Original Paper

Ophthalmic Research

Ophthalmic Res
DOI: 10.1159/000441795

Received: October 18, 2015
Accepted: October 19, 2015
Published online: ■■■

Risk Factors and Age-Related Macular Degeneration in a Mediterranean-Basin Population: The PAMDI (Prevalence of Age-Related Macular Degeneration in Italy) Study – Report 2

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Key Words

Age-related macular degeneration · Prevalence of age-related macular degeneration · Risk factors of age-related macular degeneration · Food frequency questionnaire · Smoking habit · Alcohol consumption · Raman spectroscopy · Lutein · Carotenoids

Abstract

Aim: To investigate the association of diet and other modifiable risk factors with the prevalence of age-related macular degeneration (ARMD) in rural and urban communities of a Mediterranean population in the northeast of Italy. ***Methods:*** A cross-sectional population-based study was conducted among subjects aged over 60 years. A food frequency questionnaire (FFQ) was used to assess the consumption of different food categories, i.e., protective (P), risky (R), lutein-rich (L) and neutral (N). Smoking habit and alcohol intake were also examined. Macular pigment was measured by Raman spectroscopy. ***Results:*** P food intake reduced the risk of large drusen (ARM2; OR 0.93; 95% CI 0.89–0.96) within the rural community. In this sub-group, R foods resulted in a slight association with large drusen, though the R/P food ratio was highly correlated with ARM2 (OR 1.21; 95% CI 1.12–1.31). Raman measures showed an age-dependent decrease but did not correlate with lutein intake. Smoking habit showed a positive association with ARM2 among women (OR 2.40; 95% CI 1.54–3.75), whereas alcohol consumption resulted in protective odds (OR 0.72; 95% CI 0.60–0.86). ***Conclusion:*** FFQ analysis confirmed the role of P and R foods and the benefit of a Mediterranean diet in ARMD. Moderate alcohol consumption showed a beneficial effect, whereas the deleterious role of a smoking habit was more evident in females.

Introduction

Correct identification of modifiable behavioural risk factors can potentially shape specific strategies tailored to prevent both the onset and the progression of age-related macular degeneration (ARMD). Currently, ARMD is the

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0030–3747/15/0000–0000$39.50/0

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major cause of blindness among aged populations [1, 2], and this will remain so if the current population trends continue as expected. Some factors are already known to be associated with the disease; these can be modifiable factors related to the lifestyle and environment or non-modifiable factors, the most important of which are age and genetics [3–6].

The PAMDI (Prevalence of Age-Related Macular Degeneration in Italy) study is a population-based cross-sectional study conducted on a reference population of the Mediterranean basin of 25,289 inhabitants living in either rural or urban areas of the northeast of Italy. The study showed that the overall prevalence of ARMD was similar to that reported in other major studies carried out in Western countries [7–12]. In the PAMDI study, the prevalence of ARMD was the same in rural and urban subjects, but analyses of modifiable risk factors and their impact on the potential severity of the disease are yet to be carried out. Though genetic differences among Europeans have been levelled over centuries due to migration and settling in foreign lands, individual habits remain deeply different.

The aim of the present study is to analyse the association of modifiable risk factors (nutritional patterns, smoking habits and alcohol consumption) with the different types of ARMD within a rural community, supposedly more adherent to a Mediterranean diet, and an urban community of the PAMDI population. In addition, the concentration of zanthophyllic macular pigment (MP), as measured by Raman spectroscopy (RS), and its association with other modifiable risk factors were analysed.

Methods

Study Population and Settings

The study population has been described in detail elsewhere [13], but a short summary is given below. PAMDI examined all patients between October 31, 2005, and October 31, 2006, in 2 communities in Northeast Italy: one from an urban district and the other living in two adjacent small rural communities.

The urban sample consisted of a total of 2,495 inhabitants aged 60 years or older, representing 23.4% of the local population (10,661 inhabitants), and it was representative of the total population with regard to age and sex distribution. The rural sample was composed of a total of 3,189 inhabitants aged 60 years or older, representing 21.8% of the population (14,628 inhabitants). The two rural municipalities were selected because they were considered a good trade-off for a self-sustained economy and were comparable in all aspects with the urban population, except with regard to area of living.

The procedures for data collection were standardized and included a series of measurements taken by 3 trained ophthalmologists, 2 nurses and an ophthalmic technician. General health information (height, weight, self-reported blood pressure, glycaemia, total blood cholesterol and blood HDL and LDL levels) was recorded in a systematic way. Thereafter, an interview using structured questionnaires to elicit information about employment, outdoor occupations, leisure activities, family income, marital status, smoking habit and alcohol use, exposure to direct sunlight, use of sunglasses, a short medical history (including the duration of the fertile period, from menarche to menopause) and current/past therapies, including sex hormone therapy, was carried out. Finally, a detailed ophthalmological examination took place, the details of which have been reported previously [13]. All collected data were recorded using PAMDI 1.0 software (Ibis Informatica s.r.l., Milan, Italy).

This study was approved by the University of Padua Human Research Ethics Committee and was performed in accordance with the tenets of the Declaration of Helsinki.

Evaluation Protocol

Dietary Habits. Subjects were asked to provide their medical records and complete a questionnaire [i.e. the food frequency questionnaire (FFQ) validated for the Italian population] reporting their dietary habits [14]. With regard to their potential role in ARMD pathogenesis, the foods listed in the questionnaire were grouped into 4 classes: 2 were mainly based on the content of polyunsaturated, i.e. protective (P), or saturated, i.e. risky (R), fat; a third class was composed of lutein-rich (L) foods, and the fourth class comprised the neutral (N) food group. The cross-sectional nature of this study did not allow investigation of the role of lifelong exposure to a given food intake; therefore, the FFQ was used to rank individuals according to their dietary habits. Food consumption, classified using the 4 food classes (P, R, L and N), was then quantified through frequency scores obtained by summing the number of eating occasions and servings as declared by the sampled individuals for each food category.

Smoking Habit. In order to classify the patients' smoking habits, the study participants were interviewed and, in accordance with Centers for Disease Control and Prevention definitions, divided into 3 groups: (i) non-smokers, i.e. those who reported never having smoked 100 cigarettes during their lifetime; (ii) former smokers, i.e. those who reported having smoked at least 100 cigarettes in their lifetime and, at the time of the survey, did not smoke at all, and (iii) current smokers, i.e. those who reported having smoked at least 100 cigarettes in their lifetime and, at the time of survey, smoked either every day or some days [15].

Alcohol Consumption. There is currently no universally accepted definition of alcohol consumption. Participants were asked how often, on average, they had consumed each type of beverage (beer, wine and liquor) during the past year. There were 9 possible responses, ranging from never or less than once a month to 6 or more times a day. At baseline, the participants were also asked whether their alcohol consumption had changed during the past 10 years or not. The alcohol content was estimated to be 12.8 g per 355-ml can or bottle of beer, 11.0 g per 120-ml glass of wine and 14.0 g per shot of liquor. The total alcohol intake per individual was calculated as the sum of the contributions of each of these beverages. The reproducibility and validity of food and alcohol intakes as assessed by FFQ have been documented [16].

Raman Spectroscopy. RS resonance is an objective and specific method used to record the carotenoid density in different human

Table 1. Intake scores for the different food categories in women and men and in urban and rural communities

Food category	Women (n = 444)	Men (n = 380)	p value[a]	Rural (n = 418)	Urban (n = 406)	p value[a]
P food	13.4±3.4	14.1±3.2	<0.01	14.3±3.2	13.1±3.4	<0.0001
R food	68.5±18.0	69.6±16.8	0.39	73.4±13.6	64.6±19.7	
L food	116.5±28.4	119.7±25.7	0.09	124.4±24.1	111.4±28.6	
N food	45.4±10.5	44.7±10.2	0.29	47.0±9.0	43.2±11.2	

Values are presented as means ± SD unless otherwise stated. [a] Student's t test.

tissues, including yellow MP. It is based on the Raman effect (Chandrasekhar Raman, 1930 Nobel Prize for Physics): when a molecule is illuminated with a monochromatic incident beam that overlaps its absorption band, a scattered radiation is emitted with a specific wavelength that depends on its chemical structure and exhibits a resonance enhancement. The Raman resonance signal in carotenoids is generated by single-bond and double-bond vibration of the conjugate carbons that constitute the main chemical backbone and is characterized by 2 clearly prominent Stokes lines at 1,158 and 1,528 cm, respectively, when excited with a 488-nm incident beam. The laser source projects a laser beam of 1 mW focused on the macular area for 0.25 s, the backscattered light is imaged onto the entrance slit of a Raman spectrometer with a beam splitter and an additional lens. A charge-coupled device registers simultaneously the wavelengths, and finally custom-built software registers and elaborates the signals, recorded as counts per second. Raman spectra were collected in 220 patients (53.4%) from the urban sample of the PAMDI study; they had the same distribution for age and ARMD grading as the rest of the study population. All measurements were performed in a dark room after pupillary dilation. Subjects with a refractive error wore their usual spectacle or contact lens corrections. Five measurements were recorded for each eye; the 3 highest were used for data analysis.

ARMD Definitions

ARMD included any type of ARMD. Age-related maculopathy (ARM) was defined as the absence of signs of advanced ARMD (AMD) and the presence of soft indistinct or reticular drusen (≥63 μm) with or without retinal pigment epithelium abnormalities within a standard grid. ARM was sub-classified into 2 stages: ARM1 and ARM2. ARM1 was defined as the presence of at least 1 medium-sized druse (greatest linear dimension 63–124 μm) within 3,000 μm from the foveal centre in the absence of ARM2 and AMD. ARM2 was defined as the presence of at least 1 large druse (≥125 μm) with or without retinal pigment epithelium abnormalities (hypopigmentation or hyperpigmentation) within the central macular zone (1,500 μm from the foveal centre) in the absence of signs of AMD. AMD was defined as the presence of geographic atrophy and/or exudative macular degeneration due to choroidal neovascularization (fig. 2).

The fundus photographs, taken according to the ETDRS (Early Treatment Diabetic Retinopathy Study) standard protocol (field 1M), were graded by the Reading Centre (Moorfields Eye Hospital NHS Foundation Trust, London, UK) [13] according to the international grading system for age-related maculopathy [17].

Statistical Analysis

The significance of the FFQ, smoking and alcohol consumption in relation to the risk of ARMD onset (defined as ARM2) was expressed as OR and 95% CI as determined by multiple logistic regression analysis. OR were adjusted for age, sex and geographic area of residence. Age was entered into the models after categorizing for 5-year classes. The goodness of fit of the model was judged based on the Pearson χ^2 test. The fit of the model was considered acceptable if the p value was ≥0.05. A 2-sided p value <0.05 was regarded as statistically significant. The SAS® 9.1.3 statistical package was used for all of the analyses.

Results

Of the 885 PAMDI patients examined, 845 had gradable photographs for ARMD grading. Overall, the ARMD prevalence was 62.7%; among these cases, ARM1 contributed 48.3%, ARM2 10.4% and advanced AMD 4.1%. Age was found to be a risk factor for ARM2 and AMD (ARM2: OR 1.47; 95% CI 1.39–1.55, and AMD: OR 1.62; 95% CI 1.49–1.76) but not for ARM1. The rural group appeared to be at a higher risk of developing both intermediate and large drusen (ARM1: OR 1.25; 95% CI 1.12–1.39, and ARM2: OR 1.61; 95% CI 1.35–1.94) [13].

Food Frequency Questionnaire

FFQ scores were available for 824 subjects. Women declared a lower intake of P foods than men. However, women living in the rural areas showed a significantly higher P score compared to those living in the urban area (women's P scores: rural areas 14.2 ± 3.2, urban area 12.8 ± 3.2, p < 0.001). The P, R, L and N scores were significantly higher in the rural areas compared to the urban community (table 1).

Multiple logistic regression analysis was carried out in the ARM2 sub-group and showed that P food consumption was significantly and inversely associated with ARM2 (OR 0.96; 95% CI 0.93–0.99, p = 0.008; fig. 1).

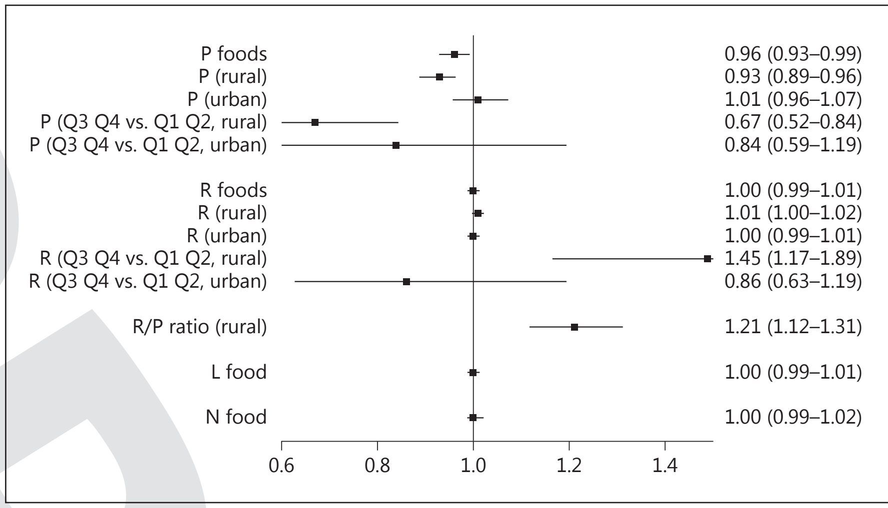

Fig. 1. Food categories as risk factors for ARM2. Multiple logistic regression analysis adjusted for age, gender and geographic area. The relative OR and 95% CI are indicated. The consumption of P food in all populations (OR 0.96; 95% CI 0.93–0.99, p = 0.008), and in particular in the rural sub-group (OR 0.93; 95% CI 0.89–0.99, p = 0.008), significantly protected from the development of large size drusen. In the rural cohort, both the two highest quartiles of R food and the ratio between R and P food (R/P) were significantly associated with more lesions. No influence of L food could be observed.

Table 2. Smoking habits of women and men and among rural and urban subjects

Smoking habit	Women (n = 457)	Men (n = 388)	p value[a]	Rural (n = 425)	Urban (n = 420)	p value[a]
Never	355 (78.1)	138 (35.6)		248 (58.5)	245 (58.5)	
Former	62 (13.6)	198 (51.0)	<0.0001	135 (31.8)	125 (29.8)	0.58
Current	38 (8.3)	52 (13.4)		41 (9.7)	49 (11.7)	

Values are presented as numbers (%) unless otherwise stated. [a] Pearson's χ^2 test.

However, when the two area communities were separately considered, the benefit of P food consumption persisted only in the rural population. Among these subjects (and not in the urban sub-group) the negative impact of R foods was statistically significant. When the rural population was stratified by quartiles, high quartiles of P scores (Q3 and Q4) and high quartiles of R scores (Q3 and Q4) showed a powerful association between protection and risk, respectively, for ARM2 retinal lesions. These associations were not significant among urban subjects. Intake of both L foods and N foods failed to show any effect on ARM2 in any community group. In order to extract further hidden associations, the ratio between R and P foods was also analysed. Within the rural cohort, this ratio showed a strong association with ARM2 prevalence, which was not significant for the urban subjects.

Smoking Habit and Alcohol Consumption

There was no significant difference in smoking habits between the urban and rural populations. The rates of current (13.4%) and former smokers (51.0%) among male subjects were significantly higher than among females (p < 0.0001), with most of them (78%) being nonsmokers (table 2). In general, smoking habit was not significantly associated with ARM2 (fig. 2). However, when a pooled analysis by gender was performed, a stronger and significant association with ARM2 was present in the female cohort (OR 2.40; 95% CI 1.54–3.75, p < 0.0001).

Men of both urban and rural communities consumed daily alcohol amounts greater than 15 g (p < 0.0001; table 3) more frequently than did women. Also, alcohol consumption slightly differed between the rural and urban populations. A significantly higher percentage of rural subjects consumed alcohol amounts greater than 30 g/day. Regression analysis showed a general significant protective action of alcohol against large drusen development (fig. 2). An age group analysis demonstrated that this association was evident for subjects aged 70 years or older, whilst an apparent inverse correlation, albeit with a high CI, was detected for the age range of 61–69 years.

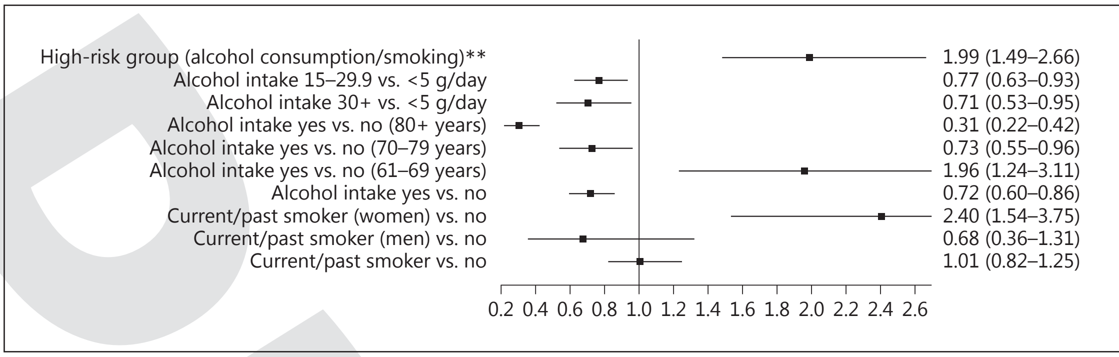

Fig. 2. Smoking habit and alcohol consumption as risk factors for ARM2. Multiple logistic regression analysis adjusted for age, gender and geographic area. In the whole population, smoking habit (current or past) was not associated with ARM2. When a pooled analysis by gender was performed, a strong and significant association with ARM2 was present in the female cohort (OR 2.40; 95% CI 1.54–3.75, $p < 0.0001$). Alcohol consumption was found to be significantly protective against large drusen development. However, a separate age group analysis demonstrated that this association was only present in subjects aged 70 years or older. The protective role of alcohol was not dose dependent and was observed both for mild (15–29 g/day) and moderate (30+ g/day) daily consumption. The analysis of combined effects of cigarette smoking and alcohol showed that the high-risk group (smokers who did not declare alcohol intake) had twice the risk of an association with ARM2 lesions. ** [redacted].

Table 3. Alcohol consumption in women and men and among rural and urban subjects

Alcohol consumption, g/day	Women (n = 457)	Men (n = 388)	p value[a]	Rural (n = 425)	Urban (n = 420)	p value[a]
0–4.9	238 (52.2)	87 (22.3)	<0.0001	164 (38.6)	161 (38.3)	0.01
5–14.9	2 (0.4)	1 (0.3)		1 (0.2)	2 (0.5)	
15–29.9	188 (41.1)	176 (45.4)		166 (39.1)	198 (47.2)	
>30	29 (6.3)	124 (32.0)		94 (22.1)	59 (14.0)	

Values are presented as numbers (%) unless otherwise stated. [a] Pearson's χ^2 test.

Comparison of mild to moderate (15–29 to 30+ g/day) versus very low alcohol intake confirmed a protective association only for the former.

In order to bring out masked relations of smoking habit and alcohol consumption, we created 2 groups: a 'low-risk' group that comprised patients who did not smoke but declared alcohol consumption (272 cases), and a 'high-risk' group that was represented by smokers who did not consume alcohol (95 cases). The prevalence of large drusen was greater in the high-risk group (14.7%) than in the low-risk group (9.9%). Multivariate statistical analysis showed that the high-risk group was more strongly associated with the presence of ARM2. Also, this relationship was present both in the urban and the rural cohorts when separately considered (OR 2.85; 95% CI 1.85–4.40, and OR 1.49; 95% CI 1.00–2.22, respectively).

Raman Spectroscopy

RS was performed in 220 subjects from the urban population. This sample represented 53.4% (420 patients) of the whole PAMDI population and was not significantly different from all subjects in terms of age or ARMD grading ($p = 0.52$ and $p = 1.00$, respectively). The mean MP level (MP count ±SD) using RS was 955.1 ± 550.8. Younger subjects had higher MP values (960.1 ± 460.5 for patients aged 61–65 years) than elderly individuals (825.3 ± 334.0 for patients aged 81–85 years), and multiple linear regression analysis demonstrated a mild inverse correlation between MP counts and age ($p = 0.07$). There was no statistically significant difference in mean MP levels between men and women ($p = 0.97$).

Though not significant, subjects with no ARMD or with ARM1 showed higher values of MP than those with large drusen (ARM2); the difference reached significance

Table 4. Raman MP density values and different grades of ARMD

ARMD grade comparison	Difference between means	p value[a]
No ARMD-ARM1	–40.09	n.s.
No ARMD-ARM2	92.46	n.s.
No ARMD-AMD	267.24	<0.0001
ARM1-ARM2	132.55	n.s.
ARM1-AMD	307.32	<0.0001
ARM2-AMD	174.77	n.s.

n.s. = Not significant. [a] Student's t test.

($p < 0.0001$) when compared with advanced lesions (AMD) (table 4). MP counts were not correlated with FFQ-estimated amounts of dietary luteins. Moreover, no other correlation with P, R or N foods could be detected.

Discussion

The PAMDI subjects represent a typical Mediterranean population whose diet is rich in P and L foods. Using a validated semi-quantitative FFQ, we found that higher intakes of P foods resulted in a lower prevalence of large drusen. The PAMDI study was originally set up to evaluate the specific effects of Mediterranean dietary habits, smoking and alcohol consumption in the process of developing clinically significant ARMD lesions, and our study demonstrates the findings.

A Mediterranean diet is primarily characterized by a high consumption of olive oil, legumes, whole-grain cereals, fruits and vegetables coupled with moderate wine drinking and a moderate consumption of fish and dairy products. At the same time, there is a low consumption of poultry, meat and its products, highly processed foods and refined sugars. The benefits of this diet in relation to cardiovascular diseases and diabetes have been demonstrated, and evidence is emerging for ARMD. The AREDS subjects who declared dietary habits more adherent to a Mediterranean diet seemed to have a reduced risk of advanced ARMD [18]. The protective activity of a Mediterranean diet against ARMD was reported in the EUREYE study. The Mediterranean centres of this study displayed a higher score of adherence to a Mediterranean diet, which was significantly associated with a decrease in the risk of neovascular ARMD [19]. As expected, rural subjects in the PAMDI study were more adherent to a Mediterranean diet, with the highest intake of P foods associated with a reduced prevalence of ARM2. Fish and raw oils, which constituted a part of the P category of foods, have established biological support for their role in ARMD pathogenesis: the omega-3 fatty acid docosahexaenoic acid (DHA) constitutes 50–60% of the total fatty acids present in the outer segments of photoreceptors, hence the need for a constant dietary supply for the continuous turnover of these. In addition, polyunsaturated fatty acids play a role in protection from oxidative stress and inflammatory and immune processes involved in the initial pathogenic steps of ARMD [20]. Data on the effects of food consumption on early ARMD are limited, but previous observational studies in humans have reported that consumption of dietary omega-3 long-chain polyunsaturated fatty acids may reduce the risk of developing AMD among patients with a moderate-to-high risk of progression to late AMD [21]. In our study, a diet rich in R foods (mainly constituted by sweets and desserts, red meat, eggs and high-fat dairy products) showed a trend of association with worse ARMD, though it was not always statistically significant. In order to amplify the respective roles of P foods and R foods, we analysed the R/P ratio, which showed a strong correlation with ARM2 among rural subjects. This finding supports the hypothesis that, despite the fact that the prevalence of ARM2 was not lower within the rural population, subjects with a high intake of P foods, combined with a reduced intake of R foods, have reduced odds of developing ARM2. From this, we may infer that the high presence of own-grown products in rural areas, with fewer additives and/or preservatives, could account for better assimilation of the protective molecules. In addition, ways of preparing, conserving and cooking food might modify the protective features of some ingredients. It might also be that subjects with a healthy diet are less likely to be heavy smokers or to be exposed to other toxic agents, thus further lowering their chance of acquiring clinically significant ARMD. The lack of a difference in ARM2 prevalence might simply be due to our limited sample size and to the multifactorial pathogenesis of ARMD, with the role of diet concealed by many other cumulative aetiologic factors. On the other hand, in Western countries the possibility of a rural community remaining strictly isolated in terms of its food supply and of it not being 'contaminated' by the surrounding urban economy is small. Therefore, the distinction between rural and urban subjects have may be affected in our study as well.

A clear correlation between smoking and ARMD onset and progression has been widely reported in the literature [22], and in our study ARM2 showed a trend of association (though not statistically significant) with current smoking habit. A recent longitudinal population-based study examined the effect of current smoking and the number of cigarettes over a 20-year period [23]. The authors reported an incidence of 24.4% for early ARMD and 4.5% for late ARMD and an association between current smoking and the transition from minimal to moderate early ARMD. In the present study, the lack of correlation with smoking status may be partially related to a recall bias. In order to investigate further masked associations, we pooled the analysis for gender. The results showed that current or previous smoker women had a significant association with the development of large drusen. This might suggest a potential role of hormone exposure as well. Indeed, oestrogens have been implicated in ARMD pathogenesis, especially in aged females, when there is no contraceptive use or postmenopausal hormone replacement therapy; these may presumably lower the risk of developing the disease [24, 25]. The Tromsø study found an indirect association between a longer duration of breast-feeding and maternal late ARMD, suggesting a strong and lifelong influence of female hormones, even from early adulthood [26].

In our study, alcohol consumption acted as a protective factor for the presence of large-sized drusen (ARM2). This result is only partially in agreement with data reported in the literature. Chong et al. [27] showed that heavy alcohol consumption (more than 3 standard drinks per day) was associated with an increased risk of early ARMD, whereas the risk of late ARMD was inconclusive. The Melbourne Collaborative Cohort Study [28] reported that drinking more than 20 g of alcohol per day resulted in an approximately 20% increase in the odds of having early AMD. We saw a protective effect of alcohol consumption only for subjects aged 70 years or older. Younger individuals, who more frequently declared a heavy alcohol intake, showed an inverse association with large drusen. Bias in the collection of data, the social and psychological impact of dramatic visual impairment and the great variation in personal lifestyle habits in the age range considered may account for the high variability observed in the role of alcohol intake in the vision-threatening late stages of ARMD.

The multi-factorial peculiarity of the disease originates from the interaction between genetic, environmental and behavioural factors. Though its complete aetiology and pathogenesis are yet to be clarified, it might be possible to alter the prevalence and incidence of ARMD by acting on modifiable risk factors [29], despite a given genetic background [30], by modifying specific habits such as smoking and dietary intake of antioxidants [21].

Lutein and zeaxanthin are found in high concentrations in the macula, and they have the fundamental role of protecting this area from photochemical damage and oxidative stress [31]. AREDS2 recorded higher levels of MP distribution and optical density among subjects who received carotenoid supplements regularly compared to the control group [32]. Although in our study we failed to demonstrate an association between MP levels and dietary patterns, the result could be due to the small sample size. Moreover, different ways of ingestion of nutrients (dietary supplement or L diet) could affect the MP levels in the macular region. MP are known to be associated with a protective role against ARMD, and consequently central MP levels could be an indicator of AMD risk [33]. Indeed, we found out a significant correlation between MP values and the severity of the disease similar to that reported previously [34], especially when comparing healthy/ARM1 subjects to those with ARM2 or advanced AMD.

Our study has several strengths including the use of standard semi-quantitative food frequency protocols validated for the Italian population. To the best of our knowledge, this is the most detailed study of a population of the Mediterranean basin, traditionally characterized by a healthy and oxidant-rich diet, analysed for the theoretical protective issues related to ARMD development.

Due to the cross-sectional characteristics of this study, it was not possible to investigate the temporal relationship between smoking history and ARMD or the effect of quitting smoking. Our results could be the starting point for an important public health message considering the possible effects and interactions of multiple risk factors like smoking habit, alcohol intake and other risk-taking behaviours such as a poor diet. In the PAMDI study, we found greater levels of alcohol consumption (15–29.9 and >30 g/day) among males, where also a greater number of smokers was present. Also, we were not able to collect material for a genetic analysis of the studied population; we hope to do so during the follow-up study.

In conclusion, our study shows that risk factors are unlikely to act independently, and it provides further evidence for the need to establish a 'personalized medicine' approach that takes into account all modifiable and non-modifiable risk factors and potentially lifelong exposures in order to influence the onset and progression of the disease in individuals.

Disclosure Statement

No potential conflicts of proprietary interest are disclosed.

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