaramiento sérico de lípidos; su polimorfismo se ha asociado con dislipidemia que, si persiste, conduce a un estado proinflamatorio y al subsecuente desarrollo de aterosclerosis.
Objetivos. Determinar la frecuencia genotípica del polimorfismo del gen *APOE* y evaluar su relación con el perfil lipídico y marcadores inflamatorios en estudiantes universitarios en Pereira (Risaralda, Colombia).
Materiales y métodos. Estudio trasversal descriptivo realizado en 77 estudiantes universitarios. Se analizaron las variables sociodemográficas, antropométricas, polimorfismo de ApoE, perfil lipídico y marcadores inflamatorios mediante cuestionarios, mediciones físicas y muestras de sangre. Se realizó un análisis bivariado para evaluar la asociación entre la presencia de dislipidemia y niveles de marcadores inflamatorios, sexo, nivel de actividad física semanal y patrón dietético.
Resultados. La edad media fue 19 años y 62.34% eran mujeres. El polimorfismo más frecuente fue ApoE rs429358 C/T (100%), seguido de ApoE rs7412 C/C (97.40%) y ApoE rs7412 C/T (2.60%). Todos los parámetros evaluados en el perfil lipídico, así como la IL-1β y la IL-6, fueron más altos en los portadores del genotipo ApoE rs7412 C/C que en los portadores de ApoE rs7412 C/T. Además, 70.13% tenían dislipidemia. Los niveles de IL-1β, IL-6 y TNFα fueron más altos en los participantes con dislipidemia que en aquellos sin esta condición, pero las diferencias no fueron estadísticamente significativas.
Conclusión. El polimorfismo ApoE rs429358 C/T fue expresado en todos los participantes, sugiriendo una predisposición genética a demencia y enfermedades cardiovasculares y cerebrovasculares según la literatura. Los portadores de ApoE rs7412 C/C mostraron niveles más altos en todos los parámetros del perfil lipídico, IL-1β e IL-6, demostrando que el perfil lipídico y los marcadores de la inflamación están ligados a la expresión específica de los genotipos del gen *APOE*.

Introduction

Lipids are biological molecules that contribute significantly to the function of cells and organisms[1] and play an essential role as structural elements in cell membranes, enabling cell integrity and homeostasis, as well as being key molecules in energy metabolism.[1,2] Cholesterol and phospholipids are essential components of all cell membranes and are necessary to maintain cell functionality and survival.[2]

It has been described that cholesterol serves as a basis for the synthesis of steroid hormones and that triglycerides (TG) are an essential source of energy for the human body as they contain fatty acids.[1,2] Since lipids such as cholesterol and TGs are insoluble in water, they must be carried in the bloodstream by hydrophile-lipophile particles known as lipoproteins.[3]

Apolipoprotein E (ApoE) is a protein that plays an important role in the transport of lipids into cells through its interaction with different cell-surface receptors[4] and is found in several classes of lipoproteins, including chylomicrons, very-low-density lipoproteins, and high-density lipoproteins (HDL).[5] Furthermore, by interacting with different receptors, this apolipoprotein promotes the clearance of chylomicrons and very-low-density lipoprotein remnants through the liver,[5] which means that any variation in the genes coding for ApoE can alter this process and, as a result, contribute to the development of primary hyperlipidemia.[2]

The gene encoding the ApoE protein is located on the long arm (q) of chromosome 19, at position 13.2-13.3 (19:q13.2-q13.3).[6] Its mutation is autosomal dominant and consists of a single-nucleotide polymorphism, resulting in three isoforms (ApoE2, ApoE3 and ApoE4)[5] that are distinguishable by the presence of arginine (Arg) or cysteine (Cys) at positions 112 or 158, which determines receptor affinity.[6-9]

The E3 isoform (112 Cys, 158 Arg) is the most common and is considered to be the reference protein.[10] The E2 isoform, with Cys in both positions, has a low affinity for low-density cholesterol (LDL) receptors, which can be associated under certain conditions with dysbetalipoproteinemia. However, ApoE2 plasma concentrations are usually higher than those of other isoforms due to a positive feedback process, leading to an association of ApoE2 with lower levels of total cholesterol (TC) and LDL compared to E3 and E4 isoforms. In this context, ApoE2 is regarded as a protective factor for adverse cardiovascular events such as myocardial infarction.[10-12]

Opposite to E2, the E4 isoform is characterized by its high affinity for receptors as it contains Arg in both positions, leading to a negative feedback process that reduces expression for the LDL receptor as well as serum ApoE4 concentrations. Consequently, this isoform is associated with elevated levels of TC and LDL cholesterol,[10,13] which, in turn, increases the risk of atherogenesis.[12]

Activation of inflammatory pathways plays a central role in the regulation of key processes in the development of atherosclerosis involving interleukins (IL).[14] It has been demonstrated that patients with advanced atherosclerotic plaques and poor lipid control have higher levels of IL-1β because of the activation of inflammasomes due to the presence of cholesterol crystals.[15] These elevated IL-1β levels are also associated with worse cardiovascular outcomes and mortality in patients with acute myocardial infarction.[16] Moreover, IL-1β triggers a cascade of intracellular molecular events that amplify inflammatory response, thereby elevating tumor necrosis factor-α (TNF-α) and IL-6 levels.[14] This intensification of inflammation leads to an increase in the expression of metalloproteinases, enzymes that degrade the extracellular matrix, weakening the plaque structure and making it more prone to rupture.[14]

It has been reported that individuals that carry at least one copy of the APOE ε4 allele have an increased chance of developing atherosclerosis,[17] which in turn increases the risk of heart attack and stroke, conditions recognized by the World Health Organization as the first and second leading causes of death worldwide.[18]

ApoE polymorphism has been studied in different places of Colombia such as the Caribbean and Pacific coasts, the eastern plains, the Amazon region,[19] Bogotá,[19,20] Buenaventura,[21] Barranquilla,[22] Quindío,[23] Valle del Cauca,[24] and Antioquia.[25] To the best of our knowledge, only one study on the ApoE polymorphism has been conducted in the department of Risaralda, which was carried out in individuals with Down syndrome and their parents, who came not only from Risaralda, but also from Quidío.[26]

In view of the above, the objectives of the present study were to determine the genotypic frequency of the *APOE* gene polymorphism and to evaluate its association with lipid profile and inflammatory markers in university students in Pereira (Risaralda, Colombia).

Materials and methods

Study type

Descriptive cross-sectional study.

Study population and sample

The study population comprised all students from the first to fifth semesters of higher education programs offered in the faculties of Medicine, Dentistry, Veterinary Medicine, and Law at the Institución Universitaria Visión de las Américas, located in Pereira (Risaralda, Colombia), with an active enrollment between February and November 2019 (N=930).

Participants were recruited by convenience sampling (face-to-face visit to classrooms to inform students about the study and invite them to participate), taking into account the following inclusion criteria: being between 18 and 30 years of age, being born in Risaralda, having at least one parent and one grandparent born in Risaralda, voluntarily accepting to participate in the study, and signing the informed consent form. Of the 930 students, 95 met these inclusion criteria and were administered an ad hoc questionnaire of 23 questions, which inquired about their sociodemographic information, family medical history, consumption of medications, consumption of psychoactive substances, level of physical activity, academic information, and dietary patterns.

Based on the results of this questionnaire, 5 students were excluded because they used antihypertensive, hypoglycemic or anti-inflammatory agents; used anabolic steroids; consumed psychoactive substances; and were active smokers and/or resided with a smoker. In addition, 13 individuals were excluded because they did not attend the anthropometric measurements and blood sampling session, procedures performed at the Biomedicine Research Laboratory of the Institución Universitaria Visión de las Américas, Pereira, obtaining a sample of 77 students. It is worth noting that this rigorous exclusion process was carried out to guarantee the integrity and homogeneity of the sample.

Variables

Using the ad hoc questionnaire, the following information was obtained for each student: age, sex, academic program, semester, weekly physical activity level (exercising less than 3 days a week or 3 days or more a week), dietary pattern (Mediterranean, defined as

consumption of vegetables, fruits, whole grains, and foods that are not highly processed or contain saturated fats,[27] or non-Mediterranean in the remaining the cases), and family medical history (defined as having a first- to third-degree blood relative with a history of hypertension, dyslipidemia, and/or coronary artery disease).

Regarding anthropometric measurements, height, weight, and waist circumference (cut-off points: 90cm for men and 80cm for women) were recorded. Also, body mass index was calculated using the formula weight(kg)/height(m^2).

In order to obtain information on *APOE* gene polymorphism, lipid profile, and inflammatory marker levels, each student had two 10mL blood samples drawn after 10 hours of fasting, one in an ethylenediaminetetraacetic acid (EDTA) tube, which was used for deoxyribonucleic acid (DNA) extraction, and one in a plain tube, which was used for biochemical analysis of the blood.

DNA isolation and genotyping of the APOE gene polymorphism

Genomic DNA was isolated using a Promega Wizard® Genomic DNA Purification kit (cat.# A1120) following the manufacturer's instructions. The quality of the isolated DNA was assessed with agarose gel. ApoE genotypes (rs7412 and rs429358) were determined by means of real-time polymerase chain reaction (RT-PCR) employing TaqMan probes (ThermoFisher Scientific cat.# 4351374, 4351379) and using QIAGEN's Rotor-Gene Q real-time PCR thermal cycler.

The ApoE polymorphism was classified into three categories: carriers of the ApoE rs7412 C/C genotype, carriers of the ApoE rs7412 C/T genotype, and carriers of the ApoE rs429358 C/T genotype.

Lipid profile

Lipid profile measurements included LDL (normal: <100mg/dL, near optimal: 100-129mg/dL, borderline high: 130-159mg/dL, and high: ≥160mg/dL), TC (Healthy: <200mg/dL, borderline high: 200-239mg/dL, and high: ≥240mg/dL), TG (normal: <150mg/dL, borderline high: 150-199mg/dL and high: ≥200mg/dL), and HDL (desirable: ≥40mg/dL for men and ≥50mg/dL for women). LDL was calculated using the Friedewald equation,[28] and the cut-off points for each marker were those proposed by the Adult Treatment Panel III.[29]

All samples were processed in the Biomedicine Laboratory of the Institución Universitaria Visión de las Américas using the diagnostic IHR kit for TG, CT, and HDL, which employs an enzymatic colorimetric method.

Finally, dyslipidemia was defined as any alteration in TC, TG, HDL, and LDL levels according to the cut-off points mentioned above.

Measurement of IL-1β, IL-6, and TNFα

The following inflammatory markers were considered: IL-1β, IL-6, and TNFα. The levels of these markers were quantified by ELISA (enzyme-linked immunosorbent assay) using the ELISA MAX™ Deluxe Set Human IL-6, IL-1β, TNFα kit (BIOLEGEND, cat.# 430504, 437004, and 430201, respectively), following the manufacturer's instructions. Concentrations of IL-1β, IL-6 and TNFα were interpolated on standard calibration curves; sample dilutions were performed according to the manufacturer's specifications.

Statistical analysis

The data collected were entered and organized in a spreadsheet created in Microsoft Excel for subsequent processing in SPSS (version 23). Data are described using absolute frequencies and percentages for categorical variables and means and standard deviations (SD) or medians and interquartile ranges (IQR), according to the distribution of the data (Shapiro-Wilk test), for continuous variables.

In addition, a bivariate analysis was performed to evaluate the association between the presence of dyslipidemia and the levels of inflammatory markers, sex, weekly physical activity level, and dietary patterns using the Chi-square or Fisher's exact tests for categorical variables and Student's t-test or Mann-Whitney U test (according to the distribution of the data) for continuous variables. A statistical significance level of $p<0.05$ was considered.

Ethical considerations

The study followed the ethical principles for biomedical research involving human subjects established in the Declaration of Helsinki[30] and the scientific, technical and administrative standards for health research in Resolution 8430 of 1993 of the Colombian Ministry of Health.[31] In addition, it was endorsed by the Research Ethics Committee of the Institución Universitaria Visión de las Américas according to minutes No. PS020 of October 1, 2019. Similarly, informed consent was obtained from all participants.

Results

The median age of the participants was 19 years (IQR: 18-21 years), 62.34% were female, and 55.84% were enrolled in the medical program. The median body mass index was 23.98kg/m² (IQR: 21.23-26.73), 61.04% did physical activity less than 3 times a week, and 70.13% had dyslipidemia. Regarding genotypic distribution, all students expressed the ApoE rs429358 C/T genotype, 97.40% expressed the ApoE rs7412 C/C genotype, and only 2.60% expressed the ApoE rs7412 C/T genotype. With regard to the inflammatory markers evaluated, the median levels of IL-1β, IL-6, and TNFα were 11.74pg/mL (IQR: 7.27-16.21pg/mL), 3.72pg/mL (IQR: 1.60-5.84pg/mL), and 86.59pg/mL (IQR: 51.06-122.12pg/mL), respectively (Tables 1 and 2).

Table 1. Characteristics of the university students from Pereira (Colombia) included in the study (n=77).

Variables		n (%)
Sociodemographic		
Age (years), median (IQR)		19 (18-21)
Sex	Female	48 (62.34)
	Male	29 (37.66)
University Program	Medicine	43 (55.84)
	Veterinary	13 (16.88)
	Dentistry	12 (15.59)
	Law	9 (11.69)

Table 1. Characteristics of the university students from Pereira (Colombia) included in the study (n=77). (Continued)

Variables		n (%)
Semester	1	22 (28.57)
	2	16 (20.78)
	3	18 (23.38)
	4	18 (23.38)
	5	2 (2.60)
	No data	1 (1.29)
Exercise less than 3 days per week		47 (61.04)
Dietary pattern		
Mediterranean		13 (16.88)
Family medical history (1-3 degree of consanguinity)		
Relatives with at least one case of		68 (88.31)
Hypertension		64 (83.12)
Dyslipidemia		39 (50.65)
Coronary artery disease		31 (40.25)
Anthropometric measurements		
Body mass index (kg/m²) median (IQR)		23.98 (21.23-26.73)
Hip circumference (cm) median (IQR)		77 (70.75-83.25)
Blood sample		
APOE gene polymorphism	rs429358 C/T	77 (100)
	rs7412 C/C	75 (97.40)
	rs7412 C/T	2 (2.60)
Lipid profile (mg/dL)	Total cholesterol mean ± SD	136.91±40.98
	Triglycerides mean ± SD	143.51±42.78
	High-density cholesterol mean ± SD	50.30±11.55
	Low-density cholesterol median (IQR)	49.13 (15.85-82.40)
Inflammatory markers (pg/mL)	IL-1β median (IQR)	11.74 (7.27-16.21)
	IL-6 median (IQR)	3.72 (1.60-5.84)
	TNFα median (IQR)	86.59 (51.06-122.12)

APOE: apolipoprotein E; IQR: interquartile range; SD: standard deviation; IL: interleukin; TNF: tumor necrosis factor.

Table 2. Distribution of participants in each lipid profile category.

Lipid profile (mg/dL)		n (%)
Total cholesterol	Normal (<200)	73 (94.81)
	Borderline high (200-239)	3 (3.89)
	High (≥240)	1 (1.30)
Triglycerides	Healthy (<150)	46 (59.74)
	Borderline high (150-199)	26 (33.77)
	High (≥200)	5 (6.49)
High density cholesterol	Desirable M (≥40mg/dL) F (≥50mg/dL)	48 (62.34)
	At risk M (<40mg/dL) F (<50mg/dL)	29 (37.66)
Low density cholesterol	Normal (<100)	64 (83.12)
	Near optimal (100-129)	11 (14.28)
	Borderline high (130-159)	1 (1.30)
	High (≥160)	1 (1.30)
Dyslipidemia	Yes	54 (70.13)
	No	23 (29.87)

F: female; M: male.

Concerning the association between the presence of ApoE genotypes, lipid profile, and inflammatory markers, we found that students with ApoE rs7412 C/C genotype had higher serum levels of TC, TG, LDL, HDL, IL-1β, and IL-6 compared to those carrying the ApoE rs7412 C/T genotype (Table 3).

Table 3. Serum parameters according to ApoE genotype.

Parameters		ApoE rs7412	
		(C/C) (n=75) $\bar{x}$ (SD)	**(C/T) (n=2) $\bar{x}$ (SD)**
Lipid profile (mg/dL)	Total cholesterol	138.49 (40.24)	77.42 (22.51)
	Triglycerides	143.91 (43.23)	128.38 (18.64)
	Low-density cholesterol	59.12 (40.02)	12.21 (16.77)
	High-density cholesterol	50.59 (11.57)	39.54 (2.02)
Inflammatory markers (pg/mL)	IL-1β	15.15 (8.17)	11.23 (0.73)
	IL-6	6.71 (8.13)	3.16 (1.17)
	TNF-α	96.23 (63.69)	132.72 (77.21)

$\bar{x}$: mean; SD: standard deviation; ApoE: apolipoprotein E; IL: interleukin; TNF: tumor necrosis factor.

On the other hand, participants with dyslipidemia had higher levels of IL-1β, IL-6, and TNFα compared to those without dyslipidemia, but these differences were not statistically significant. Furthermore, it was found that in both subgroups (with and without dyslipidemia), there was a predominance of women, individuals who did physical activity less than 3 times a week, and students who did not follow a Mediterranean dietary pattern, without any of these differences being statistically significant (Table 4).

Table 4. Distribution of inflammatory markers, sociodemographic factors, and dietary pattern according to the presence of dyslipidemia.

Parameters		Dyslipidemia (n=54)	No dyslipidemia (n=23)	*p*-value
Inflammatory markers (pg/mL) median (IQR)	IL-1β	12.35 (10.56-19.11)	10.65 (9.48-18.98)	0.227
	IL-6	3.97 (2.13-5.80)	3.48 (1.25-5.70)	0.811
	TNF-α	88.09 (56.52-125.69)	85.75 (49.98-121.51)	0.570
Sex n (%)	Male	20 (37.04)	9 (39.13)	0.862
	Female	34 (62.96)	14 (60.87)	
Weekly physical activity level n (%)	Physical activity <3 days a week	32 (59.26)	15 (65.22)	0.624
	Physical activity ≥3 days a week	22 (40.74)	8 (34.78)	
Dietary pattern (%)	Mediterranean	9 (16.67)	4 (17.39)	1
	Not Mediterranean	45 (83.33)	19 (82.61)	

IL: interleukin; IQR: interquartile range; TNF: tumor necrosis factor.
Note: It should be noted that the values of the inflammatory markers in the bivariate analysis were expressed as medians (IQR) and, therefore, the Mann-Whitney U test was used. For the remaining variables, data were expressed as frequency (%), and the Chi-square test was used, except for diet, which was analyzed using Fisher's exact test.

Discussion

The *APOE* gene encodes ApoE, a polymorphic protein involved in lipid metabolism.[10] Furthermore, it has been reported that this protein and its different isoforms are associated with variations in lipid and lipoprotein levels and, therefore, with cardiovascular risk.[10,13] Dyslipidemia and a proinflammatory state are part of the pathophysiological mechanism for the development of atherosclerosis, the main risk factor for cardiovascular disease (CVD), which is the leading cause of death worldwide.[14] The genotypic distribution of the *APOE* gene polymorphism and its relationship with the lipid profile and inflammatory markers of university students in Pereira was analyzed in this study, being this the first research of its kind in Colombia.

In the present study, the majority of participants were female (62.34%), a finding that is in agreement with what has been reported in similar studies, in which a higher frequency of women was described (54.6%-59.02%).[32-34]

Also, the most frequently expressed genotype was the polymorphic form ApoE rs429358 C/T (100%), followed by the non-polymorphic form ApoE rs7412 C/C (97.40%), and the polymorphic form ApoE rs7412 C/T (2.60%). This finding is consistent with what has been described in international and national studies in the sense that the polymorphic form ApoE rs429358 is expressed more frequently than the polymorphic form ApoE rs7412 (10.4-21.4% vs. 1.8-7.8%),[21,22,32] but it differs in that said studies report that the non-polymorphic form of ApoE rs429358 is more frequent than the polymorphic form.[21,22,32,35]

Since the polymorphic form ApoE rs429358 determines the presence of the *ApoE* ε4 allele, it can be stated that all participants in the present study have a genetic tendency to develop dementia, CVD, and cerebrovascular diseases because this allele has been associated with elevated carotid intima-media thickness (average difference: 0.013mm, 95%CI: 0.003-0.023mm),[36] lobar intracerebral hemorrhage (OR=3.66, 95%CI: 1.28-10.43; p<0.02),[37] cerebral infarction (OR=1.822, 95%CI: 1.390-2.388; p<0.001),[38] secondary chronic heart failure (OR=4.339, 95%CI: 2.986-5.723; p=0.028),[39] coronary artery disease

(OR=2.15, 95%CI: 1.40-3.28; p<0.001),[40] all-cause dementia (OR=2.14, 95%CI: 1.74-2.63; p<0.0001), and Alzheimer's disease (OR=3.27, 95%CI: 2.35-4.55, p<0.0001).[41]

In the present study, it was also observed that carriers of the non-polymorphic form ApoE rs7412 C/C had higher levels of TC, TG, LDL, and HDL compared to carriers of the polymorphic form ApoE rs7412 C/T. In this sense, considering that being a carrier of the polymorphic form ApoE rs7412 conditions the presence of the ApoE ε2 allele, it could be said that these results for TC and LDL are similar to those reported by Nuinoon *et al.*[42] in a study conducted in southern Thailand with 459 healthy individuals, in which carriers of the non-polymorphic form of ApoE rs7412 (expressed in 74.29% of the population) had higher levels of TC and LDL compared to carriers of the polymorphic form of ApoE rs7412 (10.13%). However, bearing in mind that there were only 2 carriers of the ApoE rs7412 C/T allele in the present study, a relationship of statistical significance could not be established.

Concerning the association of the APOE gene polymorphism with inflammatory markers, participants with the rs7412 C/C genotype showed higher serum levels of IL-1β and IL-6 and lower levels of TNFα compared to carriers of the rs7412 C/T genotype. It should be noted that there were no studies on similar samples; however, these results are comparable with those found by Fan *et al.*[43] in a study involving 375 individuals from the Wenzhou region of China (case group: 185 Alzheimer's patients, average age: 67.85 years; control group: 190 healthy individuals, average age: 67.35 years), in which IL-1β and IL-6 levels were higher in both the control group and the case group for carriers of the ApoE rs7412 C/C allele.

It should be noted that individuals with high levels of CRP, IL-6, and TNFα have a higher risk of developing diabetes mellitus (OR=5.71, 95% CI: 1.07-30.63; p<0.042)[44] and that high levels of IL-1β have been associated with increased mortality (HR adj=2.78, 95%CI: 1.61-4.79; p=0.0002) and increased risk of major adverse cardiovascular events (HR adj=2.42, 95%CI: 1.36-4.28; p=0.002) in patients with ST-elevation acute myocardial infarction.[16]

In the present study, university students with dyslipidemia had higher levels of IL-1β, IL-6, and TNFα compared to those without dyslipidemia, although the differences were not statistically significant. This finding is similar to that reported by Hong *et al.*[45] in a study of 1 397 adults (mean age 41.75 years) from the east coast of Fujian, China, in which they reported that IL-6 and TNFα levels were significantly higher in individuals with dyslipidemia (p<0.001). Nevertheless, since our study was carried out in a healthy population, the elevation of inflammatory markers is attributed to lipid disorders, and it could be inferred that dyslipidemia leads to a proinflammatory state.

According to their lipid profile, 54 participants (70.13%) had dyslipidemia, and most of them were women (62.96%; n=34). This finding is similar to that reported by Galvis *et al.*[46] in a study conducted in Medellín (Colombia), in which 74.7% of the 6 384 participants (median age: 61 years) had dyslipidemia and 78.7% of them were women. Cardona *et al.*[47] also reported that in a study carried out on 151 Emberá-Chamí indigenous people in Caldas (Colombia) (45% aged between 21-44 years), 68.2% of the participants had dyslipidemia, with a higher proportion of women (71.9%). These findings show a tendency of the native and female population to suffer from dyslipidemia.

Furthermore, physical activity and dietary patterns have been described as modifiable risk factors associated with dyslipidemia.[27,29] This could explain why there was a higher frequency of participants in the subgroup of students with dyslipidemia who did physical activity less than 3 times a week (59.26%) and consumed a non-Mediterranean diet (83.33%).

The limitations of the present study include its cross-sectional nature and the fact that convenience sampling was used, which could lead to selection bias; the impossibility of evaluating confounding factors that may alter lipid profile in a statistical model, given that the sample size did not allow for multivariate analysis and covariate adjustment;

and the inclusion of students from only one university in the department, which limits the extrapolation of the results to students from the entire region. Therefore, to better understand the impact of the ApoE polymorphism on the lipid profile and inflammatory markers of this population in the region, studies conducted at several universities, with larger sample sizes and random sampling, are required. Likewise, it is suggested that these future studies analyze the association between dyslipidemia and serum levels of these inflammatory markers.

Conclusions

In the present study, the ApoE rs429358 C/T polymorphism was expressed in all participants, which, according to the literature, suggests a genetic predisposition of these individuals to the development of dementia, CVD, and cerebrovascular diseases. Moreover, it was observed that students carrying the ApoE rs7412 C/C polymorphism had higher levels of TC, TG, LDL, HDL, IL-1β, and IL-6 but not of TNF-α, compared to those with the ApoE rs7412 C/T polymorphism, which may indicate that lipid profile and inflammation markers are linked to the specific expression of the *APOE* gene genotypes. However, the sample size was limited and further studies are required to analyze this association. In turn, individuals with dyslipidemia had high levels of IL-1β, IL-6, and TNFα, which supports the hypothesis that lipid disorders may induce a proinflammatory state, even in an apparently healthy population. Finally, the prevalence of dyslipidemia was higher in the group of participants with a sedentary lifestyle and a non-Mediterranean diet, highlighting the importance of modifiable risk factors in preventing this condition.

Conflicts of interest

None stated by the authors.

Funding

This study was funded by the Institución Universitaria Visión de las Américas.

Acknowledgements

None stated by the authors.

References

1. Mutlu AS, Duffy J, Wang MC. Lipid metabolism and lipid signals in aging and longevity. Dev Cell. 2021;56(10):1394-407. https://doi.org/gknq4n.
2. Real JT, Ascaso JF. Metabolismo lipídico y clasificación de las hiperlipemias. Clin Investig Arterioscler. 2021;33(Suppl 1):3-9. https://doi.org/nfjg.
3. Husain MA, Laurent B, Plourde M. APOE and Alzheimer's Disease: From Lipid Transport to Physiopathology and Therapeutics. Front Neurosci. 2021;15. https://doi.org/gmx9b4.
4. Yang LG, March ZM, Stephenson RA, Narayan PS. Apolipoprotein E in lipid metabolism and neurodegenerative disease. Trends Endocrinol Metab. 2023;34(8):430-45. https://doi.org/nd7s.
5. Bea AM, Larrea-Sebal A, Marco-Benedi V, Uribe KB, Galicia-Garcia U, Lamiquiz-Moneo I, *et al.* Contribution of *APOE* Genetic Variants to Dyslipidemia. Arterioscler Thromb Vasc Biol. 2023;43(6):1066-77. https://doi.org/nd7v.

6. Martínez S, Ochoa B, Pérez MR, Torrico F, García I, Garcia CC. Polimorfismos del gen de la apolipoproteína E en adultos mayores de 60 años con disminución de la memoria cognitiva y enfermedad de Alzheimer en diferentes poblaciones venezolanas. Biomedica. 2022;42(Sppl 1):116-29. https://doi.org/nd73.
7. Abondio P, Sazzini M, Garagnani P, Boattini A, Monti D, Franceschi C, *et al.* The Genetic Variability of *APOE* in Different Human Populations and Its Implications for Longevity. Genes (Basel). 2019;10(3):222. https://doi.org/gf2q28.
8. Macedoni M, Hovnik T, Plesnik E, Kotnik P, Bratina N, Battelino T, *et al.* Metabolic control, ApoE genotypes, and dyslipidemia in children, adolescents and young adults with type 1 diabetes. Atherosclerosis. 2018;273:53-8. https://doi.org/gdmnb3.
9. Fairfield CJ, Drake TM, Pius R, Bretherick AD, Campbell A, Clark DW, *et al.* Genome-Wide Association Study of NAFLD Using Electronic Health Records. Hepatol Commun. 2022;6(2):297-308. https://doi.org/nfjh.
10. Marais AD. Apolipoprotein E in lipoprotein metabolism, health and cardiovascular disease. Pathology. 2019;51(2):165-76. https://doi.org/gg5dr4.
11. Shao A, Shi J, Liang Z, Pan L, Zhu W, Liu S, *et al.* Meta-analysis of the association between Apolipoprotein E polymorphism and risks of myocardial infarction. BMC Cardiovasc Disord. 2022;22(1):126. https://doi.org/nd75.
12. Karjalainen J-P, Mononen N, Hutri-Kähönen N, Lehtimäki M, Juonala M, Ala-Korpela M, *et al.* The effect of apolipoprotein E polymorphism on serum metabolome - a population-based 10-year follow-up study. Sci Rep. 2019;9(1):458. https://doi.org/nd76.
13. Khalil YA, Rabès J-P, Boileau C, Varret M. APOE gene variants in primary dyslipidemia. Atherosclerosis. 2021;328:11-22. https://doi.org/gj55c3.
14. Jebari-Benslaiman S, Galicia-García U, Larrea-Sebal A, Olaetxea JR, Alloza I, Vandenbroeck K, *et al.* Pathophysiology of Atherosclerosis. Int J Mol Sci. 2022;23(6):3346. https://doi.org/gtr2t7.
15. Jiang X, Wang F, Wang Y, Gisterå A, Roy J, Paulsson-Berne G, *et al.* Inflammasome-Driven Interleukin-1α and Interleukin-1β Production in Atherosclerotic Plaques Relates to Hyperlipidemia and Plaque Complexity. JACC Basic Transl Sci. 2019;4(3):304-17. https://doi.org/gh8vw9.
16. Silvain J, Kerneis M, Zeitouni M, Lattuca B, Galier S, Brugier D, *et al.* Interleukin-1β and Risk of Premature Death in Patients With Myocardial Infarction. J Am Coll Cardiol. 2020;76(15):1763-73. https://doi.org/gsfp8j.
17. MedlinePlus. APOE gene: apolipoprotein E. Bethesda, MD: National Library of Medicine. [cited 2022 May 1]. Available from: https://medlineplus.gov/genetics/gene/apoe/.
18. World Health Organization (WHO). The top 10 causes of death. Geneva: WHO; 2022 [cited 2022 May 1]. Available from: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death.
19. Jaramillo-Correa JP, Keyeux G, Ruiz-García M, Rodas C, Bernal J. Population genetic analysis of the genes APOE, APOB(3'VNTR) and ACE in some black and Amerindian communities from Colombia. Hum Hered. 2001;52(1):14-33. https://doi.org/bp6pq8.
20. Forero DA, Pinzón J, Arboleda GH, Yunis JJ, Alvarez C, Cataño N, *et al.* Analysis of common polymorphisms in angiotensin-converting enzyme and apolipoprotein e genes and human longevity in Colombia. Arch Med Res. 2006;37(7):890-4. https://doi.org/crvztz.
21. Perdomo VA, Ortega DC, Barreto G. Polymorphisms of apolipoprotein E in the Afro-descendant population of Buenaventura, Colombia. Rev Colomb Psiquiatr (Engl Ed). 2020;51(2):99-104. https://doi.org/nfbq.
22. Ruiz M, Arias I, Rolón G, Hernández E, Garavito P, Silvera-Redondo C. Análisis del polimorfismo del gen APOE en la población de Barranquilla, Colombia. Biomedica. 2016;36(1):52-8. https://doi.org/nfbr.
23. Loango N, Gallego ML, Restrepo B, Landázuri P. Diferencias de sexo, edad y lípidos plasmáticos asociadas al polimorfismo de la apolipoproteína E en un grupo de escolares de Quindío, Colombia. Biomedica. 2009;29(3):382-91. https://doi.org/nfbs.
24. Rivera N, Perdomo VA, Barreto G. Frecuencias polimorficas del gen de Apolipoproteina E en el Valle del Cauca, Colombia. Revista de Ciencias. 2015;19(1):53-62. https://doi.org/nfbt.
25. Velez-Pardo C, Rojas W, Jimenez-Del Río M, Bedoya G. Distribution of APOE polymorphism in the "Paisa" population from northwest Colombia (Antioquia). Ann Hum Biol. 2015;42(2):195-8. https://doi.org/nfbv.
26. Rengifo L, Gaviria D, Serrano H. Polimorfismos del gen *ApoE* en individuos con síndrome de Down y sus progenitores en una población colombiana. Biomedica. 2012;32(2):224-32. https://doi.org/nfjj.
27. Sikand G, Severson T. Top 10 dietary strategies for atherosclerotic cardiovascular risk reduction. Am J Prev Cardiol. 2020;4:100106. https://doi.org/gqxjrp.
28. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972;18(6):499-502. https://doi.org/ghjc4x.
29. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. Circulation. 2002;106(25):3143-421. https://doi.org/c275.

30. World Medical Association (WMA). WMA Declaration of Helsinki – Ethical principles for medical research involving human subjects. Fortaleza: 64th WMA General Assembly; 2013.
31. Colombia. Ministerio de Salud. Resolución 8430 de 1993 (octubre 4): Por la cual se establecen las normas científicas, técnicas y administrativas para la investigación en salud. Bogotá D.C.; october 4 1993.
32. Chen XF, Wei Z, Wang T, Zhang ZL, Wang Y, Heckman MG, *et al.* Demographic and Lifestyle Characteristics, but Not Apolipoprotein E Genotype, Are Associated with Intelligence among Young Chinese College Students. PLoS One. 2015;10(11):e0143157. https://doi.org/nfc6.
33. Huang W, Zeng J, Jia L, Zhu D, O'Brien J, Ritchie C, *et al.* Genetic risks of Alzheimer's by *APOE* and *MAPT* on cortical morphology in young healthy adults. Brain Commun. 2023;5(5):fcad234. https://doi.org/nfc7.
34. Li X, Kaur Y, Wilhelm O, Reuter M, Montag C, Sommer W, *et al.* Resting-state brain signal complexity discriminates young healthy APOE e4 carriers from non-e4 carriers. Eur J Neurosci. 2023;57(5):854-66. https://doi.org/nfc8.
35. Lissaman R, Lancaster TM, Parker GD, Graham KS, Lawrence AD, Hodgetts CJ. Tract-specific differences in white matter microstructure between young adult APOE ε4 carriers and non-carriers: A replication and extension study. Neuroimage Rep. 2022;2(4):100126. https://doi.org/nfg4.
36. Doliner B, Dong C, Blanton SH, Gardener H, Elkind MSV, Sacco RL, *et al.* Apolipoprotein E Gene Polymorphism and Subclinical Carotid Atherosclerosis: The Northern Manhattan Study. J Stroke Cerebrovasc Dis. 2018;27(3):645-52. https://doi.org/nfhb.
37. Lioutas VA, Beiser AS, Aparicio HJ, Himali JJ, Selim MH, Romero JR, *et al.* Assessment of Incidence and Risk Factors of Intracerebral Hemorrhage Among Participants in the Framingham Heart Study Between 1948 and 2016. JAMA Neurol. 2020;77(10):1252-60. https://doi.org/gjjxhp.
38. Wu H, Huang Q, Yu Z, Wu H, Zhong Z. The SNPs rs429358 and rs7412 of APOE gene are association with cerebral infarction but not SNPs rs2306283 and rs4149056 of SLCO1B1 gene in southern Chinese Hakka population. Lipids Health Dis. 2020;19(1):202. https://doi.org/nfhf.
39. Peng W, Liu J, Chen G, Zheng M, Zhang L, Li A, *et al.* The correlation between ApoE gene polymorphism and non-ischemic chronic heart failure. Int J Clin Exp Med. 2017;10(12):16809-14.
40. Ghaznavi H, Kiani AA, Soltanpour MS. Association study between DNA methylation and genetic variation of APOE gene with the risk of coronary artery disease. Mol Biol Res Commun. 2018;7(4):173-9. https://doi.org/nfhj.
41. Stocker H, Trares K, Beyer L, Perna L, Rujescu D, Holleczek B, *et al.* Alzheimer's polygenic risk scores, APOE, Alzheimer's disease risk, and dementia-related blood biomarker levels in a population-based cohort study followed over 17 years. Alzheimers Res Ther. 2023;15(1):129. https://doi.org/nfhk.
42. Nuinoon M, Saiphak W, Nawaka N, Rattanawan C, Pussadhamma B, Jeenduang N. Association of *CELSR2*, *APOB100*, *ABCG5*/8, *LDLR*, and *APOE* polymorphisms and their genetic risks with lipids among the Thai subjects. Saudi J Biol Sci. 2023;30(2):103554. https://doi.org/nfhn.
43. Fan YY, Cai QL, Gao ZY, Lin X, Huang Q, Tang W, *et al.* APOE ε4 allele elevates the expressions of inflammatory factors and promotes Alzheimer's disease progression: A comparative study based on Han and She populations in the Wenzhou area. Brain Res Bull. 2017;132:39-43. https://doi.org/gbpz5v.
44. Lainampetch J, Panprathip P, Phosat C, Chumpathat N, Prangthip P, Soonthornworasiri N, *et al.* Association of Tumor Necrosis Factor Alpha, Interleukin 6, and C-Reactive Protein with the Risk of Developing Type 2 Diabetes: A Retrospective Cohort Study of Rural Thais. J Diabetes Res. 2019;2019:9051929. https://doi.org/nfht.
45. Hong N, Lin Y, Ye Z, Yang C, Huang Y, Duan Q, *et al.* The relationship between dyslipidemia and inflammation among adults in east coast China: A cross-sectional study. Front Immunol. 2022;13:937201. https://doi.org/nfh6.
46. Galvis-Pérez Y, Barona-Acevedo J, Cardona-Arias JA. Prevalencia de dislipidemias en una institución prestadora de servicios de salud de Medellín (Colombia), 2013. Rev CES Med. 2016;30(1):3-13.
47. Cardona-Arias JA. Prevalencia de factores de riesgo cardiovascular en indígenas de Riosucio-Caldas, 2010-2011. Medicina UPB. 2012;31:113-26.