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Dietary patterns were not associated with age-related macular degeneration: a cross-sectional analysis in the Irish Nun Eye Study

Rachel V. McCarter 1 · Charlotte E. Neville 1 · Giuliana Silvestri 2 · Shannon Montgomery 1 · Evelyn Moore 2 · Vittorio Silvestri 2 · Christopher R. Cardwell 1 · Ruth E. Hogg 1 · Jayne V. Woodside 1,3 · Gareth J. McKay 1

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Abstract

Background Analysing dietary patterns (DP) evaluates overall dietary intake, taking account of its complexity, quality, variance and the interaction between different foods, providing an alternative approach for the evaluation of nutritional influences on age-related macular degeneration (AMD) risk.

Aims To evaluate the relationship between DP and AMD in an older female population.

Methods Data was analysed from the cross-sectional Irish Nun Eye Study involving 1233 older women with a restricted lifestyle (mean age 76.3 years [range, 56–100 years]). The Wisconsin Age-related Maculopathy Grading System was used to classify digital colour macular fundus images and dietary intake was assessed using a food frequency questionnaire (n = 1033). A posteriori DP were derived using principal component analysis. Logistic regression models examined associations between DP and AMD risk with adjustment for confounders.

Results Two DP were identified: a ‘healthy’ pattern characterised by a high intake of oily fish, wholegrains, vegetables and fruit; and an ‘unhealthy’ pattern characterised by high-fat dairy products, sugar, sweets and chips. Of the participants included within the analysis, AMD status were categorised as controls (n = 818, 86.9%), early AMD (n = 83, 8.8%) and late AMD (n = 21, 2.2%). Regression analysis failed to identify any significant associations between healthy or unhealthy DP and AMD risk, in unadjusted and adjusted models.

Conclusion No evidence of an association between the DP identified and AMD risk was detected in this well-characterised population. Further research is required to determine the overall dietary influences on AMD risk in general population cohorts.

Keywords Age-related macular degeneration · Diet · Dietary patterns · Nutrition

Introduction

Age-related macular degeneration (AMD) is the leading cause of vision impairment within the developed world in people aged > 50 years and treatment options for slowing the progression of visual loss due to late AMD are limited [1]. Nutritional influences and dietary interventions have been shown to modulate AMD associated risk [2–8]. Previous dietary based analyses have largely focused on the evaluation of individual nutrients, foods or groups of foods to identify independent nutritional influences affecting AMD risk, although the associations observed, have not always been consistent [9–13]. The analysis of dietary patterns (DP) evaluates overall dietary intake, taking account of its complexity, quality, variance and the interaction between different foods, providing an alternative approach for the evaluation of nutritional influences on AMD risk [14, 15].

Some studies have outlined the potential nutritional or dietary influences on AMD risk [7, 16–19]. Data emerging from the Age-Related Eye Disease Study (AREDS), advocates a healthy diet with supplementation of zinc, lutein/zeaxanthin and vitamins C and E, as an effective strategy for reducing...
AMD progression from its early to visually-disabling late stage [16]. Another study by Chiu et al. also noted the potential benefits of omega-3 fatty acids for reducing AMD progression [20]. In relation to dietary carbohydrates, other studies have highlighted that the quality of carbohydrates consumed as measured by the glycaemic index, modify AMD risk [17, 20–23]. However, quantification of the glycaemic index of a specific food can be problematic, as it varies with respect to the other foods consumed at the same time [24]. Overall, this cumulative evidence showing associations with different foods and nutrients could suggest that the overall diet may be important given that the consumption of one food may affect the nutritional value and bioavailability of others, and the nutritional benefits may also be influenced by the individual’s health status or severity of AMD.

To our knowledge, only two studies have previously reported on the associations between a posteriori-derived DP and AMD. In the US-based AREDS study, Chiu and colleagues identified two major DP, labelled as ‘Oriental’ and ‘Western’, which were strongly associated with reduced and increased risk of AMD (both early and late) respectively, accounting for <20% of the total dietary variance assessed [14, 15]. An Australian study (the Melbourne Collaborative Cohort study [MCCS]) identified a significant association between ‘processed foods’ and a higher prevalence of late AMD [25]. To date, we are unaware of any study that has examined associations between DP and AMD risk in European populations. As such, the aim of this study was to evaluate a posteriori-derived DP of nutritional intake and associated risk of AMD in a well-characterised cohort of older Irish women with a restricted lifestyle.

Methods

Study population

The study population was drawn from the Irish Nun Eye Study (INES), a cross-sectional study, in which DP were analysed in association with AMD prevalence. This unique population subscribes to a set of rules that governs behaviour in terms of material possessions, emotional and physical attachment, maintenance of a daily structured religious life of abstinence and prayer with dietary and lifestyle limitations and therefore represents a relatively homogenous population. A total of 1233 females were recruited between 2007 and 2009 from 123 convents across the island of Ireland; all participants were Irish, of white ethnicity, had been residing in a convent for 25 years or more and were older than 55 years. Prior to the commencement of research, ethical approval was obtained from the Office for Research Ethics Committee Northern Ireland and informed written consent was obtained from all participants. DP analysis was performed on 1033 participants who completed a food frequency questionnaire (FFQ) as part of the study and for whom retinal images were available. The study design and sampling procedures have been described previously [26, 27].

Age-related macular degeneration characterisation

Colour macular centred fundus images were graded independently by the Network of Ophthalmic Reading Centres UK (NetwORC UK). A standardised procedure adopted from definitions of the Wisconsin Age-related Maculopathy Grading System was used to classify features of early and late AMD [28] and the definitions were based on the International Classification for Age-related Macular Degeneration [29]. The presence of features within a 6000-μm circle centred on the fovea were recorded. Drusen were categorised according to size, characteristics of homogeneity of surface features and outline. Pigmentary changes were classified into two categories: hyperpigmentation and hypopigmentation. These features were used to assign each eye to a severity grade as follows: Controls: no features of AMD or the presence of soft distinct drusen (> 63 μm and ≤ 125 μm) or pigmentary abnormalities only. Cases were defined as early AMD: soft, indistinct (≥ 125 μm) or reticular drusen only or soft distinct drusen with pigmentary abnormalities; late AMD: either geographic atrophy (i.e. well-demarcated area of retinal pigment atrophy with visible choroidal vessels) or neovascular AMD (i.e. presence of any of the following: serous or hemorrhagic retinal or retinal pigment epithelial detachment, subretinal neovascular membrane, or periretinal fibrous scar).

Assessment of dietary intake

The semi-quantitative Scottish Collaborative Group FFQ was used to assess the dietary intake of each participant (http://www.foodfrequency.org/). This validated tool consisted of 19 sections comprised of 170 food items. Participants had to indicate the frequency of consumption of each food item during the previous 2–3 month period. Frequency was measured in terms of the number of standard portions per day/week/month/rarely. Reported food intakes were converted into a daily weight using food portion sizes [30].

Dietary pattern identification

The individual food items within the FFQ were manually allocated to one of 38 food groups according to food type and macronutrient content (Table 1). Principal component analysis (PCA) with orthogonal rotation (varimax) was applied to this data to generate DP data and factor loadings for each individual food group. Examination of the scree plot was used to
determine the number of factors to be retained. To aid data interpretation, food groups which had a factor loading > 0.2 were retained for describing the DP. The PCA produced factor scores for each participant which were categorised into quartiles for each DP with the fourth quartile indicating greatest conformity to the specific DP.

**Demographic, lifestyle and anthropometric data**

A structured questionnaire was used to assess alcohol and smoking status, disease status (presence or absence) and medication usage. Diastolic blood pressure (DBP) and systolic blood pressure (SBP) were measured in a resting seated
Heart disease (IHD) and cerebrovascular accident (CVA).

25]. Model 1 was unadjusted; Model 2 was adjusted for age

n 83, 8.8%) and late AMD (n = 21, 2.2%). Images from 19

107 (11.4)

HTN, n (%) 390 (41.5)

Values are presented as mean (SD) for continuous variables and n (%) for categorical variables

AMD, age-related macular degeneration; BMI, body mass index; MABP, mean arterial blood pressure; CVA, cerebrovascular accident; HTN, hypertension; IHD, ischaemic heart disease

Table 2. The ‘healthy’ DP was characterised (in decreasing order of factor loadings) by lutein/zeaxanthin-rich vegetables, green leafy vegetables, alliums, vegetables, fruit, tomatoes, legumes, nuts, oily fish, low-fat dairy products, pizza, dressings/sauces/condiments, wholegrain breakfast cereal and red meat. The ‘unhealthy’ DP was characterised (in decreasing order of factor loadings) by chips, French fries, alcohol, high fat dairy products, soups, desserts, sugars and sweets, wholegrains, dressings/sauces/condiments, processed meat, potatoes, eggs, refined grains, refined breakfast cereal, chocolate, vegetables, red meat, white fish and shellfish. Together, the DP characterised accounted for approximately 16% of the total dietary variance within the population.

No significant differences in participant characteristics were observed across quartiles within the ‘healthy’ DP, with the exception of age (p < 0.001) and BMI (p = 0.05); females in the lowest quartile tended to be older and had a higher BMI compared to those in the other quartiles. Participants in the lowest quartile of the ‘unhealthy’ DP also tended to be older (p = 0.01) while those in the highest quartile were more likely to consume alcohol (p < 0.001) and smoke (p = 0.05) (data not shown).

Table 3. The ‘healthy’ DP was characterised (in decreasing order of factor loadings) by lutein/zeaxanthin-rich vegetables, green leafy vegetables, alliums, vegetables, fruit, tomatoes, legumes, nuts, oily fish, low-fat dairy products, pizza, dressings/sauces/condiments, wholegrain breakfast cereal and red meat. The ‘unhealthy’ DP was characterised (in decreasing order of factor loadings) by chips, French fries, alcohol, high fat dairy products, soups, desserts, sugars and sweets, wholegrains, dressings/sauces/condiments, processed meat, potatoes, eggs, refined grains, refined breakfast cereal, chocolate, vegetables, red meat, white fish and shellfish. Together, the DP characterised accounted for approximately 16% of the total dietary variance within the population.

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Table 3  Factor loading matrix for the two major dietary patterns identified in the Irish Nun Eye Study (n = 1033)

| Food groups                 | Healthy (Factor 1) | Unhealthy (Factor 2) |
|-----------------------------|-------------------|----------------------|
| Red meat                    | 0.263             | 0.234                |
| Processed meat              | –                 | 0.369                |
| White fish and shellfish    | –                 | 0.224                |
| Oily fish                   | 0.375             | –                    |
| Refined grains              | –                 | 0.302                |
| Wholegrains                 | –                 | 0.385                |
| Potatoes                    | –                 | 0.359                |
| French fries                | –                 | 0.511                |
| Chips                       | –                 | 0.554                |
| Pizza                       | 0.297             | –                    |
| Low fat dairy               | 0.305             | –                    |
| High fat dairy              | –                 | 0.466                |
| Eggs                        | –                 | 0.356                |
| Dressings                   | 0.29              | 0.382                |
| Desserts                    | –                 | 0.436                |
| Chocolate                   | –                 | 0.252                |
| Sugars and sweets           | –                 | 0.415                |
| Nuts                        | 0.386             | –                    |
| Soups                       | –                 | 0.452                |
| Alcohol                     | –                 | 0.482                |
| Fruit                       | 0.517             | –                    |
| Vegetables                  | 0.558             | 0.243                |
| L/Z rich vegetables         | 0.714             | –                    |
| Green leafy vegetables      | 0.696             | –                    |
| Legumes                     | 0.429             | –                    |
| Alliums                     | 0.59              | –                    |
| Tomato                      | 0.454             | –                    |
| Refined breakfast cereal    | –                 | 0.256                |
| Wholegrain breakfast cereal | 0.274             | –                    |

L/Z, lutein/zeaxanthin

There was no significant difference in AMD risk (i.e. controls versus AMD) across quartiles of either the ‘healthy’ or ‘unhealthy’ DP, in both the unadjusted and adjusted analyses (Table 4). Participants who adhered closely to an ‘unhealthy’ DP had a greater risk of AMD compared to those in the other quartiles, although this failed to reach significance. In the unadjusted analysis (model 1) the odds ratio for AMD in the highest fourth of the ‘healthy’ DP (i.e. most healthy) compared to the lowest fourth (i.e. least healthy) was 0.86 (95% CI 0.48–1.55; P = 0.62), while the odds ratio for AMD in the highest fourth of the ‘unhealthy’ DP (i.e. most unhealthy) compared to the lowest fourth (i.e. least unhealthy) was 1.50 (95% CI 0.82–2.75; P = 0.19). Model 2 was adjusted for age and BMI (‘healthy’ OR = 1.51 (95% CI 0.80–2.86; P = 0.20), ‘unhealthy’ OR = 1.34 (95% CI 0.71–2.54; P = 0.37). Model 3 was adjusted for model 2 covariates plus smoking and alcohol status, hypertension, DM, IHD and CVA (‘healthy’ OR = 1.50 (95% CI 0.79–2.86; P = 0.21), ‘unhealthy’ OR = 1.45 (95% CI 0.76–2.78; P = 0.26)).

Discussion

To our knowledge, this is the first study to examine associations between a posteriori-derived DP and AMD risk in a European population. Two major DP were identified using PCA and labelled as ‘healthy’ and ‘unhealthy’ with no evidence of association with AMD risk in this older population with a restricted lifestyle. Previous evidence of the association between DP and AMD risk is limited and somewhat conflicting [14, 15]. The MCCS found no association between DP and early AMD risk. However, they noted that a ‘grains and fish’ DP, characterised by frequent consumption of boiled rice, muesli, fish (not fried), chicken (not fried), vegetables, and avoidance of white bread was associated with 51% reduced odds of late AMD while a diet characterised by red and processed meats and fried foods was significantly associated with a higher prevalence of late AMD across quartiles of adherence [25]. In contrast to our findings, results from the US-based AREDS study by Chiu et al. identified strong associations between an ‘Oriental’ and ‘Western’ DP with decreased and increased risk for both early and late AMD, respectively [14]. However, comparing DP across the various studies is challenging given the complexity of the composition of the DP and the geographical variations in dietary intake. In addition, potential confounding from known or unknown variables such as genetic data (effect modification due to genotype) or variation in the classification of AMD definitions could limit detectable associations with dietary outcomes [10].

Other studies have considered various combinations of single foods and nutrients and AMD risk [11, 31]. A retrospective case-control study examining diet quality used the Alternate Healthy Eating Index (AHEI) to evaluate scores for the intake of five different food groups (grains, fruits, vegetables, meat and milk) and both total and saturated fat intake, identifying participants in the highest quartile of dietary quality with lower risk of late AMD (OR, 0.54; 95% CI, 0.33–0.81) compared to those in the lowest quartile. However, no association was found using a HEI score [31]. The Carotenoids in Age-Related Eye Disease Study (CAREDS) used FFQ data from 1313 female participants aged 55 to 74 years to generate a modified HEI (mHEI) which considered intake of whole grains, vegetables, fruits, meat, beans, eggs, fish and milk, total fat, saturated fat, sugar and alcohol [11, 32]. Their results showed a 46% lower odds for early AMD in the highest mHEI quintile compared to the lowest quintile (OR, 0.54; 95% CI, 0.33–0.88) [11]. Merle and colleagues assessed associations between progression to late AMD and adherence to a Mediterranean diet in 2525 AREDS participants [33]. An alternate Mediterranean diet (aMeDi) score
was used to evaluate the intake of nine food groups (whole grains, fruit, vegetables, legumes, nuts, red and processed meats, fish, alcohol) as well as a mono-unsaturated to saturated fats ratio. A 26% lower risk of progression to late AMD was significantly associated with an elevated aMeDi score after adjusting for age, sex, AMD grade, total energy intake, AREDS treatment, smoking, BMI, educational level, supplement use and 10 genetic variants (hazard ratio [HR], 0.74; 95% CI, 0.61–0.91; P-trend = 0.007) [33].

This study had a number of key strengths: the standardised collection of data including potential confounding factors, the photographic grading of AMD from high-resolution digital macula-centred images and the use of phenotypic data from both eyes of each participant for analysis. AMD classification was undertaken in an independent retinal grading centre without any knowledge of the associated nutritional data. The use of DP to evaluate a broader overview of dietary intake as opposed to the assessment of individual nutrients or foods alone provides a more comprehensive understanding of the synergistic interactions between food consumption and disease risk and reduces the influences of residual confounding. The use of an a posteriori approach for DP analysis is also considered to be an approach that is free from the constraints of a priori hypotheses [34, 35].

Limitations of this study include the cross-sectional design which prevents determination of causal influences associated with dietary intake. An ‘unhealthy’ DP characterised by a range of ‘unhealthy’ foods may be associated with increased risk of AMD, however due to the low prevalence of AMD in this population (n = 83 for early AMD and n = 21 for late AMD), and the fact that this cohort were reasonably healthy given their age (96% non-smokers, 91% non-drinkers and 45% with a normal BMI) and consuming a restricted diet, statistical power to detect an association with AMD may have been limited. Although, we evaluated dietary intake as a whole and the analysis included known non-dietary confounders, it is possible that residual confounding still represents a concern. However, the homogeneous lifestyle of this cohort is likely to have limited residual confounding. There are also limitations associated with the assessment of dietary intake. Although FFQs are commonly used to infer DP and dietary intake in epidemiological studies, they are nonetheless prone to inherent error and are limited in their ability to assess all dietary components. Although 170 foods were considered within the FFQ, additional foods consumed may have been missed. There are also drawbacks of DP analysis including consolidation of the food items into groups, choosing the number of factors to be retained, selecting the method of rotation and naming the factors identified. As this was a cross-sectional study, AMD status and dietary intake were only assessed at a single time point and therefore we were unable to account for temporal changes over a period of time. However, other studies have used comparable methods and highlighted the reproducibility of DP over time [36, 37].

In conclusion, this study showed no evidence of an association between DP and AMD risk in an ageing and well-characterised cohort with a restricted lifestyle. Nevertheless, increasing evidence suggests unhealthier food choices may contribute to increased AMD risk [3, 11, 31]. Critically, further longitudinal assessment and intervention studies are necessary to evaluate dietary intake of specific foods and DP as a risk factor for AMD, particularly in older adults with late AMD.

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**Compliance with ethical standards**

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

This article does not contain any studies with animals performed by any of the authors.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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