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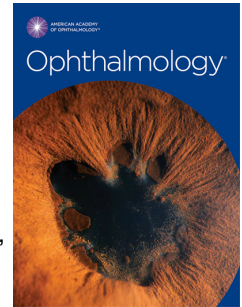
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1 **Mediterranean diet and incidence of advanced AMD: The EYE-RISK CONSORTIUM**

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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 ≥ 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 countries¹. 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 2040². 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^{3,4}. These treatments also incur major costs to society, with an
61 estimated 2.3 billion dollars of Medicare claims in 2013⁵. The risk of developing AMD is
62 jointly determined by age, individual genetic background and lifestyle^{1,6}. 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 zeaxanthin⁷⁻¹², fruits and vegetables rich in
67 these nutrients), and omega-3 polyunsaturated fatty acids^{8,9,13-15}, provided by fish and
68 nuts^{13,14,16,17}. 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 wine¹⁸. Adherence to the MeDi has been linked to lower rates
73 of mortality¹⁹, chronic diseases, stroke²⁰, cognitive decline²¹ and recently to diabetic
74 retinopathy²². Regarding AMD, very few studies are available to date²³⁻²⁷. In three

75 population-based studies, it was associated with a lower prevalence of early AMD²³,
76 neovascular AMD²⁵ and any AMD^{26, 27}, 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 AMD²⁴, 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 constructed²⁸. Two prospective studies with appropriate data for the present
91 analyses were available: the Rotterdam Study I²⁹ (RS-I) and the Alienor Study³⁰.

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)
101 and into the WHO International Clinical Trials Registry Platform (ICTRP;
102 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 visits³¹.

107 *Alienor Study*

108 At baseline (2006-2008), 963 participants aged 73 years or more were interviewed and
109 had an ophthalmological examination³⁰. 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)³⁰. 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 System³² for
128 RS-I and according to the International Classification³³ 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 Consortium²⁸.

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 μm 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 (≥ 125 μm , decreasing density from the
142 center outward and fuzzy edges) / reticular drusen only or soft distinct drusen (≥ 63 μm ,
143 with uniform density and sharp edges) and pigmentary abnormalities or by (2) soft
144 indistinct large drusen (≥ 125 μm , 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)³⁴. 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)³⁴.

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^{35, 36}. 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 al³⁷. 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^{30 38} for each study. Vascular
195 risk factors included body mass index (BMI: weight (kg)/height (m²)), 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^{39, 40}.

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 study⁴¹. 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 MeDi²³, the Coimbra Study demonstrated a lower prevalence of any

310 AMD in Portuguese participants who were having a high adherence to the MeDi^{26, 27} 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 score²⁵. 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 AMD²⁴. The AREDS study also
316 showed that fish and vegetable components were associated with a lower risk of
317 progression to advanced AMD²⁴. 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^{42, 43}.

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 events²⁰.
334 Median consumptions were similar to the goals suggested by PREDIMED for vegetables
335 (≥ 2 serving/d), fish (≥ 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 (≤ 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 stroke²⁰ or diabetes⁴⁴, 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 published²¹. 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 ^c RS-I vs Alienor for included subjects
	Included ^a (n=4 446)	Excluded ^b (n=1 867)	P value ^c	Included ^a (n=550)	Excluded ^b (n=283)	P value ^c	
	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 ²	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 ^d		N=209	0.70 ^d	<0.0001 ^d
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)		

^a Participants included in one or more analyses for incidence of advanced AMD

^b Participants excluded from all analyses

^c p value from logistic regression adjusted for age and sex

^d 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 ^a
			Low 0-3	Medium 4-5	High 6-9	
Model 1 ^b						
Rotterdam I HR (95% CI) ^c	4446	117	Reference	0.69 (0.46-1.03)	0.56 (0.33-0.96)	0.036
Alienor HR (95% CI) ^c	550	38	Reference	0.80 (0.39-1.63)	0.48 (0.18-1.26)	0.16
Overall HR (95% CI) ^d	4996	155	Reference	0.71 (0.50-1.00)	0.53 (0.33-0.84)	0.009
Model 2 ^e						
Rotterdam I HR (95% CI) ^c	4104	108	Reference	0.70 (0.46-1.06)	0.69 (0.40-1.20)	0.19
Alienor HR (95% CI) ^c	539	38	Reference	0.83 (0.38-1.80)	0.52 (0.19-1.40)	0.23
Overall HR (95% CI) ^d	4643	146	Reference	0.70 (0.49-1.01)	0.59 (0.37-0.95)	0.04

^a p for trend is calculated using the median value for each Mediterranean Diet score category.

^b Model 1, unadjusted model.

^c estimated using Cox proportional hazard model.

^d estimated using Cox proportional hazard model with additional adjustment for study.

^e 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.

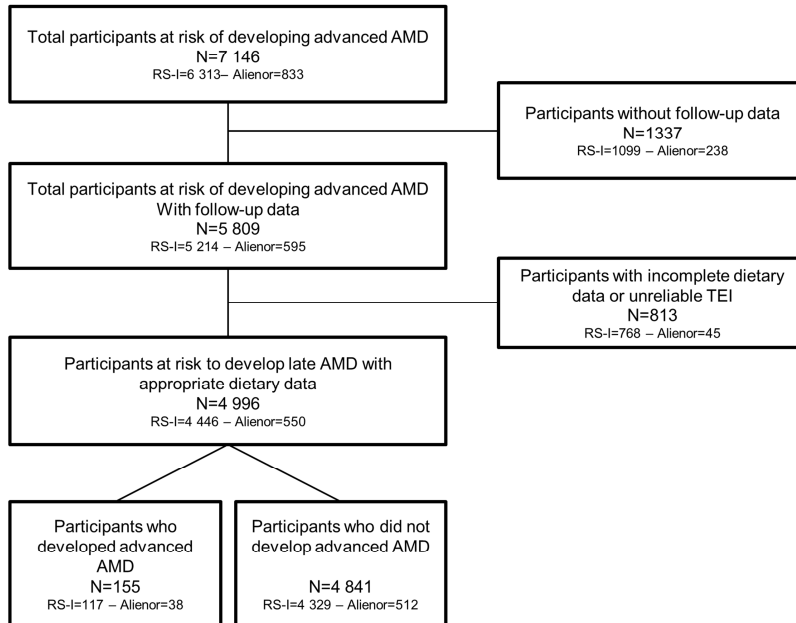
Table 3. Association between Mediterranean Diet score (MeDi) and incidence of advanced neovascular and atrophic age-related macular degeneration (AMD).

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

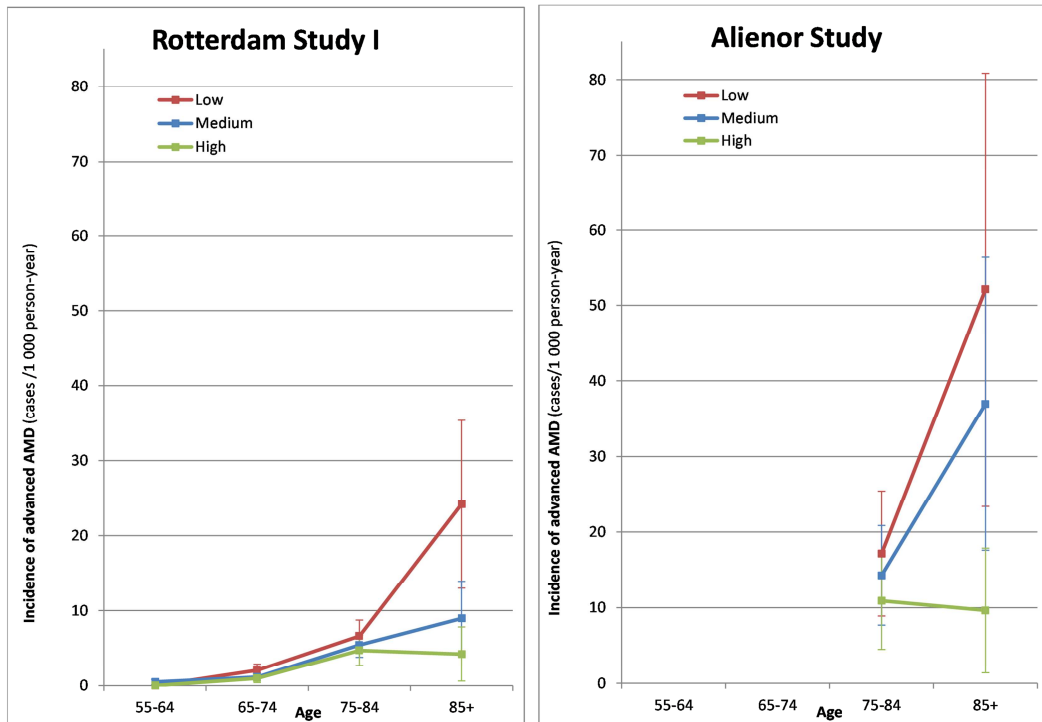
^a p for trend is calculated using the median value for each MeDi score category.

^b 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.

^c 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.