

ORIGINAL ARTICLE

ANALYSIS OF THE RS10750097 AND RS3741298 POLYMORPHISMS OF THE APOA5 GENES IN RELATION TO DYSLIPIDEMIA

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Highlights:

- (1) The RS10750097 and RS3741298 polymorphisms did not influence the development of dyslipidemia.
- (2) The BMI of the military population studied highlights the need for an awareness-raising approach.
- (3) The study reinforces the influence of epigenetics in different populations.

ABSTRACT

Dyslipidemia is characterized by a disorder in lipid metabolism and arises from external causes or predisposing genetic disorders. This observational, cross-sectional study aimed to analyze the correlation between the genetic polymorphisms RS10750097 and RS3741298 associated with the lipoprotein ApoA5-ZNF259 and the development of dyslipidemia. A sample of 200 Military Police officers from the state of Goiás was used, and genotyping of the polymorphisms was performed. Regarding the participating individuals, 93% were male and 7% were female. The polymorphisms observed in the groups with and without dyslipidemia showed a significant difference between the two groups for all variables analyzed ($p < 0.05$). The present study found that the RS10750097 and RS3741298 polymorphisms did not increase the odds ratio of the dyslipidemia group actually having dyslipidemia (OR and 95% CI < 1), which corroborates with previously described studies in different populations. Therefore, the RS10750097 and RS3741298 polymorphisms did not influence the development of dyslipidemia within the variables involved in this study and in this population, despite being part of the SNP spectrum of the APOA5 ZNF 259 region. Thus, the influence of each population's epigenetics on the results is observed, and the need for similar research in other target groups is highlighted.

Keywords: Dyslipidemia; APOA5, ZNF, polymorphism, military, genes

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INTRODUCTION

Dyslipidemia is characterized as a disorder in lipid metabolism that usually arises from external causes such as a lifestyle associated with poor habits. However, it can also be caused by genetic disorders that predispose. According to the Brazilian Society of Cardiology, dyslipidemias are classified as phenotypic or biochemical (isolated hypercholesterolemia, isolated hypertriglyceridemia, mixed hyperlipidemia, and low HDL-C) and genotypic (monogenic and polygenic). In this context, the lipids involved in the genesis of dyslipidemias primarily include cholesterol and triglycerides, which require the action of specialized carriers to promote their body distribution.^{1,2,3,4}

Lipid metabolite carriers, better known as lipoproteins, are chemical components formed by lipids and protein structures known as apolipoproteins. Therefore, apolipoproteins can be subdivided into two groups. The first, APOB, is the protein responsible for the formation of VLDL (very low-density lipoprotein), IDL (intermediate-density lipoprotein), and LDL (low-density lipoprotein) particles, and is the main apoprotein of these atherogenic structures. The second is composed of APOAI, the main apoprotein of HDL (high-density lipoprotein), popularly known as “good cholesterol”.^{3,5,6,7}

Apolipoprotein APOA5-ZNF259, the fourth member of the gene cluster on chromosome 11, was identified near the APOA1/C3/A4 gene cluster, located at locus 11q23. APOA5-ZNF259 encodes a 369-amino acid protein expressed in the liver and secreted into plasma. HDL lipoprotein, as well as VLDL particles and chylomicrons, cluster APOA5-ZNF259, which was not identified in LDL. Furthermore, increased triglycerides and total cholesterol may be directly related to APOA5-ZNF259, which has sparked interest in further studies on the relationship of this apolipoprotein with body lipid alterations.^{1,2,6,8,9}

In this context, apolipoprotein APOA5-ZNF259 is associated with a series of single nucleotide polymorphisms (SNPs) that study genes and their regions associated with the possible genesis of dyslipidemias. Polymorphisms are genetic changes that can occur in non-coding or coding sequences and lead to variations in the proteins analyzed, which can result in favorable or unfavorable outcomes. Therefore, the polymorphisms highlighted in this study – RS10750097 and RS3741298 – of the APOA5 genes in the ZNF259 region are among those reported in a North American clinical trial that investigated a greater propensity for dyslipidemia, which primarily involves increased triglycerides and cholesterol fractions, as well as a greater risk of developing coronary artery disease. However, these events may not be related to all single nucleotide polymorphisms in different populations, since the influence of the environment is not the same in each of them, requiring detailed studies in different environments.^{2,9,10,11,12}

One of the main consequences of dyslipidemia is the formation of atherosclerotic plaques, which are formed by chronic inflammatory processes. In this sense, a determining factor in the onset of atherogenesis is the deposition of plasma lipoproteins in the subendothelial space, creating plaques capable of obstructing blood flow and impairing cardiopulmonary and, consequently, systemic function.^{3,4}

Polymorphisms occur randomly and can be analyzed alongside the risk of dyslipidemia in any environment and population. Therefore, Military Police officers are a valuable target group, given that police work is highly demanding, due to the long workload, risky situations inherent to the job, and the discipline required in the military environment. Furthermore, they have associated risk factors such as physical inactivity that facilitate the development of chronic metabolic disorders.^{13,14,15}

Thus, the objective of the present research was to relate the RS10750097 and RS3741298 polymorphisms with the presence of dyslipidemia in Military Police Officers in the State of Goiás, characterizing a new study group with different variables.

METHODOLOGY

This study analyzes the association between gene polymorphisms in the RS10750097 and RS3741298 regions of the ApoA5 lipoprotein (ZNF259) and the development of dyslipidemia in Military Police officers in the state of Goiás through a cross-sectional observational study. A sample of 200 active-duty military police officers with operational duties was used. Professionals who worked solely in administrative roles were excluded from the total sample of 861 individuals. The military were stationed in Goiás, but were not necessarily born solely in the state. Participants who reported taking medications related to dyslipidemia were not included in the study.

The study groups were categorized into the group with dyslipidemia: isolated hypercholesterolemia (LDL-C $\geq$ 160 mg/dL); isolated hypertriglyceridemia (triglycerides $\geq$ 150 mg/dL); mixed hyperlipidemia (LDL-C $\geq$ 160 mg/dL and triglycerides $\geq$ 150 mg/dL, if Tg $\geq$ 400 mg/dL, non-HDL-cholesterol $\geq$ 190 mg/dL is considered, instead of LDL-C); and HDL $<$ 40 mg/dL in men and $<$ 50 mg/dL in women; and the group without dyslipidemia: LDL cholesterol $<$ 130 mg/dL, triglycerides $<$ 150 mg/dL and HDL $>$ 60 mg/dL. 3 The overall mean age of the two groups was 41.6 years and the overall mean height was 1.74 m. Laboratory tests performed on the police officers were already available in a database and no more than 12 months prior to the analysis.

Blood samples were collected from the study participants for later genotyping of the APOA5-ZNF259 RS10750097 and RS3741298 SNPs. Descriptive statistics were performed, and the absolute and relative frequencies of the studied variables were determined, which involved the presence or absence of genetic polymorphisms, with changes in total cholesterol, triglycerides, LDL cholesterol, and HDL cholesterol levels. Frequency distribution and prevalence calculations were performed using GraphPad Prism version 9 software, using the Mann-Whitney test, with a 5% significance level. The odds ratio was calculated using the chi-square test.

The study was carried out in accordance with resolution 466/2012 and after being registered on the Plataforma Brasil with CAAE: 23551514.9.0000.5083, it was approved by the Research Ethics Committee of Hospital Dona Iris with opinion no. 608.207.

RESULTS

In this cross-sectional study, a sample of 200 participants was evaluated, with a predominance of male individuals, totaling 186 individuals, or 93% of the total evaluated. The majority of participants in the dyslipidemia group were over 40 years of age, corresponding to 68% of the total group. In the group without dyslipidemia, 50% of the population was under 40 years of age, while the remaining 50% was over 40 years of age. Total cholesterol levels differed significantly between the groups, with 68.1% of those with dyslipidemia having total cholesterol above 190 mg/dL, while only 23% of those without dyslipidemia had total cholesterol above 190 mg/dL. The other two discrepant variables between the groups were triglycerides and LDL, with the dyslipidemia group having higher fractions in both biochemical parameters. Regarding the base contingent in the polymorphism RS10750097, the two groups presented A/A and A/G majorities and in the RS3741298 polymorphism a T/T and C/T majority. All data are presented in tables 1 and 2.

Table 1 – Absolute and relative percentage frequencies of the established variables

Variables	With dyslipidemia (N = 116)		No dyslipidemia (N = 84)		Total (N = 200)	
	n	f (%)	n	f (%)	n	f (%)
Age (years)						
Up to 40	36	31.1	42	50	78	39
Over 40	80	68.9	42	50	122	61
Sex						
Male	109	93.9	77	91.7	186	93
Female	7	6.1	7	8.3	14	7
Total cholesterol (mg/dL)						
< 190	37	31.9	61	72.6	98	
> 190	79	68.1	23	27.4	102	
Triglycerides (mg/dL)						
< 150	21	18.1	84	100	105	52.5
> 150	95	81.9	0	0	95	47.5
HDL (mg/dL)						
< 40 (H) < 50 (M)	51	43.9	2	2.4	53	26.5
> 40 (H) > 50 (M)	65	56.1	82	97.6	147	73.5
N-HDL (mg/dL)						
< 190	69	59.5	84	100	153	76.5
> 190	47	40.5	0	0	47	23.5
LDL						
< 160	26	22.5	84	100	110	55
> 160	86	74.1	0	0	86	43
Indeterminate	4	3.4	0	0	4	2

Legend: HDL: high-density lipoprotein; LDL: low-density lipoprotein; n-LDL: non-low-density lipoprotein fractions.

Table 2 – Absolute and relative percentage frequencies of polymorphism alleles

Variables	With dyslipidemia (N = 116)		No dyslipidemia (N = 84)		Total (N = 200)	
	n	f (%)	n	f (%)	n	f (%)
RS10750097						
A/A	55	47.4	40	47.7	95	47.5
A/G	44	38	37	44	81	40.5
G/G	17	14.6	6	7.1	23	11.5
No information	0	0	1	1.2	1	0.5
RS3741298						
C/C	12	10.3	6	7.1	18	9
T/T	58	50	47	56	105	52.5
C/T	46	39.7	30	35.7	76	38
No information	0	0	1	1.2	1	0.5

Legend: A: alanine; C: cytosine; G: guanine; T: thymine.

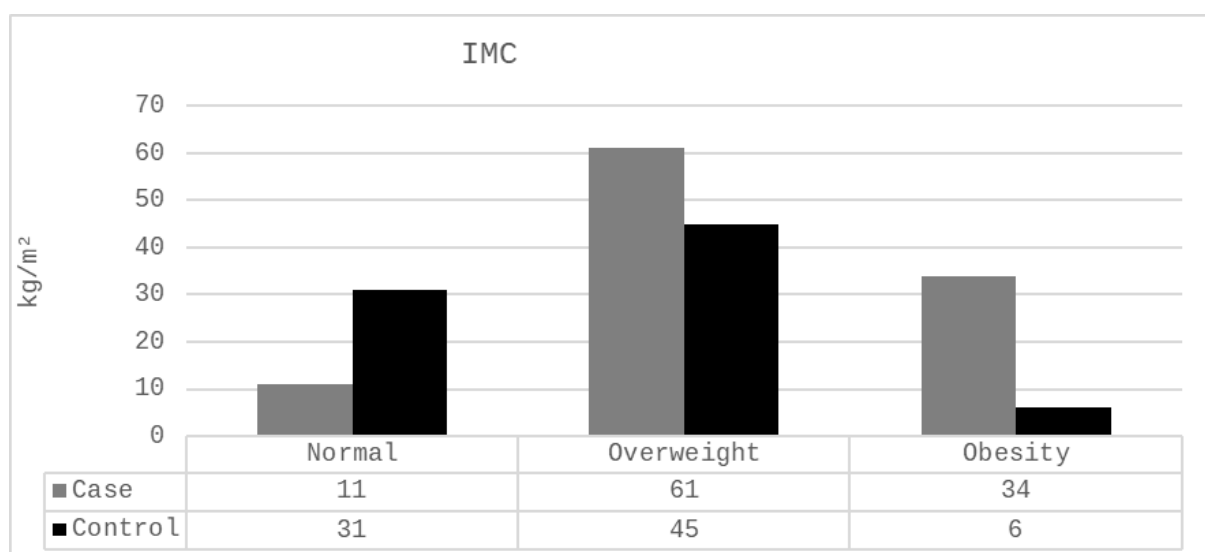
The variables total cholesterol, triglycerides, HDL, n-HDL, LDL, and weight showed statistical significance ($p < 0.05$) (Table 3).

Table 3 – Mean, standard deviation, range, and p-value of the established variables

Variables	With dyslipidemia (n=116)		No dyslipidemia (n=84)				
	Average	DP	Min-Max	Average	DP	Min-Max	P value
Total Cholesterol (mg/dL)	214.6	44.6	118-337	169.2	27.4	107-227	<0,0001
Tryglicerides (mg/dL)	270.2	192.2	63-1242	85.3	32.3	25-149	<0,0001
HDL (mg/dL)	42.3	8.2	25-66	51.3	9.3	40-102	<0,0001
N-HDL (mg/dL)	172.2	40.7	79-281	117.9	27.6	59-183	<0,0001
LDL	123.4	43.8	38,2-235,4	100.8	26.5	40,4-157,6	0.0002
Weight	87.6	13.2	60-155	77.9	10.2	51-101	<0,0001

Legend: n- number; HDL: high-density lipoprotein; N-HDL: non-high-density lipoprotein fractions; LDL: low-density lipoprotein; SD: standard deviation; Min: minimum; Max: maximum; P value < 0.05: p value considering a significance level of 5%.

Regarding the Body Mass Index (BMI), it was observed that both the group with dyslipidemia and the group without dyslipidemia had a majority of participants in the overweight range, with 52% and 53% respectively. The average BMI of military personnel with dyslipidemia is higher in all categories (Graph 1).



Graph 1 – BMI in the group with and without dyslipidemia.

Table 4 – Absolute and relative percentage frequencies of the RS10750097 polymorphism

Variables	With dyslipidemia						No dyslipidemia								95% IC	
	A/G		A/A		G/G		A/G		A/A (n=40)		G/G (n=6)					
	(n=44)		(n=55)		(n=17)		(n=37)						Inf	Sup		
	n	f%	n	f%	n	f%	n	f%	n	f%	n	f%	OR			
Total cholesterol																
<190	18	48.7	11	29.7	8	21.6	25	41.7	30	50	5	8.3				
>190	26	32.9	44	55.7	9	11.4	12	52.2	10	43.5	1	4.3	0.17	0.08 0.31		
Tryglicerides																
<150	4	19	14	66.7	3	14.3	37	44.6	40	48.2	6	7.2				
>150	40	42.1	41	43.2	14	14.7	0		0		0		0.0015 0.0001 0.02			
HDL																
<40 (M) <50 (F)	22	43.1	20	39.2	9	17.7	0	0	0	0	2	100				
>40 (M) >50 (F)	22		35		8		37	45.7	40	49.4	4	4.9	0.01 0.0007 0.19			
N-HDL																
<190	29	41.4	29	41.4	12	17.2	37	44.6	40	48.2	6	7.2				
>190	15	32.6	26	56.5	5	10.9	0		0		0		0.009 0.0005 0.15			
LDL																
<160	38	44.2	34	39.5	14	16.3	37	44.6	40	48.2	6	7.2				
>160	5	19.2	19	73	2	7.7	0	0	0	0	0	0	0.02 0.001 0.32			

Legend: n: number A: Alanine; G: Guanine; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; Non-HDL: Non-high-density lipoprotein fractions; 95% CI: Confidence interval with 5% margin of error; OR: Odds Ratio; P < 0.05: P-value considering a 5% significance level; Sup: upper limit. The values of the dominant gene A/G + A/A with recessive G/G were considered for comparison and statistical calculation purposes.

The RS10750097 polymorphism observed in the group with and without dyslipidemia reveals a significant difference between the two groups for all variables analyzed: Total cholesterol (p<0.001), Triglycerides (p<0.0001), HDL (p 0.002), non-HDL (p 0.001), and LDL (p 0.006). The same effect can also be observed when analyzing the RS 3741298 polymorphism for the same variables, corresponding to the same p values (Tables 3 and 4). However, when analyzing the 95% Confidence Interval and the Odds Ratio, it was shown that the odds ratio of dyslipidemia presenting alterations in the variables total cholesterol, triglycerides, HDL, non-HDL, and LDL due to the presence of the RS10750097 and RS3741298 polymorphisms does not exist, since both statistical parameters are below the calculated upper levels. The p-value highlighted a significant alternation since its calculation does not only evaluate the polymorphism, but also analyzes the comparison between what is normal and what is altered. The information will be presented in tables 4 and 5.

Table 5 – Absolute and relative percentage frequencies of the RS3741298 polymorphism

Variables	With dyslipidemia												No dyslipidemia												OR	95% ICInf	Sup
	C/T		T/T		C/C		C/T		T/T		C/C																
	(n=46)		(n=58)		(n=12)		(n=30)		(n=47)		(n=6)																
	n	f%	n	f%	n	f%	n	f%	n	f%	n	f%															
Total Cholesterol																											
<190	13	35.2	17	45.9	7	18.9	24	40	32	53.3	4	6.7															
>190	33	41.8	41	51.9	5	6.3	6	26.1	15	65.2	2	8.7	0.15	0.08	0.29												
Tryglicerides																											
<150	7	33.4	14	66.6	0		30	36.2	47	56.6	6	7.2															
>150	39	41	44	46.3	12	12.7	0		0		0		0.0017	0.0001	0.03												
HDL																											
<40 (M) <50 (F)	18	36	25	50	7	14	1	50	1	50	0																
>40 (M) >50 (F)	28	42.4	33	50	5	7.6	29	35.8	46	56.8	6	7.4	0.04	0.009	0.16												

N- HDL														
<190	25	31.3	46	57.5	9	11.2	30	36.2	47	56.6	6	7.2		
>190	21	45.7	22	47.8	3	6.5	0		0		0		0.01	0.0006 0.18
LDL														
<160	36	41.8	40	46.5	10	11.6	30	36.1	47	56.6	6	7.2		
>160	9	34.6	16	61.5	1	3.8	0	0	0	0	0	0	0.02	0.001 0.32

Legend: n: number; C: cytosine; G: guanine; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; Non-HDL: Non-high-density lipoprotein fractions; 95% CI: Confidence interval with 5% margin of error; OR: Odds Ratio; P < 0.05: p-value considering a 5% significance level; Sup: upper limit. For comparison and statistical calculation purposes, the values of the dominant gene C/T + T/T with the recessive C/C were considered.

DISCUSSION

Over the years, some studies have demonstrated the association of high triglyceride and LDL levels with an increased risk of atherosclerotic and cardiovascular disease in the affected population. In the present study, LDL above 160 mg/dL was observed in 74.1% of the group with dyslipidemia, while hypertriglyceridemia was observed in 81.9% of the same group, totaling more than 50% of samples in the group with dyslipidemia altered and prone to developing atherosclerotic processes. Yan Shi et al. (2016) , in a clinical trial conducted with 353 patients in China, found an association between hypertriglyceridemia and a higher chance of ischemic infarction related to small-vessel atherosclerotic processes (OR = 2.519, 95% CI = 1.174-5.405, p = 0.018).^{14,15,16}

A Spanish study demonstrated that overweight and obesity have practically doubled in prevalence since the 1980s, representing a major public health problem. Furthermore, a direct and significant association between overweight and obesity and dyslipidemia and metabolic syndrome was found. In the present study, 52% of the group with dyslipidemia and 53% of the group without dyslipidemia were overweight, corroborating the risk factors inherent to the military group, such as high workload and associated stress.¹⁷

The influence of genetic mechanisms on cholesterol metabolism is constantly being elucidated. APOA5 is a lipoprotein that plays a fundamental role in triglyceride and cholesterol metabolism. A deficiency of this lipoprotein or any alteration in its conformation leads to hypertriglyceridemia and increased LDL cholesterol. Brautbar A. et al.⁹; Forte & Ryan¹⁸ showed that single nucleotide polymorphisms correlate with metabolic alterations that interfere with APOA5 secretion and cholesterol metabolism, triglycerides and LDL. Do R. et al.¹⁹, in a study involving 9,600 participants, showed that APOA5 SNPs are correlated with early acute myocardial infarction.^{9,18,19}

The RS10750097 and RS3741298 polymorphisms are involved in the APOA5 SNP cluster in the ZNF-259 region. These genetic variants are considered common in the APOA5 gene but are not associated with increased frequency in the population with elevated triglycerides. An American study conducted in Texas found that only 26% of the population of 2,228 participants had these polymorphisms and elevated triglycerides.⁹

The present study determined that the RS10750097 and RS3741298 polymorphisms did not increase the odds ratio of cases presenting dyslipidemia (OR and 95% CI < 1). According to Brautbar A. et al.⁹, these two polymorphisms were only associated with improved HDL-C levels after implementation of dyslipidemia treatment with fenofibric acid and statins. However, no significant association of HDL levels related to the previously mentioned SNPs was observed. Only RS 3741298 was associated with elevated baseline triglyceride levels. Despite this, other APOA5 polymorphisms, such as rs964184, have already been shown to be associated with increased triglycerides and other dyslipidemic parameters. Xu C. et al. in 2013²⁰ already demonstrated the influence of some APOA5 polymorphisms on the development of metabolic syndrome with an OD of 1.33 in the general population, with no evidence for RS10750097 and RS3741298.^{2,9,20,21}

SNP genotypes can also influence dyslipidemic parameters. Mirhafez SR. et al.²³ demonstrated that the presence of the C/G and G/G genotypes in the APOA5-ZNF259 polymorphisms or the simple presence of the G allele in any genotype increases the patient's risk of developing metabolic syndrome in the future by 2.5%. Parra EJ. et. al.²² demonstrated that the presence of the G allele in the RS964184 polymorphism is associated with high triglyceride concentrations, and in the American study population, a 50% frequency of the G allele in the described SNP was observed. However, the same association was not observed in other polymorphisms.^{22,23}

In the present study, the predominance of the G allele was not observed in any of the polymorphisms analyzed, with a G/G frequency of 14.6% in the case group and 7.1% in the control group for the RS10750097 SNP, since RS3741298 did not present the G allele in any of its genotypes, which corroborates the lack of association between the propensity for dyslipidemia and the RS10750097 and RS3741298 polymorphisms.^{22,23}

Although no differences were found between the groups in some analyses in this study, it is important to explore understudied topics in specific populations that are distinct in genetic and environmental terms, filling gaps in the literature and expanding the understanding of genetic variations in different population contexts. It also consolidates previous knowledge and provides a basis for new hypotheses for future studies of other complex diseases.

CONCLUSION

Therefore, the RS10750097 and RS3741298 polymorphisms did not influence the development of dyslipidemia within the variables involved in this study and in this population, despite being part of the SNP spectrum of the APOA5 ZNF 259 region. Therefore, the influence of the epigenetics of each population on the results is observed, since in the group of Military Police Officers of the State of Goiás this association was not found, but it may be observed in another group with different characteristics in the future.

Furthermore, the high BMI found in the vast majority of the study population calls for a strong awareness-raising approach to changing habits and managing stress to contain the damage that leads to health problems among these police officers.

Finally, further research should be encouraged to study other populations that may have a genetic profile of the APOA5 RS10750097 and RS3741298 polymorphisms associated with dyslipidemia, which may lead to new therapeutic methodologies and medical approaches in the future.

REFERENCES

- ¹ The T-allele of the SMARCA4 gene has an apparent protective effect against high levels of total and LDL cholesterol. Genet Mol Res [Internet]. 2020;19(1). Available from: http://www.funpecrp.com.br/gmr/articles/year2020/vol19-1/pdf/gmr18479_-_t-allele-smarca4-gene-has-apparent-protective-effect-against-high-levels-total-and-ldl.pdf
- ² Silva R dos RF, Nascimento TL de, Silva AMTC, Costa SHN, Castro FS, Silva MAC, et al. APOA5 gene polymorphism assessment and association with hypertriglyceridemia in the military force of the State of Goiás. Res Soc Dev [Internet]. 2021 June 14;10(7):e8410716229. Available from: <https://rsdjournal.org/index.php/rsd/article/view/16229>
- ³ Xavier HT, Izar MC, Faria Neto JR, Assad MH, Rocha VZ, Sposito AC, et al. [V Brazilian Guidelines on Dyslipidemias and Prevention of Atherosclerosis]. Arq Bras Cardiol [Internet]. 2013;101(4 Suppl 1):1-20. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24217493>
- ⁴ Liu Y, Zhou D, Zhang Z, Song Y, Zhang D, Zhao T, et al. Effects of genetic variants on lipid parameters and dyslipidemia in a Chinese population. J Lipid Res [Internet]. 2011 Feb;52(2):354-360. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21149302>

- ⁵ Diabetes Canada Clinical Practice Guidelines Expert Committee, Mancini GBJ, Hegele RA, Leiter LA. Dyslipidemia. Can J diabetes [Internet]. 2018 Apr.;42 Suppl 1: S178-85. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/29650093>
- ⁶ Lazzaretti RK. Marcadores genéticos associados à dislipidemia e redistribuição de gordura corporal em indivíduos infectados pelo HIV em Terapia Antirretroviral. 2012. Available from: <http://hdl.handle.net/10183/76190>
- ⁷ Karásek D. Biologic therapy for dyslipidemia. Vnitr Lek [Internet]. 2021;67(4):206-211. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/34275305>
- ⁸ Chen YQ, Pottanat TG, Zhen EY, Siegel RW, Ehsani M, Qian Y-W, et al. ApoA5 lowers triglyceride levels via suppression of ANGPTL3/8-mediated LPL inhibition. J Lipid Res [Internet]. 2021;62:100068. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/33762177>
- ⁹ Brautbar A, Covarrubias D, Belmont J, Lara-Garduno F, Virani SS, Jones PH, et al. Variants in the APOA5 gene region and the response to combination therapy with statins and fenofibric acid in a randomized clinical trial of individuals with mixed dyslipidemia. Atherosclerosis [Internet]. 2011 Dec.;219(2):737-742. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21889769>
- ¹⁰ Fu Q, Tang X, Chen J, Su L, Zhang M, Wang L, et al. Effects of Polymorphisms in APOA4-APOA5-ZNF259-BUD13 Gene Cluster on Plasma Levels of Triglycerides and Risk of Coronary Heart Disease in a Chinese Han Population. PLoS One [Internet]. 2015;10(9):e0138652. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26397108>
- ¹¹ Xu X, Li Y, Huang Y, Ye H, Han L, Ji H, et al. Impact of gender and age on the association of the BUD13-ZNF259 rs964184 polymorphism with coronary heart disease. Anatol J Cardiol [Internet]. 2018 Jan.;19(1):42-49. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/29339699>
- ¹² Perez-Martinez P, Corella D, Shen J, Arnett DK, Yiannakouris N, Tai ES, et al. Association between glucokinase regulatory protein (GCKR) and apolipoprotein A5 (APOA5) gene polymorphisms and triacylglycerol concentrations in fasting, postprandial, and fenofibrate-treated states. Am J Clin Nutr [Internet]. 2009 Jan.;89(1):391-399. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19056598>
- ¹³ Chen X, Leng L, Yu H, Yang X, Dong G, Yue S, et al. Psychological distress and dyslipidemia in chinese police officers: a 4-year follow-up study in Tianjin, China. J Occup Environ Med [Internet]. 2015 Apr.;57(4):400-405. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25629802>
- ¹⁴ Packard CJ, Boren J, Taskinen M-R. Causes and Consequences of Hypertriglyceridemia. Front Endocrinol (Lausanne) [Internet]. 2020;11:252. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/32477261>
- ¹⁵ Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J [Internet]. 2020 Jan. 1;41(1):111-188. Available from: <https://academic.oup.com/eurheartj/article/41/1/111/5556353>
- ¹⁶ Shi Y, Guo L, Chen Y, Xie Q, Yan Z, Liu Y, et al. Risk factors for ischemic stroke: differences between cerebral small vessel and large artery atherosclerosis aetiologies. Folia Neuropathol [Internet]. 2021;59(4):378-385. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/35114778>
- ¹⁷ Ramón-Arbués E, Martínez-Abadía B, Gracia-Tabuenca T, Yuste-Gran C, Pellicer-García B, Juárez-Vela R, et al. [Prevalence of overweight/obesity and its association with diabetes, hypertension, dyslipidemia and metabolic syndrome: a cross-sectional study of a sample of workers in Aragón, Spain]. Nutr Hosp [Internet]. 2019 March 7;36(1):51-59. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/30834762>
- ¹⁸ Forte TM, Ryan RO. Apolipoprotein A5: Extracellular and Intracellular Roles in Triglyceride Metabolism. Curr Drug Targets [Internet]. 2015;16(12):1274-1280. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26028042>
- ¹⁹ Do R, Stitzel NO, Won H-H, Jørgensen AB, Duga S, Angelica Merlini P, et al. Exome sequencing identifies rare LDLR and APOA5 alleles conferring risk for myocardial infarction. Nature [Internet]. 2015 Feb. 5;518(7537):102-106. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25487149>
- ²⁰ Xu C, Bai R, Zhang D, Li Z, Zhu H, Lai M, et al. Effects of APOA5 -1131T>C (rs662799) on Fasting Plasma Lipids and Risk of Metabolic Syndrome: Evidence from a Case-Control Study in China and a Meta-Analysis. Crawford DC, editor. PLoS One [Internet]. 2013 Feb. 28;8(2):e56216. Available from: <https://dx.plos.org/10.1371/journal.pone.0056216>
- ²¹ Novotny D, Vaverkova H, Karasek D, Malina P. Genetic variants of apolipoprotein A5 T-1131C and apolipoprotein e common polymorphisms and their relationship to features of metabolic syndrome in adult dyslipidemic patients. Clin Biochem [Internet]. 2014 Aug.;47(12):1015-1021. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24709297>
- ²² Parra EJ, Mazurek A, Gignoux CR, Sockell A, Agostino M, Morris AP, et al. Admixture mapping in two Mexican samples identifies significant associations of locus ancestry with triglyceride levels in the BUD13/ZNF259/

APOA5 region and fine mapping points to rs964184 as the main driver of the association signal. PLoS One [Internet]. 2017;12(2):e0172880. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/28245265>

- ²³ Mirhafez SR, Avan A, Pasdar A, Khatamianfar S, Hosseinzadeh L, Ganjali S, et al. Zinc Finger 259 Gene Polymorphism rs964184 is Associated with Serum Triglyceride Levels and Metabolic Syndrome. Int J Mol Cell Med [Internet]. 2016;5(1):8-18. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/27386434>

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