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► **To cite this version:**

Cécile Delcourt, Isabelle Carrière, Jean-Paul Cristol, Annie Lacroux, Mariette Gerber, et al.. Dietary fat and the risk of age-related maculopathy: the POLANUT Study.: Dietary fat and ARM. *European Journal of Clinical Nutrition*, Nature Publishing Group, 2007, 61 (11), pp.1341-4. 10.1038/sj.ejcn.1602685 . inserm-00185021

HAL Id: inserm-00185021

<https://www.hal.inserm.fr/inserm-00185021>

Submitted on 5 Nov 2007

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Dietary fat and the risk of age-related maculopathy : the POLANUT Study

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Financial support :

This study was supported by the Institut National de la Santé et de la Recherche Médicale, Paris, France; by grants from the Fondation de France, Department of Epidemiology of Ageing, Paris, the Fondation pour la Recherche Médicale, Paris, the Région Languedoc-Roussillon, Montpellier, France

and the Association Retina-France, Toulouse; and by financial support from Rhône Poulenc, Essilor and Specia, and the Centre de Recherche et d'Information Nutritionnelle, Paris.

Guarantor : C. Delcourt

Contribution of authors : CD designed and managed the study and wrote the first draft. IC performed the data management and carried out the statistical analysis. AL managed the data collection. MG provided the nutritional questionnaire and participated in the study design and data analysis. JPC participated in the study design and data analysis and interpretation. All authors were involved in writing the final draft of the manuscript.

Running title: Dietary fat and ARM

ABSTRACT

This study aimed at assessing the associations of dietary fat with the risk of age-related maculopathy (ARM), in the framework of a population-based study from Southern France. Nutritional data were collected using a dietitian-administered food-frequency questionnaire. ARM was classified from retinal photographs using the international classification and included neovascular age-related macular degeneration, geographic atrophy, soft indistinct drusen, soft distinct drusen associated with pigmentary abnormalities. After multivariate adjustment, high total, saturated and monounsaturated fat intake were associated with increased risk for ARM (OR= 4.74, p=0.007; OR=2.70, p=0.04 and OR= 3.50, p=0.03, respectively). Total polyunsaturated (PUFA) was not significantly associated with ARM. Total and white fish intake were not significantly associated with ARM, but fatty fish intake (more than once a month versus less than once a month) was associated with a 60 % reduction in risk for ARM (OR=0.42, p=0.01).

Keywords : age-related maculopathy, dietary fat, unsaturated fats, epidemiology

1 **Introduction**

2 Although age-related maculopathy (ARM) is the leading cause of blindness in industrialized countries
3 (Resnikoff *et al.*, 2004), its pathogenesis remains unclear. Clearly identified risk factors are smoking
4 (Klein *et al.*, 2004) and the polymorphism of the genes of apolipoprotein E (Baird *et al.*, 2004,
5 Zarepari *et al.*, 2004) and Complement Factor H (Donoso *et al.*, 2006), pointing, respectively, to the
6 implication of lipid metabolism and inflammation in the etiology of ARM. In animal models, a high fat
7 diet, combined with human variants of apolipoproteins, leads to retinal lesions similar to those
8 observed in ARM (Espinosa-Heidmann *et al.*, 2004, Malek *et al.*, 2005). Besides, the human retina is
9 rich in ω 3 polyunsaturated fatty acids (PUFA), and in particular in docosohexaenoic acid (DHA) which
10 may play an important structural and protective role in the macula (SanGiovanni and Chew, 2005).
11 DHA is mainly provided by fish and seafood.

12 Epidemiological data on the associations between dietary fat and ARM are scarce and partly
13 inconsistent (Cho *et al.*, 2001, Heuberger *et al.*, 2001, Mares Perlman *et al.*, 1995, Seddon *et al.*,
14 2003, Seddon *et al.*, 2001, Smith *et al.*, 2000). In the present study, we assessed the relationships of
15 dietary fat and fish intake with the risk of ARM, in a population-based study from Southern France.

16

17 **Methods**

18 The POLA (Pathologies Oculaires Liées à l'Age) study is a population-based study, aiming at the
19 identification of the risk factors of cataract and age-related maculopathy (Delcourt *et al.*, 1998). Briefly,
20 from 1995 to 1997, 2584 subjects aged 60 years or more were recruited from the population of Sète, a
21 harbour on the French Mediterranean. In 1998-2000, 1947 of 2452 survivors (79.4 %) participated in a
22 follow-up ocular examination.

23 In 2002-2003, surviving participants aged 70 years or more were invited to participate in a dietary
24 survey (POLANUT Study). Of the 1393 survivors, 832 (59.7 %) participated in the POLANUT study.
25 Nutritional data were collected using a validated food frequency questionnaire consisting of 165 items
26 and a validated set of photographs for the estimations of portions (Daures *et al.*, 2000). The interview
27 was conducted by trained dieticians and lasted 45 to 60 minutes. There were three questions for fish:
28 frequency and quantity of consumption of white fish (fresh cod, sole, whiting...), fatty "blue" fish (fresh
29 tuna, canned tuna without oil, mackerel, sardine, salmon...) and fatty fish canned in oil (tuna, sardine,
30 anchovy). The last two questions were grouped for the estimation of fatty fish intake.

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In the present study, ARM status was assessed from the retinal photographs taken at the follow-up examination (1998-2000) and graded according to the International Classification (Bird *et al.*, 1995). Late ARM was defined by the presence of neovascular age-related macular degeneration or geographic atrophy. Early ARM was defined by the presence of soft indistinct drusen ($>125 \mu\text{m}$) and/or soft distinct drusen ($>125 \mu\text{m}$) associated with pigmentary abnormalities (hyper- or hypopigmentation), in the absence of AMD (Delcourt *et al.*, 2005). Of the 832 subjects who participated in the dietary survey, we excluded 20 subjects (2.4 %) with total energy intake lower than 3300 kJ/day or above 12500 kJ/day. Of the 812 remaining subjects, 701 (86.3 %) had gradable photographs and data for adjustment variables, of which 10 (12 eyes) with late ARM and 38 (46 eyes) with early ARM. Because of the small number of subjects with late ARM, we pooled early and late ARM in all statistical analyses. For dietary fats, we first calculated energy-adjusted intake, using the residuals method developed by Willett (Willett, 1998). We then determined the 20th and 80th percentile values, which formed three groups (low quintile, middle quintiles, high quintile). In order to take into account data from both eyes and their correlation, we used logistic Generalized Estimating Equations models for all analyses.

Results

After adjustment for age and gender, risk of ARM was increased in subjects with high intake of total and monounsaturated fat (p for trend= 0.008 and 0.02, respectively), and tended to be increased in those with high saturated fat intake (p for trend=0.06). Total PUFA intake was not significantly associated with ARM (Table 1). Further adjustment for body mass index, smoking and self-reported cardiovascular disease did not materially affect the results. Further adjustment on total fat considerably attenuated the associations of monounsaturated and saturated fat with the risk of ARM. Concerning fish intake, total fish intake was not significantly associated with ARM, neither were white fish or other sea foods (Table 2). After full multivariate adjustment, including total fat intake, fatty fish tended to be associated with a reduced risk of ARM, with an odds-ratio of 0.26 (95 % confidence interval: 0.11-0.64) for intake lower than 10 g/day and 0.64 (0.31-1.30) for intake greater than 10 g/day, by comparison with subjects reporting no intake of fatty fish (less than once a month). The multivariate-adjusted odds-ratio for these two categories combined, corresponding to intake of fatty

1 fish more than once a month compared to less than once a month, was 0.42 (95 % confidence
2 interval: 0.21 – 0.83, p=0.01).

3

4 **Discussion**

5 High total fat intake has been associated with increased risk for ARM in two prospective studies (Cho
6 *et al.*, 2001, Seddon *et al.*, 2003), while there was a trend which did not reach statistical significance in
7 4 cross-sectional or case-control studies (Heuberger *et al.*, 2001, Mares Perlman *et al.*, 1995, Seddon
8 *et al.*, 2001, Smith *et al.*, 2000). In all 4 studies distinguishing the types of fat, high MUFA intake was
9 associated with increased risk for ARM, while other types of fat gave inconsistent results (Cho *et al.*,
10 2001, Seddon *et al.*, 2003, Seddon *et al.*, 2001, Smith *et al.*, 2000). Associations with ω 3 PUFA, EPA
11 and DHA or fish intake were generally consistent with a modest risk reduction for high intakes (odds-
12 ratios ranging from 0.4 to 0.9 across studies), but reached statistical significance only in two studies
13 (Cho *et al.*, 2001)(Smith *et al.*, 2000), illustrating the limitations of food data relative to ω 3 PUFA .
14 Similarly to the present study, in the study by Cho *et al.*, reduction in risk for ARM was mainly
15 associated with intake of canned tuna, a main component of fatty fish intake.

16 Limitations of the present study include dietary assessment performed 3 years after retinal
17 photography; impossibility to separate early and late ARM in statistical analyses because of small
18 number of subjects; and low statistical power, in particular for the detection of modest risk reduction.

19 In conclusion, our study is consistent with increased risk of ARM in subjects with high fat, and in
20 particular high MUFA, intake. The risk for ARM was reduced in subjects consuming fatty fish more
21 than once a month.

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