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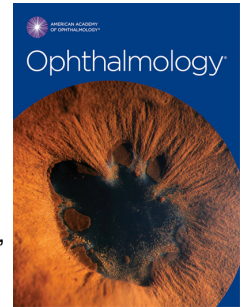
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# Accepted Manuscript



Mediterranean diet and incidence of advanced AMD: The EYE-RISK CONSORTIUM

Bénédicte M.J. Merle, PhD, Johanna M. Colijn, MD, MSc, Audrey Cougnard-Grégoire, PhD, Alexandra P.M. de Koning-Backus, MSc, Marie-Noëlle Delyfer, MD, PhD, Jessica C. Kiefte-de Jong, PhD, Magda Meester-Smoor, PhD, Catherine Féart, PhD, Timo Verzijden, MSc, Cécilia Samieri, PhD, Oscar H. Franco, MD, PhD, Jean-François Korobelnik, MD, Caroline C.W. Klaver, MD, PhD, Cécile Delcourt, PhD

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1 **Mediterranean diet and incidence of advanced AMD: The EYE-RISK CONSORTIUM**

2 Bénédicte MJ Merle, PhD<sup>1</sup>, Johanna M. Colijn, MD, MSc<sup>2,3</sup>, Audrey Cougnard-Grégoire,  
3 PhD<sup>1</sup>, Alexandra P.M. de Koning-Backus, MSc<sup>2,3</sup>, Marie-Noëlle Delyfer, MD, PhD<sup>1,4</sup>,  
4 Jessica C Kiefte-de Jong, PhD<sup>3</sup>, Magda Meester-Smoor, PhD<sup>2,3</sup>, Catherine Féart, PhD<sup>1</sup>,  
5 Timo Verzijden MSc<sup>2,3</sup>, Cécilia Samieri, PhD<sup>1</sup>, Oscar H. Franco, MD, PhD<sup>3</sup>, Jean-  
6 François Korobelnik, MD<sup>1,4</sup>, Caroline C.W. Klaver, MD, PhD<sup>2,3,5</sup>, Cécile Delcourt, PhD<sup>1</sup>  
7 for EYE-RISK consortium

8 1 Univ. Bordeaux, Inserm, Bordeaux Population Health Research Center, team LEHA,  
9 UMR 1219, F-33000 Bordeaux, France

10 2 Department of Ophthalmology, Erasmus University Medical Center, Rotterdam, The  
11 Netherlands

12 3 Department of Epidemiology, Erasmus University Medical Center, Rotterdam, The  
13 Netherlands

14 4 Service d'Ophtalmologie, Centre Hospitalier Universitaire Bordeaux, Bordeaux, France

15 5. Dept. Ophthalmology; Radboud University Medical Center; Nijmegen; the Netherlands

16 **Corresponding author:** Bénédicte MJ Merle, PhD “lifelong exposure health and aging”  
17 team, Research Center Inserm U1219, Université de Bordeaux – ISPED, 146, rue Léo  
18 Saignat, CS61292, 33076 Bordeaux Cedex.

**19 ABSTRACT****20 Objective**

21 To investigate associations of adherence to the Mediterranean diet (MeDi) with  
22 incidence of advanced AMD (the symptomatic form of AMD) in two European  
23 population-based prospective cohorts.

**24 Design**

25 Prospective cohorts: the Rotterdam Study I (RS-I) and the Alienor Study.

**26 Participants:**

27 4 446 participants aged  $\geq 55$  years from RS-I (The Netherlands) and 550 French adults  
28 aged 73 years or older from Alienor Study with complete ophthalmologic and dietary  
29 data were included in the present study.

**30 Methods**

31 Examinations were performed approximately every 5 years over a 21-year period (1990  
32 to 2011) in RS-I and every 2 years over a 4-year period (2006 to 2012) in Alienor Study.  
33 Adherence to the MeDi was evaluated using a 9 component score based on intake of  
34 vegetables, fruits, legumes, cereals, fish, meat, dairy products, alcohol and the  
35 monounsaturated-to-saturated fatty acids ratio. Associations of incidence of AMD with  
36 MeDi were estimated using multivariate Cox proportional Hazard models.

**37 Main outcomes measures**

38 Incidence of advanced AMD based on retinal fundus photographs.

**39 Results**

40 Among the 4 996 included participants, 155 developed advanced incident AMD (117  
41 from RS-I and 38 from Alienor Study). The mean follow-up time was 9.9 years (range  
42 0.6 to 21.7) in RS-I and 4.1 years (range 2.5 to 5.0) in Alienor Study.

43 Pooling data for both RS-I and Alienor study, participants with a high (6-9) MeDi score  
44 had a significantly reduced risk for incident advanced AMD compared to participants  
45 with a low (0-3) MeDi score in the fully-adjusted Cox model (HR, 0.59 [95% CI, 0.37-  
46 0.95], p for trend=0.04).

**47 Conclusion**

48 Pooling data from RS-I and Alienor, higher adherence to the MeDi was associated with a  
49 41% reduced risk of incident advanced AMD. These findings support the role of a diet  
50 rich in healthful nutrient-rich foods such as fruits, vegetables, legumes and fish in the  
51 prevention of AMD.

## 52 INTRODUCTION

53 Age-related macular degeneration (AMD) is the leading cause of blindness in  
54 industrialized countries<sup>1</sup>. This degenerative disease affects the central part of the retina,  
55 which is crucial for daily living tasks such as reading, driving and recognition of faces.  
56 Worldwide, 196 million people will be affected by AMD in 2020, increasing to 288 million  
57 in 2040<sup>2</sup>. Advanced forms of the disease (neovascular or atrophic AMD) associated with  
58 a deep visual impairment, are generally preceded by asymptomatic early stages. While  
59 no treatment is currently available for atrophic AMD, effective treatments are available  
60 for the neovascular form<sup>3,4</sup>. These treatments also incur major costs to society, with an  
61 estimated 2.3 billion dollars of Medicare claims in 2013<sup>5</sup>. The risk of developing AMD is  
62 jointly determined by age, individual genetic background and lifestyle<sup>1,6</sup>. Prevention  
63 strategies based on the modifiable risk factors of AMD may help decrease the major  
64 medical and social burden associated with AMD.

65 Epidemiological studies have observed a reduced risk of AMD associated with high  
66 consumption of antioxidants (lutein and zeaxanthin<sup>7-12</sup>, fruits and vegetables rich in  
67 these nutrients), and omega-3 polyunsaturated fatty acids<sup>8,9,13-15</sup>, provided by fish and  
68 nuts<sup>13,14,16,17</sup>. However a single nutrient/food approach cannot capture the synergistic  
69 effects of food and nutrients consumed in combination in the diet. The Mediterranean  
70 diet (MeDi) is characterized by high consumption of plant foods and fish, low  
71 consumption of meat and dairy products, olive oil as the primary fat source and a  
72 moderate consumption of wine<sup>18</sup>. Adherence to the MeDi has been linked to lower rates  
73 of mortality<sup>19</sup>, chronic diseases, stroke<sup>20</sup>, cognitive decline<sup>21</sup> and recently to diabetic  
74 retinopathy<sup>22</sup>. Regarding AMD, very few studies are available to date<sup>23-27</sup>. In three

75 population-based studies, it was associated with a lower prevalence of early AMD<sup>23</sup>,  
76 neovascular AMD<sup>25</sup> and any AMD<sup>26, 27</sup>, although dietary modifications due to AMD  
77 cannot be excluded in these cross-sectional studies. In a post-hoc analysis of a  
78 randomized clinical trial, the MeDi was associated with a lower incidence of advanced  
79 AMD<sup>24</sup>, but the selected nature of the sample limits its generalizability. We therefore  
80 investigated the associations between MeDi and incidence of advanced AMD in a large  
81 sample from two population-based prospective studies.

## 82 METHODS

### 83 Study population

84 The EYE-RISK project aims at identifying risk factors, molecular mechanisms and  
85 therapeutic approaches for AMD (<http://www.eyerisk.eu/>). It uses epidemiological data  
86 describing clinical phenotype, molecular genetics, lifestyle, nutrition and in-depth retinal  
87 imaging derived from existing European epidemiological cohorts to provide major  
88 insights needed for prevention and therapy of AMD. Within the EYE-RISK consortium, a  
89 unique harmonized database of individual data from 16 European epidemiological  
90 studies was constructed<sup>28</sup>. Two prospective studies with appropriate data for the present  
91 analyses were available: the Rotterdam Study I<sup>29</sup> (RS-I) and the Alienor Study<sup>30</sup>.

#### 92 *Rotterdam Study I*

93 At baseline 7 983 eligible persons aged 55 years or older were interviewed and  
94 examined. Ophthalmological examinations and fundus photography were taken at each  
95 round starting in 1990-1993 (RS-I-1). Follow-up rounds were completed in 1993-1995  
96 (RS-I-2), 1997-1999 (RS-I-3), 2002-2004 (RS-I-4) and 2009-2011 (RS-I-5).

97 The RS has been approved by the Medical Ethics Committee of the Erasmus MC  
98 (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and  
99 Sport (Population Screening Act WBO, license number 1071272-159521-PG). The RS  
100 has been entered into the Netherlands National Trial Register (NTR; [www.trialregister.nl](http://www.trialregister.nl))  
101 and into the WHO International Clinical Trials Registry Platform (ICTRP;  
102 [www.who.int/ictrp/network/primary/en/](http://www.who.int/ictrp/network/primary/en/)) under shared catalogue number NTR6831.



103 After pharmacologic mydriasis, 35° stereoscopic color fundus photos of the macula  
104 (Topcon TRV-50VT; Topcon Optical Co., Tokyo, Japan) were taken in each of the first 3  
105 visits, and 35° digital images (Topcon TRC 50EX) were taken for the fourth and fifth  
106 visits<sup>31</sup>.

### 107 *Alienor Study*

108 At baseline (2006-2008), 963 participants aged 73 years or more were interviewed and  
109 had an ophthalmological examination<sup>30</sup>. Of these, 624 and 614 were reexamined at the  
110 second (2009-2010) and third (2011-2012) visits, respectively. The design has been  
111 approved by the Ethical Committee of Bordeaux (Comité de Protection des Personnes  
112 Sud-Ouest et Outre-Mer III) in May 2006 ([http://www.alienor-study.com/langue-english-  
113 1.html](http://www.alienor-study.com/langue-english-1.html)).

114 The eye examinations took place in the Department of Ophthalmology of the University  
115 Hospital of Bordeaux. Two 45° non-mydratic color retinal photographs were taken using  
116 a high-resolution digital non-mydratic retinograph (Topcon TRC-NW6S)<sup>30</sup>. At the third  
117 visit (2011-2012), for participants who were not able to come to the hospital, the eye  
118 examination took place at home and 40° retinal photographs were taken using a digital  
119 non-mydratic portable retinograph (Optomed Smartscope M5).

120 For both studies, all participants provided written informed consent in accordance with  
121 the Declaration of Helsinki to participate in the study.

122

123

124

**125 AMD classification**

126 Retinal photographs of both eyes were graded by trained graders of each study and  
127 were interpreted according to a modification of the Wisconsin Age-Related System<sup>32</sup> for  
128 RS-I and according to the International Classification<sup>33</sup> for Age-Related Macular Degeneration. All advanced AMD  
129 cases were adjudicated and confirmed by retina specialists of the corresponding study.  
130 Phenotype harmonization was performed within the EYE-RISK Consortium<sup>28</sup>.

131

**132 Incidence**

133 At each visit, each subject was classified according to the worst eye into one of the  
134 following exclusive groups: no AMD, early AMD, advanced AMD. Advanced AMD was  
135 defined by the presence of neovascular or atrophic AMD.

136 Neovascular AMD included serous or hemorrhagic detachment of the retinal pigment  
137 epithelium (RPE) or sensory retina, subretinal or sub-RPE hemorrhages, and fibrous  
138 scar tissue. Geographic atrophy was defined as a discrete area of retinal  
139 depigmentation, 175  $\mu\text{m}$  in diameter or larger, characterized by a sharp border and the  
140 presence of visible choroidal vessels. Early AMD (in the absence of advanced AMD)  
141 was defined by the presence of (1) soft indistinct ( $\geq 125 \mu\text{m}$ , decreasing density from the  
142 center outward and fuzzy edges) / reticular drusen only or soft distinct drusen ( $\geq 63 \mu\text{m}$ ,  
143 with uniform density and sharp edges) and pigmentary abnormalities or by (2) soft  
144 indistinct large drusen ( $\geq 125 \mu\text{m}$ , decreasing density from the center outward and fuzzy  
145 edges) / reticular drusen and pigmentary abnormalities (corresponding to grades 2 and 3

146 of the Rotterdam Classification). No AMD was defined by the absence of early AMD and  
147 advanced AMD.

148 Incidence of advanced AMD was defined as the subject progressing from no or early  
149 AMD at baseline to advanced AMD (either neovascular or atrophic AMD) at any time-  
150 point during the study period. The date of occurrence of advanced AMD was calculated  
151 as the midpoint of the interval between the last visit without advanced AMD and the first  
152 visit with advanced AMD. Follow-up ended at the date of occurrence of advanced AMD,  
153 or the date of the last gradable photograph. Subjects with advanced AMD or no  
154 gradable eyes at baseline were excluded from the analysis.

155 For the purpose of AMD subtype analysis, neovascular AMD comprised all subjects  
156 presenting some neovascular lesions, with or without coexisting atrophy. Atrophic AMD  
157 was defined as pure geographic atrophy (in the absence of neovascular AMD).

158

### 159 **Dietary assessment**

160 In RS-I, participants completed a checklist at home and had a face-to-face interview  
161 conducted by a trained dietitian at the research center using a 170-items validated semi-  
162 quantitative food frequency questionnaire (FFQ)<sup>34</sup>. The food items were converted into  
163 quantities consumed per day (g/day). By using the computerized Dutch Food  
164 Composition Table, these dietary data were converted to total energy intake (TEI)  
165 (kcal/day) and nutrient intakes (g/day)<sup>34</sup>.

166 In Alienor, participants were visited at home by a specifically trained dietician who  
167 administered a 40-items validated FFQ and a 24-hour dietary recall<sup>35, 36</sup>. The food items

168 were converted into number of servings per day. The 24-hour recall was used to  
169 estimate nutrient intake (g/day) and TEI (kcal/day) and to compute the monounsaturated  
170 fatty acids (MUFAs) to saturated fatty acids (SFAs) ratio.

171 Adherence to the MeDi was assessed using the MeDi score developed by Trichopoulou  
172 et al<sup>37</sup>. This score including 9 components: vegetables, fruits, legumes, cereals, fish,  
173 meat, dairy products, alcohol and the MUFAs-to-SFAs ratio was applied to both studies.  
174 The daily intake of each food/beverage group was calculated as quantity in g/day in RS-I  
175 and as the number of servings/day in Alienor. Participants with unreliable TEI were  
176 excluded (valid TEI range: women: 600–3200; men: 600–4200 kcal). For each  
177 component hypothesized to benefit health (vegetables, fruits, legumes, cereals and fish,  
178 MUFAs-to-SFAs ratio), 1 point was given if intake was above the sex-specific median  
179 values and zero otherwise. For components presumed to be detrimental to health (meat  
180 and dairy products), 1 point was given if intake was below the sex-specific median  
181 values and zero otherwise. For alcohol, 1 point was given for moderate consumption  
182 and zero otherwise (moderate consumption: women: 1-10; men: 5-15 g/day). Sex-  
183 specific median were calculated separately for each study. The total MeDi score was  
184 computed by adding the scores (0 or 1 point) for each component for each participant.  
185 Scores ranged from 0 (non-adherence) to 9 (perfect adherence). Subjects were  
186 classified according to 3 categories of the MeDi score: low (0–3), medium (4–5), or high  
187 (6–9).

188

189

## 190 **Covariates**

191 Age (years), sex, education (primary, secondary, higher), smoking (never smoker,  
192 smoker <20 pack-years (PY), smoker  $\geq$ 20 PY, PY=packs (20 cigarettes) smoked per  
193 day X years of smoking), multivitamins/minerals supplement use (Yes/No) were  
194 measured using self-reported questionnaires at baseline<sup>30 38</sup> for each study. Vascular  
195 risk factors included body mass index (BMI: weight (kg)/height (m<sup>2</sup>)), diabetes (treated or  
196 self-reported), hypertension (blood diastolic blood pressure  $\geq$ 90mmHg or systolic blood  
197 pressure  $\geq$ 140mmHg or treated or self-reported), and hypercholesterolemia (treated or  
198 self-reported). *Complement Factor H (CFH) Y402H (rs1061170)* and *Age-Related*  
199 *Maculopathy Susceptibly 2 (ARMS2) A69S (rs10490924)*, the two main AMD-related  
200 SNPs were assessed in each study<sup>39, 40</sup>.

201

## 202 **Statistical analysis**

203 Subjects excluded from analyses were compared to those included using logistic  
204 regression model adjusted for age and sex for each characteristic separately. The same  
205 method was used to compare characteristics of subjects included between the two  
206 cohorts.

207 The associations of MeDi score with incidence of advanced AMD were analyzed using  
208 Cox proportional hazards models with delayed entry and age as a time scale, which  
209 allow for a better adjustment for age than the classical Cox models based on time from  
210 entry in the study<sup>41</sup>. Model 1 was unadjusted and model 2 was adjusted for sex, AMD  
211 grade at baseline (no or early AMD), TEI (continuous), education, BMI, smoking,  
212 multivitamins/minerals supplement use, diabetes and hypercholesterolemia. Variables

213 retained in model 2 were factors associated with incidence of AMD and/or with MeDi  
214 score, after adjustment for age and sex ( $p < 0.10$ ). For the pooled analysis, including data  
215 from both studies, models were further adjusted for the study (fixed study effect).  
216 Low MeDi score was designated as the reference group. P-trend was calculated by  
217 using the median value of the MeDi score for each category. In all Cox models, the  
218 proportional hazard assumptions were tested.

219 Participants from RS-I and Alienor were different regarding some characteristics. To  
220 estimate the potential effect of these differences, interactions between study and each  
221 covariate were assessed and none was significant. Thus, as the proportional hazard  
222 assumptions were satisfied and there were no interactions, to account for differences  
223 between the two studies, all models combining both studies were adjusted for a fixed  
224 study effect.

225

### 226 *Secondary analyses*

227 We also assessed whether associations of MeDi score with incident advanced AMD  
228 may be due to individual dietary components by examining associations between the  
229 individual components of the MeDi score and advanced AMD. Each component was  
230 introduced independently into model 2. In secondary analyses, *CFH* Y402H and *ARMS2*  
231 A69S polymorphisms were added to model 2. Interactions between *CFH* Y402H and  
232 *ARMS2* A69S polymorphisms and MeDi score were also analyzed. Interaction terms for  
233 the number of risk alleles and MeDi score were assessed separately for each genetic  
234 variant using model 2. All  $p$ -values representing a 2-tailed test of significance with

235  $\alpha=0.05$  and SAS version 9.4 (SAS Institute Inc. Cary, NC, USA) was used for all  
236 analyses.

ACCEPTED MANUSCRIPT

237 **RESULTS**

238 Of the 7 146 participants at risk of developing advanced AMD, 1 337 had no follow-up  
239 data for both eyes. In addition, 813 were excluded due to missing/unreliable dietary data  
240 (**Figure 1**). Overall 4 996 (4 446 from RS-I and 550 from Alienor) participants free from  
241 advanced AMD at baseline with complete and reliable dietary data together with follow-  
242 up information were included in our analyses.

243 Among the 4 996 included participants, 155 developed advanced incident AMD (117  
244 from RS-I and 38 from Alienor). The mean follow-up time was 9.9 years (range 0.6 to  
245 21.7) in RS-I and 4.1 years (range 2.5 to 5.0) in Alienor.

246 In both studies, participants included in the analyses tended to be younger than those  
247 excluded (**Table 1**). In RS-I, after adjustment for age and sex, included participants  
248 tended to be more women, to have a higher education, to have a history of smoking and  
249 diabetes, a lower TEI, a higher MeDi score and to carry less often a *CFH* Y402H CC  
250 genotype than excluded participants. In Alienor, included participants were more likely to  
251 have a higher education, than excluded participants.

252 Participants from RS-I, tended to be younger, to have a lower education, to have a  
253 history of smoking, to have less hypertension and less hypercholesterolemia as well as  
254 a higher TEI, a lower adherence to the MeDi score and to have less early AMD than  
255 participants from Alienor. Also *CFH* Y402H polymorphism was slightly different between  
256 the two studies.

257 Participants from Alienor tended to have a higher median of consumption of vegetables,  
258 cereals and fish, whereas subjects from RS-I tended to have a higher median of



259 consumption of dairy products. Consumption of fruits, legumes, meat and the MUFAs-to-  
260 SFAs ratio were similar (**eTable 1**).

261 For both studies, the incidence of advanced AMD was lower among subjects who had a  
262 high adherence to the MeDi score (**Figure 2**). The effect of MeDi is more noticeable  
263 among older people (85+), at higher risk of AMD, but as the proportional hazard  
264 assumption is respected, associations are considered similar among the different age  
265 groups.

266 In the unadjusted model, similar estimations were obtained in both studies, with a HR of  
267 0.56 [95% CI 0.33 to 0.96] in RS-I and 0.48 [95% CI 0.18 to 1.26] in Alienor for  
268 participants with a high MeDi score, by comparison with a low MeDi score (**Table 2**).

269 When pooling both studies, a high MeDi score was significantly associated with a lower  
270 risk for incident advanced AMD (HR, 0.53 [95% CI, 0.33-0.84], p-trend=0.009). These  
271 associations remained similar and significant after further adjustment for sex, TEI, AMD  
272 grade at baseline, education, BMI, smoking, supplement use of multivitamins/minerals,  
273 diabetes and hypercholesterolemia, (HR, 0.59 [95%CI, 0.37-0.95], p-trend=0.04).

274 In secondary analyses, we further adjusted for *CFH* Y402H and *ARMS2* genes and the  
275 HR remained unchanged (data not shown).

276 Interactions terms between MeDi and *CFH* Y402H and *ARMS2* genes were not  
277 statistically significant (p for interaction=0.89 and 0.18, respectively, data not shown).

278 Adherence to MeDi score was not significantly associated with the risk for incident  
279 neovascular AMD neither in RS-I nor in Alienor or in the pooled analysis (**Table 3**). It  
280 was significantly associated with the risk for incident atrophic AMD in RS-I (HR=0.41, p-

281 trend=0.046) but the association did not reach significance in Alienor (HR=0.52, p-  
282 trend=0.52). In the pooled data analysis, a higher MeDi score was significantly  
283 associated with a reduced risk for incident atrophic AMD (HR, 0.42 [95%CI, 0.20-0.90],  
284 p-trend=0.04).

285 We assessed whether the benefit of high adherence to the MeDi score was due to a  
286 specific component. Using the sex-specific median as cutoffs, no component was  
287 significantly associated with incidence of advanced AMD (**eTable 2**).

288 **DISCUSSION**

289 High adherence to the MeDi was associated with a 41% reduced risk of incident  
290 advanced AMD in the pooled analysis. None of the nine components, including  
291 vegetables, fruits, legumes, cereals, fish, the MUFAs-to-SFAs ratio, meat, dairy products  
292 and alcohol consumption, was significantly associated with incidence of advanced AMD,  
293 highlighting the importance of assessing dietary patterns rather than single components.  
294 In our studies, a high adherence to the MeDi was significantly associated with a reduced  
295 risk of incident atrophic AMD. A similar association was observed for neovascular AMD  
296 but did not reach statistical significance.

297 By evaluating the individual and the pooled associations of the adherence to the MeDi  
298 and incidence of advanced AMD in two well established and harmonized European  
299 population-based prospective cohorts, this study expands on prior studies, mainly cross-  
300 sectional, case-control, and clinical trials on this topic. Visual impairment due to AMD  
301 could influence dietary practices; prospective studies, by assessing diet prior the onset  
302 of the disease, limits reverse causation. Thus, prospective design is more accurate and  
303 less biased than a cross-sectional or case-control design to evaluate the association  
304 between diet and AMD. In addition, although using a prospective design, clinical trials  
305 are limited by the selected nature of the sample. Results from population-based studies  
306 are more generalizable.

307 Our results are partially consistent with previous cross-sectional studies: the CAREDS  
308 study reported a lower prevalence of early AMD in American women with high  
309 adherence to the MeDi<sup>23</sup>, the Coimbra Study demonstrated a lower prevalence of any

310 AMD in Portuguese participants who were having a high adherence to the MeDi<sup>26, 27</sup> and  
311 the European Eye Study (Eureye) showed a lower prevalence of neovascular AMD in  
312 subjects with a high MeDi score while atrophic AMD was not associated with MeDi  
313 score<sup>25</sup>. Our findings confirm the post-hoc analyses of the AREDS clinical trial. In this  
314 sample of American participants aged 55 to 80 years, a high MeDi score was associated  
315 with a 26% lower risk of progression to advanced AMD<sup>24</sup>. The AREDS study also  
316 showed that fish and vegetable components were associated with a lower risk of  
317 progression to advanced AMD<sup>24</sup>. Our results were in the same direction but did not  
318 reach the statistical significance when sex-specific median cutoffs were used. No  
319 significant interactions were observed between MeDi score and *CFH* Y402H and  
320 *ARMS2* genes. Our findings report a significant association with advance AMD.  
321 Regarding subtypes, only atrophic AMD was significantly associated with MeDi score.  
322 For neovascular AMD even if the association was not statistically significant, the HRs  
323 were similar to those for atrophic AMD. These differences could be explained by a low  
324 number of incident cases. In the Eureye Study, the only study to show separate results  
325 for the two advanced forms of AMD, association was significant with neovascular AMD.  
326 While in our studies this association with neovascular AMD was not statistically  
327 significant, HRs were similar to those for Eureye study.

328 Our results thus support public health efforts to emphasize adherence to the MeDi for  
329 everyone. The biological basis for the potential benefits of the MeDi is associated with a  
330 decrease in oxidative stress and inflammation, which are also involved in the  
331 pathophysiology of AMD<sup>42, 43</sup>.

332 The PREDIMED study, a clinical trial among persons at high cardiovascular risk,  
333 showed that adhering to a MeDi reduced the incidence of major cardiovascular events<sup>20</sup>.  
334 Median consumptions were similar to the goals suggested by PREDIMED for vegetables  
335 ( $\geq 2$  serving/d), fish ( $\geq 3$  serving/w) and meat ( $< 1$  serving/d) in Alienor and for meat in RS-  
336 -I. For both studies, median of fruits and legumes were below the goals of PREDIMED  
337 ( $\leq 3$  serving/d) as well as median of vegetables, and fish in RS-I. Even though the  
338 medians in our study were lower for vegetables and fruits, the association with the MeDi  
339 score was significant, suggesting the importance of a global approach to prevent the  
340 development of AMD.

341 By showing a prospective association between AMD and MeDi, an energy-unrestricted  
342 diet mainly composed of nutrient-rich food, our study confirms the importance of dietary  
343 quality focused on healthful foods and dietary patterns rather than single nutrients or  
344 low-energy diet for AMD.

345 In observational studies, residual confounding is always a concern. In the present study,  
346 results were similar in the basic model (unadjusted model) and the fully-adjusted model  
347 (adjusted for sex, TEI, AMD grade at baseline, cardiovascular risk factors, educational  
348 level and dietary supplement use), suggesting that our results are not highly  
349 confounded. In the fully-adjusted model, association between MeDi and incidence of  
350 AMD seems to be weaker in RS-I. This could be explained by a lower statistical power  
351 due to a low incidence of participants developing advanced AMD combined to the  
352 increasing number of covariates compared to the unadjusted model. In addition, our  
353 findings are based on prospective follow-up, thereby limiting reverse causation.  
354 However, only randomized clinical trials can prove the causal nature of the associations.

355 Such randomized clinical trials testing dietary interventions have proven to be efficient in  
356 the prevention of stroke<sup>20</sup> or diabetes<sup>44</sup>, for instance, but none are available in the field  
357 of AMD.

358 Selection bias cannot be completely dismissed, as participants included in this analysis  
359 were different from non-participants in both RS-I and Alienor. Moreover, participants  
360 included from RS-I were different from those from Alienor regarding some  
361 sociodemographic and medical characteristics as well as follow-up time duration and  
362 frequency. Incidence rates of AMD were also higher in Alienor than in RS-I. These  
363 differences might be explained by the older age at baseline and a closer follow-up (every  
364 2 years instead of 5 years in RS-I, with home examinations for participants unable to  
365 come to the hospital in Alienor but not in every RS-I follow-up visit), or by different  
366 incidence rates in France and the Netherlands.

367 The MeDi score uses cutoffs based on each study population and results can only be  
368 generalizable to similar populations. To calculate the MeDi score, we used validated  
369 FFQs for both studies, adapted to the specific dietary habits of each population (France  
370 and the Netherlands). As the FFQ in Alienor was a 40-items FFQ, we used the 24h  
371 recall to calculate the MUFAs-to-SFAs ratio and the TEI to increase the exactitude of  
372 their ascertainment, as previously published<sup>21</sup>. The distribution of the MeDi score was  
373 different between the two studies, participants from RS-I were less adherent. This result  
374 was expected in a North European population.

375 Despite these major differences in populations (different countries, different time  
376 periods, different generations and different diet habits) and methods (different follow-up

377 time and frequency, different dietary assessment methods), the association between  
378 MeDi and incidence of advanced AMD was similar in both cohorts. This association thus  
379 appears to be robust.

380 To strengthen our analyses, we excluded subjects with unusually high or low TEI and  
381 adjusted for several factors known to be related to MeDi and AMD. We used a well-known  
382 and validated score to assess diet and probable synergistic effects between nutrients  
383 and food groups. Our MeDi score was developed by using sex-specific thresholds  
384 according to each study to better account for differences between men and women and  
385 studies. Other strengths include a large sample from two well documented and data-  
386 harmonized population-based prospective cohorts in the framework of the European  
387 EYE-RISK project.

388 In conclusion, combined results from our two observational studies suggest that  
389 adopting an energy-unrestricted diet rich in healthful nutrient-rich foods such as fruits,  
390 vegetables, legumes and fish, and, reducing the unhealthy foods such as red and  
391 processed meats, savory and salty industrialized products may contribute to the  
392 prevention of AMD.

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542 **Figure 1.** Selection of participants for analyses.

543 **Figure 2.** Incidence of advanced AMD according to adherence to Mediterranean Diet

544 (MeDi) score.

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**Table 1.** Baseline characteristics of the Rotterdam Study I (RS-I) and the Alienor Study, according to participants included and excluded from analyses.

Characteristics	Rotterdam Study I			Alienor Study			P value <sup>c</sup> RS-I vs Alienor for included subjects
	Included <sup>a</sup> (n=4 446)	Excluded <sup>b</sup> (n=1 867)	P value <sup>c</sup>	Included <sup>a</sup> (n=550)	Excluded <sup>b</sup> (n=283)	P value <sup>c</sup>	
	No. (%)			No. (%)			
Age, mean (SD), y	66.9 (7.3)	73.4 (10.0)	<0.0001	79.2 (4.2)	81.1 (4.3)	<0.0001	<0.0001
Sex			0.006			0.61	0.08
Men	1813 (40.8)	766 (41.0)		209 (38.0)	108 (38.2)		
Women	2633 (59.2)	1101 (59.0)		341 (62.0)	175 (61.8)		
Education	N=4426	N=1808	<0.0001		N=283	0.03	<0.0001
Primary	2200 (49.7)	1151 (63.6)		301 (54.7)	180 (63.6)		
Secondary	1823 (41.2)	529 (29.3)		130 (23.7)	56 (19.8)		
Higher	403 (9.1)	128 (7.1)		119 (21.6)	47 (16.6)		
Smoking, pack-years	N=4131	N=1644	0.009	N=547	N=278	0.77	<0.0001
Never smoker	1501 (36.3)	667 (40.6)		356 (65.1)	179 (64.4)		
<20	1173 (28.4)	413 (25.1)		95 (17.4)	51 (18.3)		
≥20	1457 (35.3)	564 (34.3)		96 (17.5)	48 (17.3)		
Multivitamin/mineral supplement use	N=4442	N=1867	0.11		N=281	0.32	0.05
No	4070 (91.7)	1660 (88.9)		475 (86.4)	237 (84.3)		
Yes	370 (8.3)	207 (11.1)		75 (13.6)	44 (16.7)		
Body mass index, mean (SD), kg/m <sup>2</sup>	N=4426	N=1775	0.26	N=542	N=274	0.87	0.17
	26.3 (3.6)	26.2 (4.0)		26.0 (4.0)	25.9 (4.1)		
Diabetes	N=4444		0.003		N=281	0.33	0.63
No	3941 (88.7)	1693 (90.7)		489 (88.9)	243 (86.5)		
Yes	503 (11.3)	174 (9.3)		61 (11.1)	38 (13.5)		
Hypertension			0.28		N=281	0.48	<0.0001
No	1883 (42.3)	593 (31.8)		86 (15.6)	46 (16.4)		
Yes	2563 (57.7)	1274 (68.2)		464 (84.4)	235 (83.6)		
Hypercholesterolemia	N=4442		0.18		N=281	0.76	<0.0001
No	4317 (97.2)	1837 (98.4)		275 (50.0)	146 (52.0)		
Yes	125 (2.8)	30 (1.6)		275 (50.0)	135 (48.0)		
CFH (rs1061170)	N=3972	N=1581	0.02	N=450	N=235	0.81	0.03
TT	1649 (41.5)	632 (40.0)		212 (47.1)	101 (43.0)		
CT	1801 (45.3)	709 (44.8)		181 (40.2)	110 (46.8)		
CC	522 (13.2)	240 (15.2)		57 (12.7)	24 (10.2)		
ARMS2 (rs10490924)	N=3971	N=1582	0.16	N=450	N=235	0.12	0.11
GG	2490 (62.7)	1028 (65.0)		309 (68.7)	145 (61.7)		
GT	1339 (33.7)	500 (31.6)		126 (28.0)	85 (36.2)		



TT	142 (3.6)	54 (3.4)		15 (3.3)	5 (2.1)		
Total energy intake, mean (SD), kcal		N=687	0.0002		N=242	0.90	<0.0001
	1968 (484)	2016 (609)		1719 (530)	1704 (549)		
Mediterranean Diet score		N=398	0.04 <sup>d</sup>		N=209	0.70 <sup>d</sup>	<0.0001 <sup>d</sup>
Low 0-3	1376 (31.0)	153 (38.4)		171 (31.1)	58 (27.8)		
Medium 4-5	2123 (47.7)	181 (45.5)		236 (42.9)	100 (47.8)		
High 6-9	947 (21.3)	64 (16.1)		143 (26.0)	51 (24.4)		
AMD grade at baseline			0.11			0.05	0.001
No AMD	4179 (94.0)	1654 (88.6)		444 (80.7)	241 (85.2)		
Early AMD	267 (6.0)	213 (11.4)		106 (19.3)	42 (14.8)		

<sup>a</sup> Participants included in one or more analyses for incidence of advanced AMD

<sup>b</sup> Participants excluded from all analyses

<sup>c</sup> p value from logistic regression adjusted for age and sex

<sup>d</sup> p value from logistic regression adjusted for age, sex and total energy intake

**Table 2.** Association between Mediterranean Diet (MeDi) score and incidence of advanced age-related macular degeneration (AMD).

	No. at risk for advanced AMD	No. incident cases	Mediterranean Diet Score			P for trend <sup>a</sup>
			Low 0-3	Medium 4-5	High 6-9	
Model 1 <sup>b</sup>						
Rotterdam I HR (95% CI) <sup>c</sup>	4446	117	Reference	0.69 (0.46-1.03)	0.56 (0.33-0.96)	0.036
Alienor HR (95% CI) <sup>c</sup>	550	38	Reference	0.80 (0.39-1.63)	0.48 (0.18-1.26)	0.16
Overall HR (95% CI) <sup>d</sup>	4996	155	Reference	0.71 (0.50-1.00)	0.53 (0.33-0.84)	0.009
Model 2 <sup>e</sup>						
Rotterdam I HR (95% CI) <sup>c</sup>	4104	108	Reference	0.70 (0.46-1.06)	0.69 (0.40-1.20)	0.19
Alienor HR (95% CI) <sup>c</sup>	539	38	Reference	0.83 (0.38-1.80)	0.52 (0.19-1.40)	0.23
Overall HR (95% CI) <sup>d</sup>	4643	146	Reference	0.70 (0.49-1.01)	0.59 (0.37-0.95)	0.04

<sup>a</sup> p for trend is calculated using the median value for each Mediterranean Diet score category.

<sup>b</sup> Model 1, unadjusted model.

<sup>c</sup> estimated using Cox proportional hazard model.

<sup>d</sup> estimated using Cox proportional hazard model with additional adjustment for study.

<sup>e</sup> Model 2, adjusted for sex, total energy intake, AMD grade at baseline, education, body mass index, smoking, supplement use of multivitamins/minerals, presence of diabetes and hypercholesterolemia.

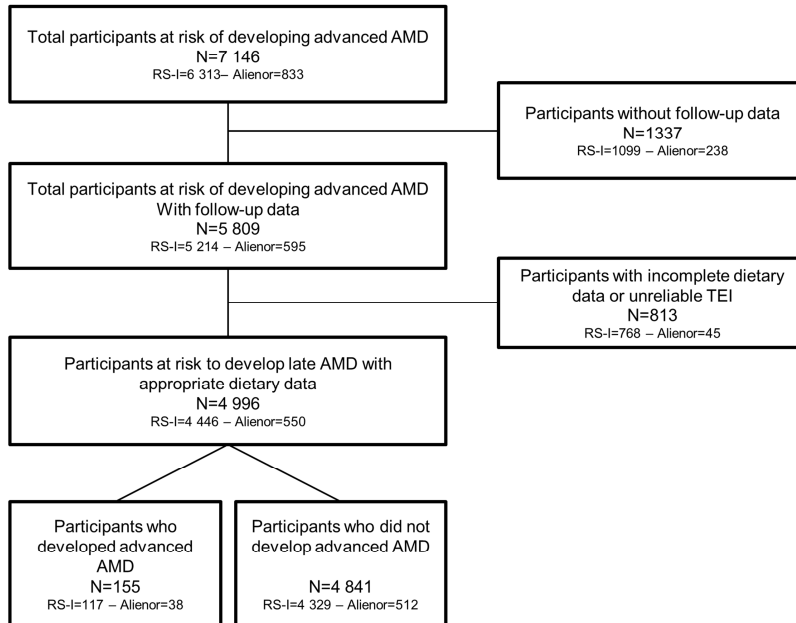
**Table 3.** Association between Mediterranean Diet score (MeDi) and incidence of advanced neovascular and atrophic age-related macular degeneration (AMD).

	No. at risk for advanced AMD	No. incident cases	Mediterranean Diet Score categories			P for trend <sup>a</sup>
			Low 0-3	Medium 4-5	High 6-9	
<b>Neovascular AMD</b>						
Rotterdam I	4104	68				
HR (95% CI) <sup>b</sup>			Reference	0.87 (0.51-1.51)	1.03 (0.53-1.99)	0.91
Alienor	538	18				
HR (95% CI) <sup>b</sup>			Reference	0.80 (0.25-2.63)	0.75 (0.20-2.91)	0.65
Overall	4642	86				
HR (95% CI) <sup>c</sup>			Reference	0.78 (0.48-1.27)	0.88 (0.49-1.57)	0.64
<b>Atrophic AMD</b>						
Rotterdam I	4104	52				
HR (95% CI) <sup>b</sup>			Reference	0.61 (0.34-1.10)	0.41 (0.16-1.03)	0.046
Alienor	538	21				
HR (95% CI) <sup>b</sup>			Reference	1.08 (0.38-3.06)	0.52 (0.13-2.12)	0.52
Overall	4642	73				
HR (95% CI) <sup>c</sup>			Reference	0.70 (0.42-1.15)	0.42 (0.20-0.90)	0.04

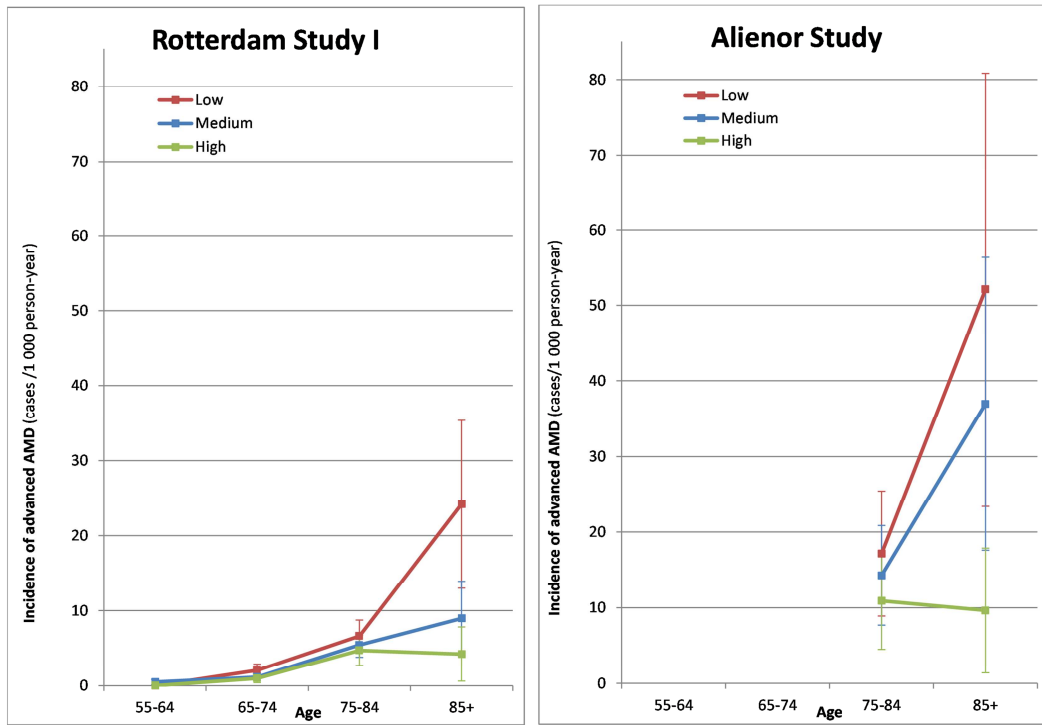
<sup>a</sup> p for trend is calculated using the median value for each MeDi score category.

<sup>b</sup> Cox proportional hazard model adjusted for sex, total energy intake, AMD grade at baseline, education, body mass index, smoking, supplement use of multivitamins/minerals, diabetes and hypercholesterolemia.

<sup>c</sup> Cox proportional hazard adjusted for sex, total energy intake, AMD grade at baseline, study, education, body mass index, smoking, supplement use of multivitamins/minerals, diabetes and hypercholesterolemia.



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**Highlights**

We examined the association of the Mediterranean diet with incident AMD in two European population-based prospective cohorts. A higher adherence to the Mediterranean diet was associated with a reduced risk of developing advanced AMD.