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Title: Adherence to a Mediterranean diet, lifestyle and age-related macular degeneration

Running title: Adherence to a Mediterranean diet and AMD

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Abbreviations used: AMD, age-related macular degeneration; aMeDi, alternate Mediterranean diet score; AREDS, Age-Related Eye Disease Study; ARMS2, age-related maculopathy susceptibility 2; *BCVA,* best-corrected visual acuity; BMI, body mass index; CFH, complement factor H; ICGS, *International Classification and Grading System for ARM and AMD;* mediSCORE, adherence to the Mediterranean diet score; VEGF, vascular endothelial growth factor.

ABSTRACT

BACKGROUND. Age-related macular degeneration (AMD) is the main cause of irreversible blindness in the elderly in developed countries and is known to be influence by nutritional factors.

OBJECTIVE. To characterize the lifestyle and nutritional risk profile in a Portuguese population with and without AMD.

METHODS. This study was designed as an extension to the Coimbra Eye Study, an epidemiologic, population-based, cross-sectional and observational study. It included 883 subjects, among whom 449 with early AMD and 434 without AMD. All underwent a full risk assessment, including lifestyle-related risk factors and a thorough food frequency questionnaire. This allowed us to build an adherence score to the Mediterranean diet (mediSCORE, range 0-9) constructed from individual food intakes. Food intake was also further analyzed by conversion to micronutrient consumption.

RESULTS. Our results suggest that physical activity has a protective role in AMD ($p = 0.018$ after multivariate adjustment, OR 0.69 [0.51-0.93]). High adherence (mediSCORE ≥ 6) was found to be protective, with borderline statistical significance ($p = 0.061$, OR 0.66 [0.41 – 1.04]). Furthermore, food group analysis unveiled a protective role for increased fruit consumption ($p = 0.029$). Finally, micronutrient analysis revealed a protective role associated with increased consumption of caffeine, fibers, beta-carotene, vitamin C and vitamin E ($p < 0.05$).

CONCLUSIONS. High adherence to the Mediterranean diet seems to be protective, though this result did not reach statistical significance. This might be explained by increased consumption of fruits and some anti-oxidant micronutrients, which emerged as statistically significant protective factors. Further studies are required to establish dietary recommendations with clinical application.

KEYWORDS: amd, nutrition, epidemiology, Mediterranean diet, micronutrients

INTRODUCTION

Age-related macular degeneration (AMD) is the main cause of irreversible blindness in the elderly in developed countries[1,2]. If, on the one hand, in neovascular disease forms effective therapy is available, namely anti-VEGF agents, on the other hand, in the non-exudative forms, 85% of cases, we are limited to anti-oxidant/mineral supplementation, which might delay disease progression[3]. Two landmark studies are remarkable in this area. The first one, the Age-Related Eye Disease Study (AREDS), a multicenter, randomized and interventional study, has shown that progression to advanced AMD was reduced with supplementation with high doses of zinc and anti-oxidants, comparatively to a placebo[3]. This study was followed by the AREDS2 study[4], also a multicenter, randomized and interventional study which has shown that supplementation with macular xanthophylls (lutein and zeaxanthin), but not omega-3 fatty acids, seem to further reduce the risk of progression to advanced AMD[4]. In parallel, some studies have supported a protective role for dietary consumption of foods rich in lutein and omega-3 fatty acids[5,6]. While exogenous supplementation seems to be effective, adherence is a real issue, as is the fact that commercially available formulations do not always follow the dosages defined in the landmark AREDS and AREDS2 studies[7]. This supports a role for modulating AMD risk through diet as a whole, without exogenous supplementation[8,9].

The Mediterranean diet is characterized by high consumption of fruits, vegetables, legumes, cereals, fish and olive oil, a low-to-moderate consumption of dairy products, a low consumption of meat and a regular but moderate consumption of alcohol, namely wine[10]. Two epidemiological studies have suggested that adherence to a Mediterranean diet may be associated with a decreased risk for AMD[9,11]. However, these studies were conducted in the United States, where the typical Mediterranean diet is probably rare.

By contrast, this type of diet is customary in Portugal, which is a Mediterranean country.

In this study we performed an epidemiological cross-sectional study in a large population-based sample with and without early AMD from a rural location in Portugal regarding the associations of AMD with dietary intake. We hypothesized a possible protective role associated with the Mediterranean diet and studied the association of AMD with other dietary patterns by food groups and dietary micronutrient consumption.

METHODS

Study Design

We designed a cross-sectional case-control extension to the "Coimbra Eye Study"[12] –a cross-sectional population-based study on the prevalence of early and late AMD, that includes subjects over 55 years-old recruited from primary health-care units from two locations in the center of Portugal – one in the coastal area (Mira) and the other 70 km away from the sea (Lousã). For the present study, in this latter location, a subgroup of previously enrolled patients, with and without early AMD, was invited to participate in a comprehensive evaluation of dietary habits, life style and comorbidities, as well as an anthropometric characterization. This work has been approved by the Ethics Committee. All patients provided written, informed consent.

Subjects Inclusion

We built upon the "Coimbra Eye Study" [12] database for one interior location in the center of Portugal (Lousã). All patients in this database had underwent a complete bilateral ophthalmological examination, with evaluation of best-corrected visual acuity (BCVA), anterior segment biomicroscopy, tonometry and digital mydriatic color fundus photograph (Topcon® TRC-50EX, Topcon Corp, Tokyo, Japan). Images were reviewed in a centralized reading center (Coimbra Ophthalmology Reading Center, CORC – AIBILI) and a differential analysis for AMD lesions was conducted by two senior, independent and certified ophthalmologists, using the *International Classification and Grading System (ICGS) for ARM and AMD*[13]. The full study protocol of the "Coimbra Eye Study" is described in detail elsewhere[12]. For the present study, we aimed to build a age and gender matched sample of subjects with early AMD (ICGS stage 1-3 – soft distinct drusen >63 µm or reticular drusen and/or pigmentary irregularities, excluding atropich or neovascular AMD) and without AMD (ICGS stage 0 – no AMD features or only drusen <63 µm).

Collection of demographic, biometric, lifestyle, education, comorbidities and nutritional data.

All included subjects responded to a thorough questionnaire that included demographic, education, lifestyle (smoking and physical activity), comorbidities as well as a food frequency questionnaire. The food frequency questionnaire, composed of 86 items including common foods and beverages consumed in Portugal, was already validated for the Portuguese population[14]. The questionnaire was administered in person by specially trained interviewers and were checked for completeness. For each of the items, participants were asked to report the frequency of their consumption in the last year, the portion size and whether or not this consumption was seasonal. The interviewer also measured each participants weight, height (for body mass index, BMI, calculation) and abdominal perimeter.

Processing nutritional data

The food frequency was then calculated for average daily consumption values, adjusted for the size of the portion to yield a value in grams (g) per type of food. Also included was a factor for seasonal variation consumption, if indicated by the participant (0.25 for a period of 3 months). These consumptions were grouped in 9 food groups: vegetables, legumes, fruits and nuts, cereals, fish, meat, dairy products, alcohol and a ratio of monounsaturated lipids (mainly olive oil) to saturated lipids. Additionally, the quantitative composition of micronutrients of food consumed by the participants was obtained with the Food Processor Plus Food Processor Plus software (ESHA Research, Salem, Oregon).

Adherence to the Mediterranean diet

We have adopted a model of adherence to the Mediterranean diet, already used for non-ophthalmological disease models[15,16] and initially validated for a Greek population of 22 043 subjects[17]. An adherence scale was built (mediSCORE), ranging from 0 to 9, and was calculated from the sum of 9 food group indicator variables, mentioned above. Each of these indicator variables can take a value of 0 or 1, which was attributed by comparing to a cut-off defined by the median sex-specific food group consumption in grams. Following the original model[17], consumption above this cut-off of beneficial diet components (vegetables, legumes, fruits and nuts, cereals and fish) was assigned a value of 1, and below this cut-off a value of 0. Conversely, consumption below the cut-off of detrimental components (meat and dairy products) was assigned a value of 1 and above this cut-off a value of 0. For alcohol consumption, a moderate consumption was deemed as beneficial, so a value of 1 was attributed for consumption between 10 and 50 grams/day of alcohol for men and between 5 and 25 grams/day for women; for consumptions outside this range a value of 0 was attributed. Finally, as a proxy of overall beneficial fat intake, we considered a ratio of monounsaturated to saturated lipids and similarly defined sex-specific cut-offs using the median; consumption above this median was assigned a value of 1 and below this median a value of 0. Cut-off values are presented in **Table 1**. High adherence was defined as a mediSCORE equal or greater than 6 (range: 6-9), corresponding to the last tertile of the distribution (**Figure 1**) and deemed as nutritionally relevant.

Statistical Analysis

The statistical analysis included a descriptive and inferential component. For both, STATA®, version 13.1 (StataCorp, College Station, EUA) and Microsoft Excel®, version 2016 (Microsoft Corporation, Redmond, Washington, EUA) were used. Our variables of interest were compared between groups with and without AMD. After testing for normality, we have used independent samples t test or the Mann-Whitney independent samples test for continuous variables; for binary variables we have used the Pearson's chi-squared test and univariate linear and logistic regression models. A multivariate logistic regression model including physical activity was built to address common confounders (age, BMI, smoking habits and fruit consumption). In micronutrient analysis, in order to address the multiple comparisons problem, we have used a Benjamini-Hochberg procedure to control for false discoveries (a false discovery rate of 0.10 was chosen, adequate for the exploratory nature of this analysis)[18]. A two-sided significance level (α) of 0.05 was used.

RESULTS

From 3409 subjects in the "Coimbra Eye Study", 1000 subjects that fulfilled our enrollment criteria were invited to participate and a total of 883 subjects completed our study protocol.

Demographics, biometrics, lifestyle, years of education, and comorbidities

As shown in **Table 2**, our sample included 449 (50.9%) with early AMD and 434 (49.1%) without AMD. Our comparison groups, with and without AMD, did not differ significantly in the distribution of sex and age (as expected due to matching), years of education, BMI or abdominal perimeter. Comorbidities, namely prevalence of diabetes, hypertension and dyslipidemia, were also similarly distributed in both groups. Regarding smoking habits, the prevalence of current or past smokers as well as smoking pack-years were not significantly different between groups. Self-reported frequent physical activity (any kind), was significantly less frequent in the group with AMD (24.7% vs 32.3%, p=0.01, OR 0.69 [95% CI 0.51 – 0.92]). This difference remained significant after adjusting for possible confounders (age, BMI, smoking habits and fruit consumption) in a multivariate logistic regression model (p=0.02, OR 0.69 [95% CI 0.51 – 0.93]).

Adherence to the Mediterranean diet (mediSCORE) and specific food groups

High adherence to the Mediterranean diet (cut-off mediSCORE ≥ 6) seems to be associated with decreased prevalence of AMD in our sample (**Figure 2**), almost reaching full statistical significance (39.3% vs 50.2%, p = 0.057, OR 0.64 [95% CI 0.41 – 1.01]. Accounting for the influence age, gender and calories consumptions yields an adjusted OR of 0.66 [95% CI 0.41 – 1.04], p=0.061, supporting this effect direction. Additionally, when looking at the individual food groups that compose the mediSCORE (**Table 3**), fruits and nuts consumption above the sex-specific median is higher in the group without AMD (54.5% vs 45.5%, p = 0.029). For instance, in a univariate logistic regression model, 150 g of fruit consumption is associated with an OR of 0.89 (p=0.018, [95% CI 0.82 – 0.98]), while adjusting for age, gender and calories consumptions yields an OR of 0.90 (p=0.028, [95% CI 0.82 – 0.98]).

Exploratory micronutrient analysis

We conducted an exploratory analysis on the impact of the micronutrient composition of the subjects' diet and AMD frequency using the Food Processor Plus software (ESHA Research, Salem, Oregon). For inferential statistics purposes, consumptions were compared between tertiles, below percentile 33 and above percentile 66, as to define low and high micronutrient consumption, respectively. We have found a significantly higher consumption of caffeine, fibres, beta-carotene, vitamin C and vitamin E in the group without AMD (**Table 4**). These findings remain significant after applying a Benjamini-Hochberg procedure to control for false discoveries, using a false discovery rate of 0.10. No significant differences were found regarding the consumption of monounsaturated fats, omega-3, omega-6, zinc or alcohol.

DISCUSSION

Physical activity and lifestyle factors

We have found that routine physical activity is associated with a decreased frequency of AMD in our sample, even after adjusting for possible confounders. Although a robust body of knowledge supports exercise as a protector[19,20], one cannot rule out a possible “healthy user bias”, where non-observed variables related to physical activity are causally related to this possible protective effect. Interestingly, barring nutritional data, described below, physical activity was the only significant association found in our sample, that included demographical, biometrical, educational and smoking habits. Indeed, while smoking is a well-established risk factor in AMD, a significant difference in smoking habits was not found in our sample. We believe that a low smoking burden in our sample combined with the cross-sectional design might have limited our ability to detect such differences.

The Mediterranean diet and food consumption habits

We have adapted a known and validated model of adherence to the Mediterranean diet[17], the mediSCORE, based on grouped consumptions in nine all-inclusive food groups - vegetables, legumes, fruits, cereals, fish, meat, dairy products, alcohol and a ratio of monounsaturated lipids to saturated lipids. When considering high adherence to the diet (mediSCORE ≥ 6) a protective effect was suggested, though not reaching full statistical significance. This effect is supported in the literature by a recent prospective longitudinal study on the AREDS cohort demonstrating that high adherence to the Mediterranean diet (using the alternate Mediterranean diet score, aMeDi ≥ 6) was associated with reduced progression to advanced AMD[11].

Furthermore, when looking individually at each food group, increased fruit consumption was the only one associated with decreased frequency of AMD in our sample. This result not only has biological plausibility[21,22], due to the high content in anti-oxidants, but has also been previously described in the literature in at least one study[23]. Therefore, we believe that fruit consumption might drive the protective effects in AMD of the Mediterranean diet, and our nutrient analysis below seems to support this hypothesis.

Dietary micronutrients

While exogenous micronutrient supplementation protective role has been unequivocally demonstrated in the landmark AREDS and AREDS2 studies[3,4], not much is known regarding naturally occurring dietary nutrients and their role as a modifiable risk factor. In our exploratory analysis, we have targeted those micronutrients more frequently described in the literature. We have found a significantly higher consumption of caffeine, fibers, beta-carotene, vitamin C and vitamin E in the group without AMD. Conversely, no significant differences were found regarding the consumption of monounsaturated fats, omega-3, omega-6, zinc or alcohol. Regarding caffeine, our results are conspicuous. Only one study looked at a possible effect of dietary caffeine in AMD and a protective role was not apparent[24]. Nevertheless, as a natural, xanthine-rich, anti-oxidant, with a traditionally high consumption in the Portuguese population, we believe it to be a promising micronutrient in this area that demands further studies. The efficacy of beta-carotene, vitamin C and vitamin E exogenous supplementation is well established from the AREDS study[3]. Yet, the protective effect of dietary doses of these micronutrients is lesser known, though some studies do support such an effect[5,25,26]. We have not found omega-3 consumption to be protective in our sample, which falls in line with the results from the AREDS2 study for exogenous supplementation[4]. Nonetheless, an extension to the Rotterdam study[27] has shown that subjects with deleterious mutations in CFH and ARMS2 polymorphisms might counterbalance their inherent genetic risk by and increased consumption of fish, ómega-3 and anti-oxidants. Finally, regarding alcohol consumptions, despite many contradictory results, some studies suggest a small protective effect associated with moderate consumption[28], which we have not been able to replicate in our sample.

Conclusion

In this study we have aimed to characterize the nutritional risk profile of AMD in a rural population in the center of Portugal. Our results suggest that regular physical activity might have a protective effect, even after adjusting for possible confounders. We have applied an innovative and validated model of adherence to the Mediterranean diet, a "prototype" of a healthy diet. There seems to be a protective effect, that did not reach full statistical significance, associated with high adherence to this diet. Additionally, when looking individually at food groups, increased fruit consumption emerged as a protective factor. Finally, our exploratory micronutrient analysis was remarkable for a possible protective effect associated with increased consumption of caffeine, not previously reported, as well as fibres, beta-carotene, vitamin C and vitamin E. Our study reinforces the importance of dietary habits as a possible protective factor in AMD. Further studies in this area are required.

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http://www.ncbi.nlm.nih.gov/pubmed/1557977.

FIGURES AND TABLES

Figure 1. Distribution of the model of adhesion to the Mediterranean diet (mediSCORE) in our cohort (n=883).

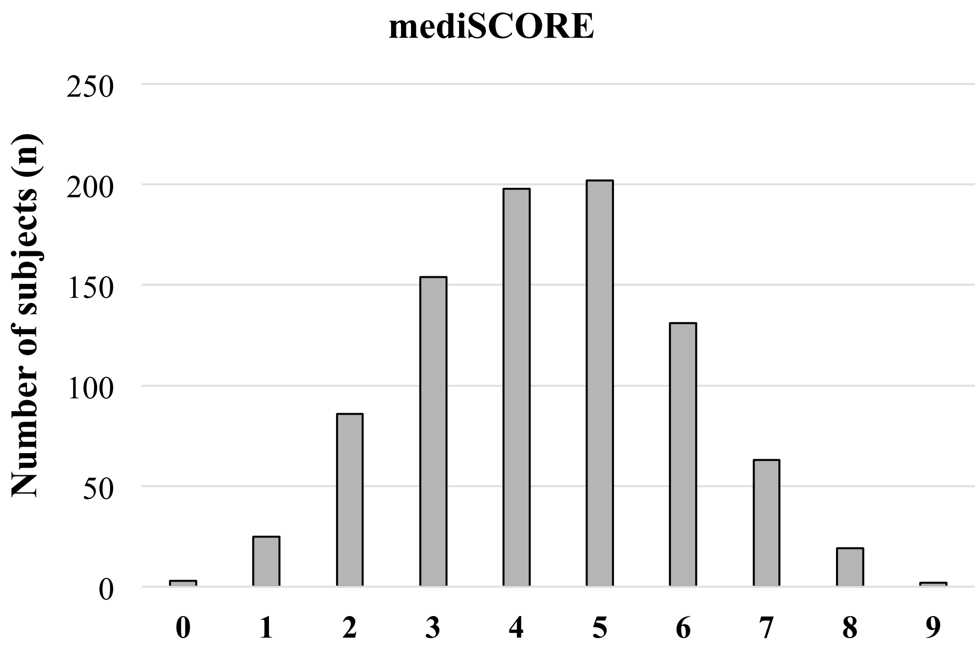
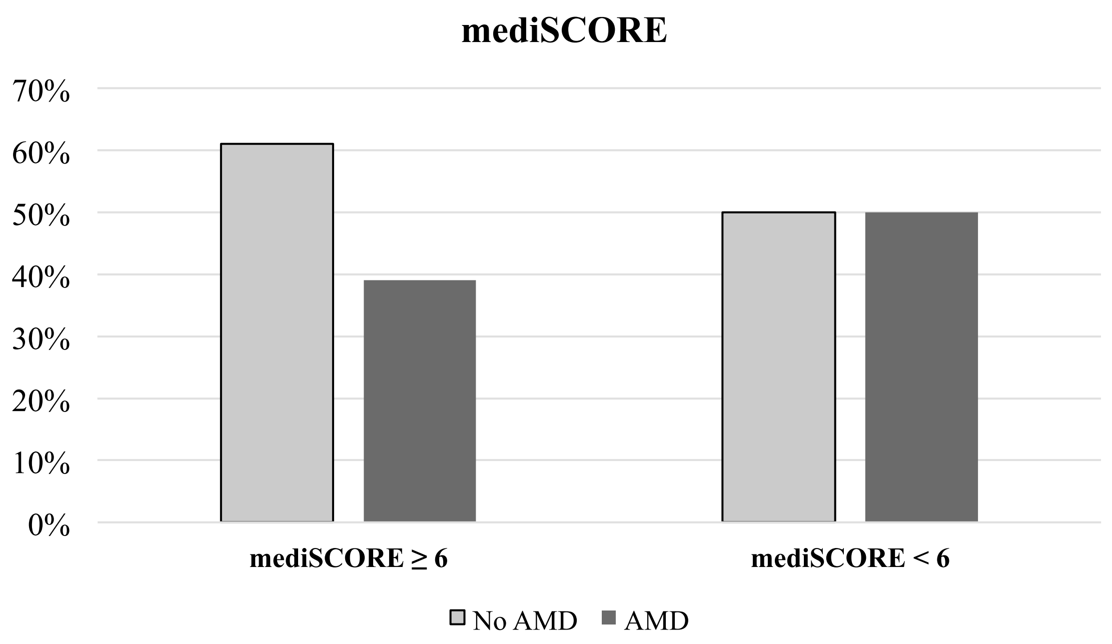


Figure 2. Distribution of adhesion to the Mediterranean diet (mediSCORE) using high adhesion to the diet (mediSCORE ≥ 6) as a cut-off.



High adhesion to the diet (cut-off mediSCORE ≥ 6), after adjusting for the influence age, gender and calories consumptions is associated with a smaller frequency of AMD, almost reaching full statistical significance (39.3% vs 50.2%, p = 0.061, OR 0.66 [95% CI 0.41 – 1.04].

Table 1. Scoring system for the model of adherence to the Mediterranean diet (mediSCORE) – sex-specific medians are presented.

mediSCORE	Cut-off for 0		Cut-off for 1	
	Women	Men	Women	Men
Vegetables[1], g/day	< 136.3	< 147.0	≥ 136.3	≥ 147.0
Legumes[2], g/day	< 35.4	< 42.0	≥ 35.4	≥ 42.0
Fruits and nuts[3], g/day	< 368.2	< 382.3	≥ 368.2	≥ 382.3
Cereals[4], g/day	< 248.7	< 304.8	≥ 248.7	≥ 304.8
Fish[5], g/day	< 88.6	< 96.7	≥ 88.6	≥ 96.7
Meat[6], g/day	> 81.2	> 106.9	≥ 81.2	≥ 106.9
Dairy products[7], g/day	> 302.9	> 278.9	≥ 302.9	≥ 278.9
Alcohol, g/day	<5 or >25	<10 or >50	5-25	≥0-50
Ratio of monounsaturated lipids / saturated lipids	< 1.8	< 1.8	≥ 1.8	≥ 1.8

[1] 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

[2] Peas, beans (red, brown, fava, etc), chickpeas, lupins, lentils

[3] Apples, pears, oranges, tangerines, bananas, kiwis, strawberries, cherries, peaches, plums, melons, watermelons, figs, loquats, apricots, hazelnuts, almonds, nuts, peanuts, pistachios

[4] Bread (wheat, rye, barley, whole or in mixtures), oats, corn bread, direct derivatives (corn flakes), rice

[5] Chicken, rabbit, turkey, cow, pork, goat, goatling, meat derivatives (ham and similars, bacon, sausages)

[6] Fat and lean fishes, codfish, fish preserves, squid, octopus, shellfish

[7] Milk (whole, half or skimmed), yoghurts, cheese, ice creams, dairy-based desserts

Table 2. Sample characterization (n=883) by demographics, education years, biometrics, lifestyle and comorbidities.

	No AMD (n = 434)	**AMD** (n = 449)	p [a]
Demographics			
Age, mean (SD)	69.0 (7.5)	69.7 (7.9)	0.172
Male (%)	198 (44.1)	187 (43.1)	0.762
Education			
Education years, mean (SD)	5.1 (3.3)	4.8 (3.1)	0.190
Biometrics			
BMI, mean (SD)	28.4 (4.2)	28.3 (4.4)	0.078
Abdominal perimeter, mean (SD)	98.5 (14.0)	98.2 (14.5)	0.744
Lifestyle			
Smoker or ex-smoker (%)	122 (27.2)	106 (24.5)	0.361
Pack-years, mean (SD)[b]	9.8 (23.6)	7.8 (20.5)	0.195
Regular physical activity (%)	**145 (32.3)**	**107 (24.7)**	**0.012***
Comorbidities			
Diabetes (%)	106 (23.6)	101 (23.3)	0.906
Hypertension (%)	297 (49.2)	307 (50.8)	0.142
Dyslipidemia (%)	248 (55.2)	238 (54.8)	0.901

[a] Between groups comparisons using Pearson's chi-squared test for categorical variables and Student's t-test for continuous variables; the symbol * denotes statistical significance at $p < 0.05$. [b] Average smoking pack-years; "never" smokers are considered as having 0 pack-years.

Table 3. Percentage of subjects with food group consumption above (for beneficial food groups – vegetables, legumes, fruits, cereals, fish, ratio of monounsaturated lipids to saturated lipids and moderate alcohol intake) and below (for detrimental food groups – meat and dairy products) the sex-specific median.

mediSCORE groups	No AMD	AMD	*p* [a]
1. Vegetables (%)	51.5	49.1	0.400
2. Legumes (%)	50.2	49.8	0.711
3. Fruits and nuts (%)	**54.5**	**45.5**	**0.029***
4. Cereals (%)	50.5	49.6	0.813
5. Fish (%)	51.2	48.8	0.815
6. Meat (%)	52.0	48.1	0.519
7. Dairy products (%)	49.6	50.5	0.440
8. Alcohol (%)	47.9	49.2	0.173
9. Ratio of monounsaturated lipids / saturated lipids (%)	50.9	49.1	0.267

[a] Between groups comparisons using the Pearson's chi-squared test; the symbol * denotes statistical significance at $p < 0.05$.

Table 4. Distribution of subjects with micronutrient consumption above the second tertile.

Nutrient	No AMD	AMD	p [a]
Alcohol[1]	48.8	51.2	0.301
Beta-carotene[2]	57.8	42.2	0.002*
Caffeine[3]	56.7	43.3	0.029*
Fibers[4]	56.1	43.9	0.023*
Monounsaturated fats[5]	48.8	51.2	0.301
Omega-3[6]	51.5	48.4	0.934
Omega-6[7]	50.5	49.5	0.773
Vitamin C[8]	54.1	45.9	0.037*
Vitamin E[9]	57.8	42.2	0.019*
Zinc[10]	51.2	48.8	0.710

[a] Between groups comparisons (consumption below the 1st tertile vs consumptions above the 2nd tertile) using the Pearson's chi-squared test; the symbol * denotes statistical significance at $p < 0.05$. These findings remain significant after applying a Benjamini-Hochberg procedure to control for false discoveries, using a false discovery rate of 0.10.

[1] Alcohol - 1st tertile: 0; 2nd tertile: ≥ 11.6 g

[2] Beta-carotene - 1st tertile: < 867.6 mcg; 2nd tertile: ≥ 1416.4 mcg

[3] Caffeine - 1st tertile: < 31.8 mg; 2nd tertile: ≥ 78.8 mg

[4] Fibers - 1st tertile: < 21.9 g; 2nd tertile: ≥ 29.0 g

[5] Monounsaturated fats - 1st tertile: < 30.5 g; 2nd tertile: ≥ 41.9 g

[6] Omega-3 - 1st tertile: < 1.2 g; 2nd tertile: ≥ 1.5 g

[7] Omega-6 - 1st tertile: < 7.0 g; 2nd tertile: ≥ 9.3 g

[8] Vitamin C - 1st tertile: < 107.6 mg; 2nd tertile: ≥ 150.1 mg

[9] Vitamin E - 1st tertile: < 8.6 mg; 2nd tertile: ≥ 11.1 mg

[10] Zinc - 1st tertile: < 9.1 mg; 2nd tertile: ≥ 12.0 mg