Genetics and the Mediterranean Diet: What is the Risk for Age-Related Macular Degeneration?

Genética e Dieta Mediterrânica: Qual o Risco para a Degenerescência Macular da Idade?

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ABSTRACT

INTRODUCTION: Age-related macular degeneration is a degenerative disease of the macula responsible for severe vision loss. It is a multifactorial and complex disease, with genetics, lifestyle and environmental factors contributing for its establishment and progression. The adherence to the Mediterranean diet has been suggestive of being protective for disease, but the evidence on the interaction between diet and genetics is scarce.

With this work, we intend to assess the effect of the adherence to the Mediterranean diet on age-related macular degeneration stratified by the genetic risk score, in a well-characterized Portuguese population.

METHODS: Participants performed ophthalmological exams and answered a validated food and a lifestyle questionnaire. The adherence to the Mediterranean diet was assessed with mediSCORE, a score ranging from 0 (low adherence) to 9 (high adherence). The score was determined individually for each participant, as the sum of the score of 9 food groups in which the food items from questionnaire were organized. A cut-off value of ≥ 6 was used as high adherence. Grading was performed using Rotterdam Classification. Participants' genotyping was performed in collaboration with The European Eye Epidemiology Consortium. The Genetic Risk Score was calculated for each participant considering the number of alleles at each variant and their effect size. Odds ratio (OR) for the adherence to the Mediterranean diet within strata of high and low genetic risk score were calculated, adjusted for age, sex, physical exercise, and smoking.

RESULTS: People at high genetic risk for age-related macular degeneration benefited from adhering to the Mediterranean diet with a 60%-risk reduction (OR=0.386, 95%CI 0.182-0.821, p=0.013). For subjects with low genetic risk (OR=0.435, 95% CI 0.177-1.072, p=0.070), a risk reduction was also seen, but not significantly. In subjects with a high genetic risk, age increased the risk of having AMD in a 2- and 3 time-fold, for ages 70-75 (p=0.034) and over 75 (p<0.001), respectively.

The same was seen for smoking (OR=2.165), though not significantly (p=0.068). Performing physical exercise presented as a protective factor (OR=0.564, p=0.035).

CONCLUSION: Genetics and Mediterranean diet interact to cause age-related macular degeneration, suggesting there is an interplay between genetics and lifestyle factors.

KEYWORDS: Diet, Mediterranean; Life Style; Macular Degeneration/diet therapy; Macular Degeneration/genetics; Portugal; Risk Factors.

RESUMO

INTRODUÇÃO: A degenerescência macular da idade (DMI) é uma doença degenerativa da mácula, responsável por perda de visão grave. Factores genéticos e ambientais podem contribuir para a doença. Alguns estudos já sugeriram que a dieta mediterrância pode ser protectora da doença, mas o estudo da interacção entre a dieta e a genética é limitado.

O nosso objetivo foi avaliar o efeito da adesão à dieta mediterrânica na DMI, estratificado por risco genético para a doença, numa população portuguesa bem caracterizada.

MÉTODOS: Os participantes fizeram exames oftalmológicos e responderam a questionários de frequência alimentar e de estilo de vida. A adesão à dieta mediterrânica foi medida com o mediSCORE, que varia entre 0 (baixa adesão) e 9 (alta adesão). O valor total do mediSCORE foi calculado individualmente, como a soma dos valores dos 9 grupos alimentares nos quais os alimentos do questionário foram organizados. Um valor de *cut-off* ≥6 foi utilizado para determinar adesão alta. A classificação das imagens foi feita com a Classificação de Roterdão. A análise genética foi realizada em colaboração com The European Eye Epidemiology Consortium. O risco genético foi calculado com um *score*, individualmente, considerando o número de alelos de cada variante e o seu tamanho de efeito. Foram calculados os *odds ratio* (OR) para a desão à dieta mediterrância estratificados por risco genético, ajustados à idade, sexo, exercício físico e hábitos tabágicos.

RESULTADOS: Os participantes com alto risco genético para a DMI beneficiaram da alta adesão à dieta mediterrânica, com uma redução de cerca de 60% no risco (OR=0,386, 95%CI 0,182-0,821, p=0,013). Os participantes com baixo risco genético apresentaram uma redução no risco, mas não estatisticamente significativa (OR=0,435, 95% CI 0,177-1,072, p=0,070). Nos participantes com alto risco genético, a idade aumentou o risco de DMI em 2 a 3 vezes, nos intervalos 70-75 anos (p=0,034) e >75 anos (p<0,001), respectivamente. Hábitos tabágicos aumentaram o risco (OR=2,165), não significamente (p=0,068). O exercício físico foi protector para a doença (OR=0,564, p=0,035).

CONCLUSÃO: A genética e a dieta mediterrânica interagem para o aparecimento da DMI, sugerindo que diferentes factores de risco, ambientais e genéticos, podem associar-se no desenvolvimento do risco para a doença.

PALAVRAS-CHAVE: Degenerescência Macular/dietoterapia; Degenerescência Macular/genética; Dieta Mediterrânica; Estilo de Vida; Factores de Risco; Portugal.

INTRODUCTION

Age-related macular degeneration (AMD) is the leading form of severe vision loss in people aged 55 or more in western countries. The prevalence of AMD has been estimated in 8.69%, expected to increase due to the aging of the population.[1]

Age-related macular degeneration is a complex and multifactorial disease, with different factors being associated with the risk for disease or the disease progression. Genetics, age and active smoking habits are well accepted risk factors, but others, such as cardiovascular risk problems, sun exposure and an unhealthy diet have also been associated.[2–4] Of outstanding importance, Mediterranean diet has been regarded as protective for AMD,[5–11] as it has been in other diseases, such as cardiovascular[12,13] neurological[14] and oncological.[15] As so, genetics and Mediterranean diet are of particular interest. There are 52 SNPs distributed for 34 loci that have been well associated with AMD, and this is unchangeable.[4] Maintaining a healthy lifestyle, including adhering to a Mediterranean diet, is optional and a decision made by each patient who, even genetically at risk, may have the chance to alter its disease course.

Few studies have assessed the interaction between ge-

netics and the adherence to the Mediterranean diet with conflicting results. While some show no association between the genetic profile and the adherence to the Mediterranean diet, others showed that this association was beneficial either for high-genetic risk profiles, low-genetic risk profiles or just related with specific single nucleotide polymorphisms (SNPs).[7–10]

The objective of this work was to assess the effect of the adherence to the Mediterranean diet on AMD stratified by the genetic risk score (GRS), in a well-characterized Portuguese population.

MATERIAL AND METHODS

THE STUDIES

These results are based on the Five-year Incidence of Age-related Macular Degeneration in the Central Region of Portugal Study (NCT02748824), in the Mira cohort, and the Food Habits Questionnaire in the Portuguese Population Aged 55 or more Study (NCT01715870). Both studies are population-based and cross sectional and part of the Coimbra Eye Study.

The studies complied with the tenets of the Declaration of Helsinki and International Conference on Harmonization - Good Clinical Practice Guidelines. The studies obtained AIBILI's Ethics Committee approval. Patients signed the informed consent before performing any study procedures and were explained of possible consequences.

PROCEDURES

Patients performed different ophthalmological exams: best-corrected visual acuity with Early Treatment Diabetic Retinopathy Study (ETDRS) charts, colour fundus photography (CFP) (Topcon® fundus camera, TRC-NW8; Topcon Corp., Tokyo, Japan), Spectral Domain Optical Coherence Tomography (SD-OCT), fundus autofluorescence (FAF), and Infra-Red (IR) imaging (Spectralis HRA+OCT Heidelberg Engineering, Heidelberg, Germany). Additionally, patients were assessed by an ophthalmologist and collected blood for genetic analysis. A trained nurse collected the clinical data and performed the food and lifestyle habits questionnaires. The lifestyle questionnaire regarded data on demographics, weight, height and abdominal perimeter, educational, smoking habits, physical activity, and cardiovascular comorbidities. The food questionnaire, which is validated for the Portuguese population,[16] is composed of 86 items (dairies, eggs and meat and fish, oils and fats, bread and cereals, sweets and pastries, legumes, fruits and beverages and miscellaneous). For each food item, patients were asked the intake frequency (never or less than 1 time/month, 1-3 times/month, 1 time/week, 2-4 times/week, 5-6 times/week, 1 time/day, 2-3 times/day, 4-5 times/day, 6 or more times/day), as well as the average serving size and whether the food item was seasonal.

Each food item intake was calculated as the average daily consumption, adjusted for the serving size, in grams. In case of seasonal intake, a value of 0.25 was considered to weight, representing a period of 3 months.

ASSESSMENT OF PARTICIPANTS PHENOTYPE

The worst eye from each participant was used for grading and assess AMD phenotype. The grading procedures of the exams was performed by certified ophthalmologists at CORC (Coimbra Ophthalmology Reading Centre, AIBILI, Portugal. When available, the grading of the two eyes was considered for this analysis.

DEFINITION OF CASES AND CONTROLS AND STUDY SUBJECTS

The five-year Incidence of age-related macular degeneration in the Central Region of Portugal Study used the Rotterdam Classification.[17,18] Cases were determined as participants staged 2a (soft, indistinct or reticular drusen) and 2b (soft, distinct drusen with pigmentary irregularities), 3 (soft, indistinct drusen with pigmentary irregularities) and 4 (geographic atrophy or choroidal neovascularization). Controls were considered participants staged 0 (no AMD or drusen <63 μm), above 60 years old, and stage 1 (soft, distinct drusen or pigmentary irregularities) and above 70 years old. The cut-off vale of age was used to assure participants graded as controls would not progress to AMD in the future.

Genotyping and Genetic Risk Score:

The genetic analysis of the study participants was performed under the scope of the EYERISK project, in collaboration with the E3 - The European Eye Epidemiology Consortium, using a single-molecule molecular inversion probe and next generation sequencing to target SNPs and coding and splice-site regions of 10 AMD-related genes (*ARMS2*, *C3*, *C9*, *CD46*, *CFB*, *CFH*, *CFI*, *HTRA1*, *TIMP3* and *SLC16A8*) and 3 genes associated with inherited macular dystrophies (*ABCA4*, *CTNNA1*, and *PRPH2*). Ten SNPs were genotyped by KASP genotyping assays to ensure a full genotyping of the 52 variants identified by the International AMD Genomics Consortium (IAMDGC). Sixty-nine SNPs[4] were successfully genotyped. Information specific to the genetic procedures can be found elsewhere.[19]

The GRS was calculated individually, considering the number of risk alleles, and their effect size from the genome-wide association study (GWAS) of the IAMDGC fully conditioned analysis, as follows: To calculate the GRS, participants had to present all major risk variants (*CFH* rs570618, *CFH* rs10922109, *C2*/*CFB*/*SKIV2L* rs429608, *ARMS2*/*HTRA1* rs3750846 and *C3* rs2230199). Should one or more of these variants be missing, the GRS was considered null. A high GRS was considered equal or superior to the median GRS of the population.

No data imputation was performed.

ASSESSMENT OF ADHERENCE TO THE MEDITERRANEAN DIET - MEDISCORE

A validated score, mediSCORE,[20] was used to evaluate the level of adherence to the Mediterranean diet. This score groups the items from the food questionnaire into nine broader groups: vegetables, legumes, fruits, cereals, fish, meat, dairies, alcohol, and a ratio of monounsaturated lipids (mainly olive oil) to saturated lipids (fats). It attributes a value of 0 or 1, according to the sex-specific food item median consumption, in grams, of the Mira cohort population, assessed in the food questionnaire. MediSCORE considers vegetables, legumes, fruits, cereals, and fish healthy groups. For these groups, consumption above the sex-specific median was consigned with the value 1. Meat and dairies are considered deleterious and, as so, consumption above the median was consigned with the value 0. Alcohol and fat have a different assessment. For alcohol, the value of 1 was attributed to consumptions ranging from 10 to 50 g/day for men and from 5 to 25 g/day for women, considered not prejudicial. As for fat, a ratio of monounsaturated/saturated lipids was considered beneficial if above the sex-specific median consumption and assigned the value of 1.

For each participant, either case or control, a value ranging between 0 and 9 was calculated, as the sum of the score of each of the 9 food groups from mediSCORE. As the third tercile of our sample's distribution of the mediSCORE was close to the value 6, we determined a cut-off value of ≥6 as a high adherence to the Mediterranean diet.

Table 1 presents the cut-off values used to assess a beneficial or detrimental consumption of each food group of the MediSCORE.

STATISTICAL ANALYSIS

Cases and control were compared. Mann-Whitney U Test was used for variables continuous and Pearson's chi-squared test (or Fisher's exact test) were used for categorical variables. Categorical variables were presented with absolute frequency and percentage and continuous variables were presented with mean and standard deviation.

A logistic regression model was used to assess the association of the adherence to the Mediterranean diet (mediSCORE) and the genetic susceptibility (GRS) with AMD. To take into account the correlations between eyes from the same patient, Generalized Estimating Equations (GEE) were used. The analysis was adjusted for age, sex, smoking and physical exercise.

Significance level was set to 0.05. Statistical analyses were performed using Stata (16.1, StataCorp LLC, College Station, TX) and R Statistical Software (v4.0.2; R Core Team 2020).

RESULTS

GENERAL

A total of 612 participants, with 161 cases and 451 con-

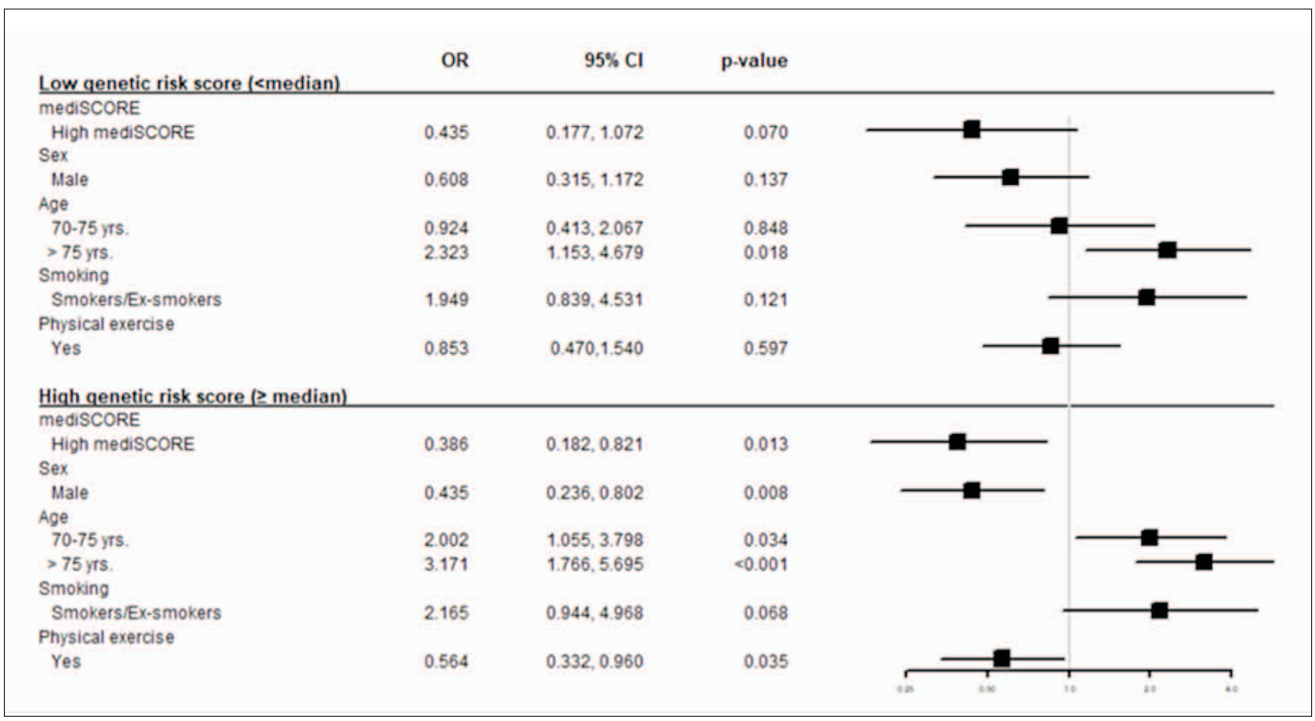

Figure 1. Forest plot for the effect of the adherence to the Mediterranean diet on AMD stratified by the gene tic risk score (GRS), adjusted for age, sex, physical exercise and smoking.
ORs (95% CIs) were estimated by using logistic regression model with generalized estimating equations (GEE) with individual eye as the unit of analysis, adjusted for age, sex, smoking and physical exercise.
AMD – age-related macular degeneration; OR – odds ratio; CI – confidence Interval; GRS – Genetic Risk Score; mediSCORE - adherence to the Mediterranean Diet score.

Table 1. Scoring system for the model of adherence to the Mediterranean diet (mediSCORE) – sex-specific medians are presented for the coastal town (Mira n=1008).

mediSCORE	Cut-off for 0		Cut-off for 1	
	Women	Men	Women	Men
Vegetables[a], g/day	< 204.4	< 211.2	≥ 204.4	≥ 211.2
Legumes[b], g/day	< 37.9	< 38.7	≥ 37.9	≥ 38.7
Fruits and nuts[c], g/day	< 280.6	< 287.6	≥ 280.6	≥ 287.6
Cereals[d], g/day	< 233.3	< 257.3	≥ 233.3	≥ 257.3
Fish[e], g/day	< 154.0	< 163.3	≥ 154.0	≥ 163.3
Dairy products[f], g/day	> 254.0	> 261.1	≤ 254.0	≤ 261.1
Meat[g], g/day	> 78.6	> 93.5	≤ 78.6	≤ 93.5
Alcohol[h], g/day	<5 or >25	<10 or >50	5-25	10-50
Ratio of monounsaturated lipids / saturated lipids	< 1.8	< 1.7	≥ 1.8	≥ 1.7

[a]Cabbage (5 types), broccoli, cauliflower, brussels sprouts, rapini, turnip greens, spinach, green beans, green peas, lettuce, cress, onions, carrots, turnip, fresh tomatoes, green and red peppers, cucumber; [b]Peas, beans (red, brown, fava, etc), chickpeas, lupins, lentils; [c]Apples, pears, oranges, tangerines, bananas, kiwis, strawberries, cherries, peaches, plums, melons, watermelons, figs, loquats, apricots, nuts; [d]Bread (wheat, rye, barley, whole or in mixtures), oats, corn bread, direct derivatives (corn flakes), rice, potato; [e]Fat and lean fishes, codfish, fish preserves, squid, octopus, shellfish; [f]Milk (whole, half or skimmed), yoghurts, cheese, ice creams, dairy-based desserts; [g]Chicken, rabbit, turkey, cow, pork, goat, meat derivatives (ham and similar, bacon, sausages); [h]Wine, beer, spirits.

Table 2. General characteristics (demographic, behavioural and genetic) between cases and controls

	Cases (N = 161)	Controls (N = 451)	*p*-value
Gender, N (%)			0.120
Female	101.0 (62.7%)	251.0 (55.7%)	
Male	60.0 (37.3%)	200.0 (44.3%)	
Age, mean (SD)	74.8 (6.8)	71.8 (6.4)	**<0.001**
Smoking, N (%)			0.600
Non-smoker	136.0 (84.5%)	386.0 (86.0%)	
Smoker/Ex-smoker	25.0 (15.5%)	63.0 (14.0%)	
Obesity, N (%)			0.140
BMI < 25 kg/m^2	47.0 (29.4%)	106.0 (23.5%)	
BMI ≥ 25 kg/m^2	113.0 (70.6%)	345.0 (76.5%)	
Educational status, N (%)			0.200
Basic education	136.0 (84.5%)	382.0 (84.7%)	
High school	10.0 (6.2%)	36.0 (8.0%)	
Higher education	3.0 (1.9%)	16.0 (3.5%)	
Without education	12.0 (7.5%)	17.0 (3.8%)	
Physical exercise, N (%)			0.008
No	104.0 (64.6%)	237.0 (52.5%)	
Yes	57.0 (35.4%)	214.0 (47.5%)	
Genetic Risk Score, N (%)			**<0.001**
Low GRS	62.0 (38.5%)	244.0 (54.1%)	
High GRS	99.0 (61.5%)	207.0 (45.9%)	
mediSCORE, N (%)			**<0.001**
High	15.0 (9.3%)	105.0 (23.3%)	
Low	146.0 (90.7%)	346.0 (76.7%)	

Bold values represent statistically significant differences between cases and controls with p > 0.05, using the Pearson's Chi-squared test (or Fisher´s exact test, when appropriate) for categorical variables and the Mann-Whitney U Test for continuous variables.

SD – standard deviation; BMI – body mass index; GRS – Genetic Risk Score; mediSCORE - adherence to the Mediterranean diet score

trols, were genotyped, presented all major variants and completed the food and lifestyle questionnaire,

We first compared cases and controls to characterize our population. Demographic, behavioural, and genetic characteristics comparison is presented in Table 2.

Controls were younger (p<0.001), performed more physical exercise (p=0.008), presented a higher mediSCORE value (p<0.001) (ie, a higher adherence to the Mediterranean diet) and presented a lower GRS (p<0.001).

The distribution of the GRS is significantly different between cases and controls (1.173 ± 1.984 for cases and 0.640 ± 1.083 for controls, p<0.001), ranging from -2.905 to 5.526 in cases and from -1.717 to 4.737 in controls (data not shown).

INTERACTION BETWEEN GRS AND ADHERENCE TO THE MEDITERRANEAN DIET

The association between mediSCORE and AMD within strata of the GRS is depicted as a forest plot in Fig. 1.

A 60%-risk reduction in AMD (OR=0.386, 95%CI 0.182-0.821, p=0.013) was seen for high GRS subjects, whereas for low-GRS subjects, a risk reduction was also seen, but not statistically significant (OR=0.435, 95% CI 0.177-1.072, p=0.070).

As for age, as expected, the risk of having AMD was 2- to 3 times superior in intervals 70-75 (p=0.034) and over 75 (p<0.001), in participants genetically at risk for AMD. The same results were seen for smoking (OR=2.165), though not significantly (p=0.068). Performing physical exercise presented as a protective factor (OR=0.564, p=0.035) for AMD.

DISCUSSION AND CONCLUSION

The Mediterranean diet is considered a healthy dietary pattern, and has been broadly studied in different areas, such as oncology,[15] neurology[14] and cardiovascular.[13] In ophthalmology, it has been previously reported as protective for AMD or AMD progression, as it is rich in antioxidants, unsaturated fats, lutein and zeaxanthin,[23,24] that can act as an-

tithrombotic and anti-inflammatory.[25,26] One of the pathways of AMD pathophysiology is oxidative stress, that may lead to mitochondrial dysfunction and, hence, to the loss of photoreceptors, accumulation of cellular debris and macular atrophy, which are disease drivers. Antioxidants, fatty acids and carotenoids (lutein and zeaxanthin) contribute for the integrity of the retinal membrane of the photoreceptors and the balance of the redox system to physiologic levels.[27–29]

In our study, the genetic profile altered the benefit of the Mediterranean diet in protecting against AMD. People with a high genetic risk significantly benefited more from adhering to the Mediterranean diet, with a decrease in the risk of about 61%, whereas low-risk genetic subjects did not. These results comply with those of Merle *et al*[7] that showed a statistically significant protective effect of Mediterranean diet in the progression of AMD in those people genetically at risk, in the Age-related Eye Disease Study (AREDS) population. Additionally, in both studies, ours and Merle's, people with a low genetic risk for AMD showed to be protected for AMD or progression, but not at a statistically significant level, which highlights the role of genetics interacting with the Mediterranean diet. Other studies have shown comparable results. The EYE-RISK Consortium has assessed the association of lifestyle and genetics, lifestyle meaning the absence of smoking habits and high intake of vegetables, fruits and fish, which resembles part of a Mediterranean diet.[30] In spite of the gain of a healthy lifestyle in the general population in reducing the risk for AMD, the gain was higher in people with a higher GRS. Equally, the risk for late AMD was superior in people genetically at risk with an unhealthy lifestyle. Other studies presented similar results, evidencing antioxidants and omega 3 fatty acids reduced the risk of early AMD and geographic atrophy in people with high genetic risk for AMD conferred by the SNPS *CFH* rs1061170 and *ARMS 2* rs10490924.[31,32] Once again, antioxidants and omega 3 fatty acids are nutrients present in the Mediterranean diet, which confer beneficial properties. We also report that performing physical exercise was protective for the risk AMD in people at genetic risk. Combined, these pieces of evidence show that the benefit of a healthy lifestyle, and particularly Mediterranean diet, can be altered by genetic susceptibility, which leads to a personalized approach in non-pharmacological therapies. We would like to highlight the strengths of our study. This is the first and only study in the Portuguese population to assess the interaction of two factors. Additionally, we defined the GRS based on the 52 variants, rare and common, identified by IAMDGC,[4] which is the hallmark of AMD genetics, against 10 SNPs that defined the GRS in Merles' study. Also, our population was well phenotyped, with multimodal grading performed by trained ophthalmologists and we used a validated food questionnaire and a validated score to assess the adherence to the Mediterranean diet.

We also must acknowledge that our study has limitations, like the relatively small sample and the fact that we are studying a cohort of a specific region of Portugal, which may shape the genetic analysis.

In conclusion, our results suggest that assessing the individual genetic risk for disease may be relevant in the assessment of non-pharmacological strategies in the protection of AMD from a personalized medicine point of view. This gains particular interest in the cases of non-pharmacological strategies relying on modifiable risk factors, easily changeable, to delay AMD or its progression.

PRESENTATIONS:

This work was presented at ARVO 2021 (poster) and EURETINA 2022 (oral presentation).

CONTRIBUTORSHIPS TATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO:

PB: Design and elaboration of the article
CF, RC: Analysis, data interpretation and critical review
MLC, JBM, YL, CBH, JCB, RS: Critical review
All authors read and approved the final version

RESPONSABILIDADES ÉTICAS

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

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Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pela Comissão de Ética responsável e de acordo com a Declaração de Helsínquia revista em 2013 e da Associação Médica Mundial.

Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

ETHICAL DISCLOSURES

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.

Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as

revised in 2013).

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