1 **Lifetime exposure to ambient ultraviolet radiation and the risk for cataract**

2 **extraction and age-related macular degeneration: the Alienor Study**

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30 **ABSTRACT**

31 Purpose: While exposure to ultraviolet radiation is a recognized risk factor for cataract, its association

32 is more controversial with age-related macular degeneration (AMD). We report the associations of

33 lifetime exposure to ambient ultraviolet radiation (UVR) with cataract extraction and AMD.

34 Methods: The Alienor Study is a population-based study of 963 residents of Bordeaux (France), aged

35 73 years or more. Lifetime exposure to ambient UVR was estimated from residential history and

36 Eurosun satellite-based estimations of ground UVR. It was divided in 3 groups (lower quartile,

37 intermediate quartiles, upper quartile), using the intermediate quartiles as the reference. Early and late

38 AMD were classified from retinal colour photographs. Cataract extraction was defined as absence of

39 the natural lens at slit lamp.

40 Results: After multivariate adjustment, subjects in the upper quartile of lifetime ambient UVR exposure

41 were at increased risk for cataract extraction (OR=1.53, 95 % confidence interval (CI): 1.04-2.26,

42 p=0.03) and for early AMD (OR= 1.59, 95 % CI: 1.04-2.44, p=0.03), by comparison with subjects in the

43 intermediate quartiles. Subjects in the lower quartile of UVR exposure were also at increased risk for

44 early AMD (OR=1.69, 95 % CI: 1.06-2.69, p=0.03), by comparison with those with medium exposure.

45 Associations of late AMD with UVR exposure was not statistically significant.

46 Conclusions: This study further confirms the increased risk for cataract extraction in subjects exposed

47 to high ambient UVR. Moreover, it suggests that risk for early AMD is increased in subjects exposed to

48 high UVR, but also to low UVR, by comparison with medium exposures.

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50 Keywords: macular degeneration, cataract, light exposure, ultraviolet radiation, risk factors,

51 epidemiology

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54   Cataract and age-related macular degeneration (AMD) are leading causes of blindness and visual

55   impairment worldwide [1]. Both of these diseases are multifactorial, involving non-modifiable (e.g. age,

56   gender, genetics) and modifiable factors [2, 3]. The control of these modifiable factors may represent a

57   preventive strategy for decreasing the incidence of these diseases and of the related visual

58   impairment. Among other modifiable factors (in particular smoking and nutrition) [2, 3], the potential role

59   of sunlight exposure in the aetiology of these diseases has been investigated [4] [5]. The absorption of

60   solar radiations by biological tissues results in photochemical reactions and the formation of reactive

61   oxygen species (including singlet oxygen) which may damage all cellular components (lipids, proteins,

62   DNA)[6]. The part of solar radiations that interacts with the eye is known as "optical radiations" and

63   includes wavelengths from ultraviolet (100-400 nm), visible light (400-760 nm) to infrared (760-10,000

64   nm). Ultraviolet radiations represent the most energetic part of optical radiations, and are thus

65   responsible for a large part of photochemical damage.

66   The crystalline lens is particularly exposed to phototoxic damage, because it absorbs most of

67   ultraviolet radiations (UVR), together with the cornea. This has been confirmed by epidemiological

68   studies, which have shown consistent associations of cataract (resulting from lens opacification) with

69   sunlight exposure and, in particular, UVR exposure [7-13]. , Ultraviolet exposure has been consistently

70   associated with the risk for cataract in numerous studies, performed in different continents with

71   different methodologies, showing dose-dependent relationships, and specific associations with cortical

72   cataracts. It is now a recognized risk factor for cataract [2].

73   By contrast, epidemiological data regarding the associations of light exposure with the risk for AMD

74   remain scarce and inconsistent. Several studies have suggested an increased risk for AMD in subjects

75   highly exposed to sunlight [14-17], but others showed no significant associations [18-20] and some even

76   suggested a decreased risk for AMD in the most exposed subjects [21, 22].

77   In the present study, we report the associations of lifetime exposure to ambient UVR with the risk for

78   cataract extraction and AMD, in the framework of a population-based cross-sectional study of elderly

79   subjects from the South of France.

80

81 **Subjects and Methods**

82 *Study aims*

83 The Alienor (Antioxydants, Lipides Essentiels, Nutrition et maladies OculaiRes) Study is a population-

84 based prospective study aiming at assessing the associations of age-related eye diseases (AMD,

85 glaucoma, cataract, dry eye syndrome) with nutritional factors (in particular antioxidants, macular

86 pigment and fatty acids).[23] It also takes into account other major determinants of eye diseases,

87 including gene polymorphisms, lifestyle and vascular factors.

88

89 *Study sample*

90 Subjects of the Alienor Study were recruited from an ongoing population-based study on the vascular

91 risk factors for dementia, the Three City (3C) Study [24]. The 3C Study included 9,294 subjects aged 65

92 years or more from three French Cities (Bordeaux, Dijon and Montpellier), among which 2,104 were

93 recruited in Bordeaux. Subjects were contacted individually from the electoral rolls. They were initially

94 recruited in 1999-2001 and followed-up about every two years since. The Alienor study consists in eye

95 examinations, which are offered to all participants from the third follow-up (2006-2008) of the 3C

96 cohort in Bordeaux. Among the 1,450 participants re-examined in 2006-2008, 963 (66.4 %)

97 participated in the first eye examination of the Alienor Study.

98 This research followed the tenets of the Declaration of Helsinki. Participants gave written consent for

99 the participation in the study. The design of this study has been approved by the Ethical Committee of

100 Bordeaux (Comité de Protection des Personnes Sud-Ouest et Outre-Mer III) in May 2006.

101

102 *Eye examination*

103 The eye examination took place in the Department of Ophthalmology of the University Hospital of

104 Bordeaux. It included a recording of ophthalmological history, measures of visual acuity, refraction,

105 two 45° non mydriatic color retinal photographs (one centred on the macula, the other centred on the

106 optic disc), measures of intraocular pressure and central corneal thickness and tear film break-up time

107 test. A self-completed questionnaire on risk factors specific to the eye (including residential history for

108　estimation of light exposure) and dry eye symptoms was filled at home and brought back on the day of

109　the eye examination.

110　Retinal photographs were performed using a high-resolution digital non mydriatic retinograph (TRC

111　NW6S, Topcon, Japan). Photographs were interpreted in duplicate by two specially trained

112　technicians. Inconsistencies between the two interpretations were adjudicated by a retina specialist for

113　classification of AMD and other retinal diseases, or by a glaucoma specialist for classification of

114　glaucoma. All cases of late AMD, other retinal diseases and glaucoma were reviewed and confirmed

115　by specialists. Graders had no access to light exposure variables, or any of the potential confounders.

116

117　***Cataract extraction***

118　In each eye, cataract extraction was defined as the absence of the natural crystalline lens at slit lamp.

119

120　***Classification of AMD***

121　Retinal photographs were interpreted according to the international classification[25] and to a

122　modification of the grading scheme used in the Multi-Ethnic Study of Atherosclerosis for drusen size,

123　location and area[26]. Eyes were classified according into one of the three exclusive groups: no AMD,

124　early AMD, late AMD.

125　Late AMD was defined by the presence of neovascular AMD or geographic atrophy within the grid

126　(3000 microns from the foveola). Neovascular AMD included serous or hemorrhagic detachment of the

127　retinal pigment epithelium (RPE) or sensory retina, subretinal or sub-RPE hemorrhages and fibrous

128　scar tissue. Geographic atrophy was defined as a discrete area of retinal depigmentation, 175 microns

129　in diameter or larger, characterized by a sharp border and the presence of visible choroidal vessels.

130　Five cases of late AMD had no gradable photographs and were classified using ophthalmological

131　history of AMD and AMD therapy (in particular intravitreal antiangiogenic agents and photodynamic

132　therapy), and confirmed by their treating ophthalmologist.

133　Early AMD was defined by the presence of soft distinct drusen and/or soft indistinct drusen and/or

134　reticular drusen and/or pigmentary abnormalities. Soft distinct and indistinct drusen were larger than

135   125 microns in diameter and with uniform density and sharp edges or decreasing density from the

136   center outwards and fuzzy edges, respectively. Pigmentary abnormalities were defined as areas of

137   hyperpigmentation and/or hypopigmentation (without visibility of choroidal vessels).

138

139   ***Ambient UVR exposure***

140   For each participant, average annual ambient UVR exposure was estimated using the residential

141   history, by weighting annual ambient UVR at each location by the time spent at that location.

142   Residential history from birth (locations, time spent at each location) was self-declared up to the first

143   eye examination (2006-2008). In France, locations were divided in 101 geographical areas,

144   corresponding to the 101 administrative « departments » (95 in metropolitan France and 6 overseas

145   departments). Concerning foreign countries, ambient UVR was generally estimated for the capital of

146   the country, except when the capital was very off-centered, in which case a more central location was

147   chosen. Very large countries (United States, China, etc) were excluded from this analysis, since an

148   estimation of solar radiation in a single geographic location is meaningless.

149   Average annual ambient solar radiation was assessed for the first 65 years of life, since almost all

150   subjects (97.3 %) lived in Bordeaux area beyond this age.

151

152   *Ultraviolet radiation*

153   In each location, UVR was extracted from Eurosun UV database (www.eurosun-project.org). Briefly,

154   UV irradiation levels were initially extracted from surface solar irradiance derived from the Meteosat

155   satellite's images. From these irradiation levels, the UV component was computed by a model which

156   exploits the algorithm set up by the Royal Institute of Meteorology, Belgium, published in the European

157   Solar Radiation Atlas (spectral model of Joukoff ESRA). The algorithm converts the total irradiance (E)

158   into its spectral distribution E(λ), every 10nm, and gives estimates for total UV (280-400 nm), UVA

159   (315-400 nm) and UVB (280-315 nm). The calculation of individual exposure assumes that the

160   irradiation levels in different regions remained constant over the years. The information provided by

161   Eurosun corresponds to the average of daily UV radiation over the period 1988-2007 for each location.

162 We conducted analysis of change in UV radiation over the period 1988-2007 in Eurosun maps and

163 found only minor changes of less than 1% yearly change. This observations were in line with the

164 results obtained from COST 726 which also reported a stability of UV irradiation in Europe for a period

165 of 50 years of data up to 2002 (the project COST 726's report and details are available at http://www-

166 med-physik.vu-wien.ac.at/uv/cost726/cost726.htm.). So these analyses from Eurosun data and

167 observation from COST 726 action are suggesting a stability of UV which let us assume no change

168 over time. These estimates were available for European and North African countries, with a resolution

169 of 5km. However, they are not available for other countries (Americas, Sub-saharian Africa, Asia,

170 Oceania).

171

172 *Estimation of missing ultraviolet radiation data using global solar radiation*

173 In each location, global ambient annual solar radiation (a measure of solar energy including all

174 wavelengths) was estimated using astronomical equations and the statistics of sunshine hours, using

175 the same methodology as in the POLA Study [13] . Overall, global ambient annual solar radiation

176 estimates were available in 116 locations (101 French departments, 7 European countries, 3 North

177 African countries, 5 other countries). In 105 locations (95 French departments, 7 European countries,

178 3 North African countries), both UVR and global solar radiation (GSR) estimates were available.

179 Pearson's correlation coefficient between these two variables was 0.952. For the 11 areas with

180 missing UVR but available solar radiation (6 French overseas departments and 5 countries), we thus

181 estimated ambient UVR from global solar radiation, using linear regression modeling. The regression

182 equation derived from the 105 locations with both UVR and GSR was: UVR= 5613.105 + 0.0729 x

183 GSR (r^2=0.91). The same analyses were performed for UVA and UVB, leading to the following

184 equations: UVA=5467.398 + 0.0710 x GSR ; UVB=145.708 + 0.00189 x GSR.

185 Finally, estimates of UVR exposure still could not be estimated for some countries. When, for a given

186 subject, the number of years spent in such countries was less or equal to 3 years, these countries

187 were eliminated from the calculations. For 71 subjects, average ambient UVR was therefore calculated

188 on 62, 63 or 64 years instead of 65. In addition, 113 subjects were excluded from the analyses

189 because they had spent more than 3 years in countries where UVR could not be estimated.

190

Other variables

192 The following potential confounders have been selected, based on literature results reporting

193 significant associations of AMD and/or cataract and/or light exposure with age, sex, educational level,

194 diabetes, hypertension, asthma, oral corticosteroid use, smoking, physical activity, body mass index

195 (BMI), plasma glucose and lipids, dietary intake of energy, antioxidants, lutein and zeaxanthin and

196 omega3 fatty acids[2, 3]. We also included the two major genetic polymorphisms associated with AMD

197 Complement Factor H (CFH) Y402H (rs1061170) and Age-Related Maculopathy Susceptibility 2

198 (ARMS2) A69S (rs10490924) polymorphisms[27-29]. These genetic polymorphisms were also strongly

199 associated with AMD in the Alienor study[30 31]. By comparison with subjects homozygous for the most

200 frequent allele (TT for CFH Y402H and GG for ARMS2 A69S), subjects homozygous for the less

201 frequent allele (CC for CFH Y402H, TT for ARMS2 A69S) exhibited 5- to 15- fold increased risk for

202 AMD. Heterozygous subjects (TC for CFH Y402H and GT for ARM2 A69S) exhibit intermediate risks

203 (2- to 5- fold increased risks). Indeed, all of these factors may represent confounders in the

204 relationship of AMD with lifetime ambient UVR, since lifestyle (smoking, physical activity, diet), health

205 conditions and genetic characteristics have been reported to vary according to geographical location,

206 and thus with lifetime ambient UVR[32-34].

207 Data were collected during a face-to-face interview using a standardized questionnaire administered

208 by a trained psychologist or nurse. At baseline (1999-2000), general data included: demographic

209 characteristics, educational level and smoking. BMI (kg/m^2) was calculated as weight/height^2 using

210 weight and height. Physical activity was assessed by 2 questions: "Do you practice sports?" (yes/no)

211 and "Do you perspire when you practice sports?" (Never/sometimes/most of the time/always). A 3-

212 level variable was computed to describe intensity of physical activity, as already published.[35] Plasma

213 glucose and lipids were measured at the Biochemistry Laboratory of the University Hospital of Dijon

214 from baseline fasting blood samples. Dietary intake of energy, antioxidants, lutein and zeaxanthin and

215 omega3 fatty acids were estimated from a 24h recall performed through face-to-face interview by

216 specifically trained dietitians in 2001-2002 [35, 36]. Genetic polymorphisms were determined by the Lille

217 Génopôle, from the DNA samples collected at baseline (1999–2001).

218

219

Statistical methods

221 First, associations of ambient solar radiation with socio-demographic factors, lifestyle, biological and

222 dietary parameters were performed using chi-square test or analysis of variance.

223 Associations of cataract extraction and AMD with ambient UVR were estimated using logistic

224 Generalized Estimating Equations (GEE) models [37], which allow taking into account the data from both

225 eyes and their intra-individual correlations. Adjusted odds-ratios were estimated using cataract

226 extraction or AMD as the dependent variable, and ambient UVR and potential confounders as the

227 independent variables. Ambient UVR was divided in three groups (lower quartile, intermediate

228 quartiles, upper quartile), the medium category being the reference. With regard to AMD, two models

229 were performed (for early and late AMD, respectively), subjects without any AMD being the reference

230 in both models. With regard to cataract, subjects without cataract extraction were the reference group.

231 With regard to cataract extraction, potential confounders retained in the analysis were known risk

232 factors for cataract [2] (age, gender, smoking, diabetes, oral corticosteroid use and asthma) and factors

233 significantly associated with ambient UVR (at $p<0.05$). Similarly, with regard to AMD, potential

234 confounders retained in the analysis were well known risk factors, which are strongly associated with

235 AMD in our cohort (age, gender, smoking [30], CFH [30] and ARMS2 [31] polymorphisms, dietary intake of

236 omega3 fatty acids [36]) and factors significantly associated with ambient UVR (at $p<0.05$). No

237 collinearity was detected between the variables included in the final models. No major confounding

238 was detected (variation by more than 10 % of the estimates of the odds-ratios when deleting one

239 confounder from the models). All statistical analyses were performed using statistical software (SAS,

240 version 9.1; SAS Institute Inc., Cary, NC).

241

RESULTS

243 Figure 1 presents the distribution of annual ambient UVR exposures (total UV, UVA and UVB),

244 estimated from residential history. These variables showed important inter-individual variability,

245 ranging respectively, from 32.39 kJ/cm^2 to 50.93 kJ/cm^2, 31.55 kJ/cm^2 to 49.61 kJ/cm^2 and 0.81

246 kJ/cm^2 to 1.32 kJ/cm^2. The central peaks correspond to subjects who spent all their life in the

247   Bordeaux area. As shown in Table 1 for total UVR, these subjects constitute the middle group

248   (intermediate quartiles), who were born and lived all their life in the South of France. By contrast, two

249   thirds of subjects from the lower quartile of ambient solar radiation were born in Central or Northern

250   France, where they spent about 23 years on average. Among subjects from the upper quartile, more

251   than a quarter were born in Northern Africa and remained there for 32 years on average

252   (corresponding to the independence of these countries in the 1960s) and 8.13 % were born in

253   Southern Europe. Although the definition of the intermediate quartiles is narrow (39.649-40.173

254   kJ/cm2), there is significant variability, with a mean of 38.375 kJ/cm^2 in the lower quartile, compared

255   with 42.718 kJ/cm^2 in the upper quartile. Similar findings were found for UVA and UVB (data not

256   shown).

257   Socio-demographic, lifestyle and biological characteristics of participants appear different according to

258   their lifetime solar exposure. As shown in Table 2, compared with subjects from the middle quartiles,

259   subjects in the higher quartile were more often males (42.58 % versus 31.74 %) and tended to have a

260   higher frequency of the TC genotype of CFH Y402H (47.12 % versus 37.43 %) and lower frequency of

261   TT genotype of CFH Y402H (45.03 % versus 49.21 %), while subjects from the lower quartiles had a

262   higher educational level (48.80 % with University degree versus 26.97 %) and tended to have a higher

263   frequency of the TC genotype of CFH Y402H (47.15 % versus 37.43 %) and lower frequency of TT

264   genotype of CFH Y402H (40.93 % versus 49.21%). As shown in Table 3, both subjects from the upper

265   and lower quartiles had more smoked during their life (18.36 % and 22.93 % having smoked more

266   than 20 pack-years respectively), by comparison with intermediate exposures (12.50 %). Subjects in

267   the upper quartile also had higher total energy intake (1835.7 Kcal/day versus 1678.2 Kcal/day).

268   These variables (education, smoking, CFH Y402H genotypes and total energy intakes) were therefore

269   considered as potential confounders in the analyses of association of solar radiation with cataract

270   extraction and AMD.

271   Cataract extraction status was available in at least one eye of 958 subjects (99.5%). Of those, 837 had

272   complete data for light exposure variables. In addition, 143 subjects had missing values in potential

273   confounders, leaving 694 subjects in the fully adjusted models, representing 1388 eyes among which

274   542 had undergone cataract surgery. Participants with missing data were not significantly different

275   from those without missing data, with regard to age, gender, ambient UVR or genetic polymorphisms

276   (data not shown). As shown in Table 4, after adjustment for confounders, by comparison with

277 participants exposed to medium ambient total UVR, participants exposed to high ambient total UVR

278 were at increased risk for cataract extraction (OR=1.53, 95 % CI: 1.04-2.26, p=0.03), while participants

279 with low exposure had similar risk as those with medium exposures (0.75 (0.51-1.12)). Similar results

280 were observed for UVA and UVB. Among the potential confounders included in the multivariate

281 models, those significantly associated with cataract surgery were age (OR=1.18 for 1-year increase,

282 95 % CI: 1.13-1.22, p<0.0001), gender (OR=1.86 for females versus males, 95 % CI: 1.23-2.80,

283 p=0.003), having smoked 20 pack-years or more (OR= 2.23, 95 % CI: 1.37-3.64, p=0.001), history of

284 asthma (OR=1.99 1.15-3.42, p=0.01).

285 AMD status was available in at least one eye of 875 subjects (91 %). Of those, 769 had complete data

286 for light exposure variables. In addition, 172 subjects had missing values in potential confounders,

287 leaving 597 subjects in the fully adjusted models, representing 1154 eyes among which 238 with early

288 AMD and 49 with late AMD. Participants with missing data were not significantly different from those

289 without missing data, with regard to age, gender, ambient UVR or genetic polymorphisms (data not

290 shown).Participants exposed to high ambient total UVR tended to be at increased risk for early AMD

291 (OR=1.59, 95 % CI: 1.04-2.44, p=0.03), by comparison with participants with medium exposures

292 (Table 5). In addition, participants exposed to low ambient solar radiation were increased risk for early

293 AMD (OR=1.69, 95 %CI: 1.06-2.69, p=0.03), by comparison with medium exposures. By contrast, no

294 statistically significant associations of late AMD with UVR exposures were found. Overall, results were

295 very similar for total UV, UVA and UVB exposures. Among the potential confounders included in the

296 multivariate models, those significantly associated with early AMD were age (OR=1.06 for 1-year

297 increase, 95% CI: 1.02-1.10, p=0.008), gender (OR=1.95 for females versus males, 95% CI: 1.19-

298 3.21, p=0.01), ARMS2 A69S GT genotype (OR=1.62, 95 % CI: 1.12-2.35, p=0.01), ARMS A69S TT

299 genotype (OR=12.09, 95 % CI: 4.63-31.55, p<0.0001) and CFH Y402H CC genotype (OR=1.89, 95%

300 CI: 1.13-3.16, p=0.01). The factors significantly associated with late AMD were age (OR=1.24, 95%

301 CI: 1.14-1.35, p<0.0001), gender (OR=2.93, 95 % CI: 1.16-7.43, p=0.02), ARMS A69S TT genotype

302 (OR=59.71, 95 % CI: 15.53-229.57, p<0.0001), CFH Y402H TC genotype (OR=3.49, 95% CI: 1.31-

303 9.30, p=0.009), CFH Y402H CC genotype (OR=6.68, 95 % CI: 2.05-21.77, p=0.001), dietary omega3

304 fatty acids intake (OR=0.63, 95% CI: 0.41-0.96, p=0.03) and secondary education (OR=7.46, 95 % CI:

305 1.63-34.05, p=0.01). We detected no significant interactions of genetic polymorphisms with UVR

306 exposure.

307

DISCUSSION

309 While confirming the well-known association of cataract with high ambient UVR, [7-13] the present study

310 suggests a U-shaped association of early AMD with ambient UVR, with increased risk both in low- and

311 high-UVR exposures. The effects of UVR on human health generally follows such a U-shaped (or J-

312 shaped) relationship[38]. Indeed, on one hand, high exposures have well documented effects on skin

313 diseases (skin cancers, sunburns and chronic sun damage…) and several eye diseases (acute

314 photokeratitis and conjunctivitis, acute solar retinopathy, pterygium, cortical cataract…)[38]. On the other

315 hand, cutaneous UVR exposure is necessary for endogenous production of vitamin D, so that low

316 UVR exposures are associated with an increased risk for osteo-muscular diseases and possibly of

317 other diseases related to vitamin D deficiency (in particular several cancers, cardiovascular disease,

318 autoimmune diseases) [38-40]. Indeed, besides its effects on bone health, vitamin D has many cellular

319 effects, including regulation of cellular differentiation, proliferation, apoptosis and angiogenesis [40], and

320 anti-inflammatory properties [41]. Many of these processes are implicated in the physiopathology of

321 AMD and some studies have suggested that low vitamin D status may be associated with an

322 increased risk for AMD [42-45]. Whether vitamin D deficiency may explain the higher risk for AMD

323 observed with low sunlight exposure in the present study will need to be determined in future studies.

324

325 Only few epidemiological studies have addressed the potential link of AMD with UVR exposure, with

326 inconsistent results. This is probably due to major methodological difficulties in the assessment of

327 UVR exposure. Indeed, UVR exposure and its health effects result from distal factors (such as latitude,

328 season, cloud cover, stratospheric ozone levels and lower atmospheric pollution), conditioning

329 ambient UVR, in addition to proximal factors (in particular occupational and leisure exposures to

330 sunlight, use of hats and sunglasses, skin pigmentation and sun sensitivity…)[46] conditioning individual

331 exposure and response to exposure. Moreover, previous studies have shown that health effects of

332 UVR exposure are cumulative over the lifetime. Thus, estimation of lifetime ocular UVR exposure

333 requires detailed questionnaires on lifetime distal and proximal factors, combined with complex

334 modeling of their effects on ocular UVR exposure. Since most epidemiological studies in the field of

335 AMD, including the present study, addressed not only the effect of sunlight exposure, but also of many

336   other factors (smoking, cardiovascular risk factors, genetics, nutrition…), only partial information on

337   distal and/or proximal factors was collected, limiting the validity of the estimates of UVR exposure, and

338   the comparability of studies.

339   The Maryland Watermen Study included detailed questionnaires of ocular exposures, combined with

340   field and laboratory data, in order to assess ocular UVR exposure. In this study, ocular UVR exposure

341   was not significantly associated with prevalent AMD [47]. In the Beaver Dam Eye Study, ambient UV-B

342   exposure, estimated from residential history, was not significantly associated with prevalent [15] or

343   incident [16, 17] AMD, but subjects having spent more than 5 hours/day outside during summer in their

344   youth were more likely to have prevalent[15] and incident AMD[16, 17]. In the POLA Study [22], performed in

345   the South of France, the risk for prevalent early AMD was higher in subjects exposed to low ambient

346   solar radiation. In the Blue Mountains Eye Study, prevalent AMD was associated both with high and

347   low sun sensitivity index, by comparison with medium sun sensitivity index[48], although this was not

348   confirmed in the prospective analysis of the same cohort[20]. Finally, an Australian case-control study,

349   AMD was associated with poorer tanning ability and lower time of ocular sunlight exposure[21].

350   In the present study, only estimates of ambient UVR exposure were available, based on residential

351   history and satellite-based estimates of UVR, while no data were available on sun-related behaviors,

352   skin pigmentation or sun sensitivity. This may have led to significant misclassification of exposures,

353   since actual ocular UVR exposure may be quite different from ambient UVR exposure in those

354   subjects with very low time spent outdoors. However, it seems most likely that misclassification was

355   unrelated to ambient UVR (i.e. that there would be similar proportions of people with low/high outdoors

356   activities in areas with different ambient UVR), and was thus unlikely to have biased the associations

357   of eye diseases with UVR exposure. Moreover, the well known association of UVR exposure with

358   cataract was confirmed in the present study, suggesting that our measure of UVR exposure had some

359   validity.

360   While the lack of information on proximal factors is clearly a limitation, the use of satellite-based

361   estimates of UVR is a strength. Indeed, most previous studies relied on formulas, estimating UVR

362   mainly from latitude and altitude. While these are major determinants of UVR, weather conditions also

363   contribute to actual ground UVR, in particular because of attenuation by cloud cover. UVR estimations

364   in the present study rely on Meteosat satellite measurements of total solar irradiance by the earth's

14

365   surface by reflection, over thirty years.

366   Using detailed estimation of ocular lifetime exposure, the Maryland Watermen study and the EUREYE

367   study have suggested that AMD risk may be associated with blue light exposure [14] [49], which is also

368   supported by animal and laboratory studies [6, 50]. In the present study, we could only estimate ambient

369   UVR, since no data on blue light are currently available in the Eurosun project. It is however difficult to

370   distinguish the effect of the different wavelengths, since they are naturally highly correlated. For

371   instance, in the present study, global solar radiation (a measure of solar energy including all

372   wavelengths) showed a correlation coefficient of 0.95 with UV radiation, measured in 105 geographical

373   areas.

374   The present study has several limitations. One limitation of our study could come from the

375   representativeness of the sample. The Alienor subsample tends to over-represent younger subjects

376   and high socioeconomic status, among subjects participating to the 3C Study[23]. The individuals

377   included in this study may therefore be healthier and have different lifestyles, particularly concerning

378   sunlight exposure, than the general population. These differences may have affected the distribution

379   of sunlight exposure or the prevalence of eye diseases. However, subjects participating in the 3C

380   study and included in the Alienor study were not different from those who were not included for most

381   parameters of interest in our study [23]. Furthermore, as described previously [23], the age-gender-

382   specific prevalence rates of AMD in the Alienor study were similar to that observed in other studies

383   performed in Europe [51, 52] and other industrialized countries [53]. Data collection was performed in the

384   same way in all individuals regardless of their AMD stage and photograph graders had no access to

385   sunlight exposure data. Therefore, we can assume that the error was not differential and was unlikely

386   to have biased the estimation of any of the associations of AMD with ambient solar radiation.

387   In observational studies, confounding is always a concern. We therefore adjusted for potential

388   confounders, including all known risk factors for cataract and AMD. However, we cannot totally

389   exclude residual confounding. In the present study, it is in particular striking that not only socio-

390   demographic and lifestyle variables varied with ambient UVR exposure, but also genetic background

391   (mainly CFH Y402H). While there are major differences in distribution of CFH Y402H alleles among

392   ethnic groups (with low frequency of the at-risk C allele in non-Europeans[54, 55]), to our knowledge,

393   there are no available data on its geographical distribution within the European continent (where most

394 of the Alienor participants were born). However, large variations of allele frequencies between

395 European countries have been reported, in particular for Apolipoprotein E [33]. Since AMD has a strong

396 genetic component, and there may be geographical variation in the distribution of gene

397 polymorphisms, gene polymorphisms may be confounders in the relationship of AMD with any factor

398 affected by geographical variation (including UVR exposure, but also lifestyle, diet…). This underlines

399 the importance of taking into account both environmental and genetic confounders in studies of

400 associations of eye diseases with sunlight exposure. None of the previously published studies took

401 potential genetic confounders into account. In the present study, although we took into account the

402 two major genetic risk factors for AMD (CFH Y402H and ARMS A69S), we cannot exclude that these

403 groups of subjects differ for other genetic factors related to AMD (complement factors CF1, C2, C3

404 and CFB, LIPC, CETP…[3]).

405 Since this study was cross-sectional, recall bias may have affected the results. However, only few

406 prospective studies are available in this field. Our study included only a small number of cases of late

407 AMD, which induced low statistical power for detecting associations with ambient solar radiation and of

408 interactions of genetic polymorphisms with UVR exposure. Finally, cataract status was determined

409 only on the basis of cataract surgery, rather than on the presence of lens opacities, which were not

410 available in our study because of lack of pupil dilation. This may have caused misclassification of

411 cataract status and therefore may have biased the estimates.

412 In conclusion, our study confirms the high risk for cataract in subjects exposed to high ambient solar

413 radiation. It also suggests a U-shaped association of early AMD with UVR exposure, with an increased

414 risk for both low- and high-exposures. This will need to be confirmed in future, possibly prospective,

415 studies. The reasons for a potentially increased risk for early AMD with low solar radiation remain

416 unclear and need to be further studied.

417

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Table 1. Light exposure-related characteristics of participants according to lifetime ambient total UVR exposure of the Alienor Study (Bordeaux, France, 2006-2008) (N=837)

	Total UVR, kJ/cm^2			
	≤ 39.649	]39.649-40.173[	≥40.173	p-value
	(N=209)	(N=419)	(N=209)	
Mean total UVR, kJ/cm^2 (sd)	38.375 (1.26)	39.887 (0.08)	42.718 (2.29)	
Place of birth (n (%)) (N=837)				
South of France	66 (31.58)	392 (93.56)	102 (48.80)	P<0.0001
Central France	52 (24.88)	9 (2.15)	14 (6.70)	
Northern France	88 (42.11)	12 (2.86)	14 (6.70)	
Southern Europe	0 (0.00)	4 (0.95)	17 (8.13)	
Northern Africa	0 (0.00)	1 (0.24)	57 (27.27)	
Other	3 (1.44)	1 (0.24)	5 (2.39)	
Time spent at place of birth, years (median (range)) (N=837)				
South of France	68 (39-89)	79 (55-94)	74 (35-92)	P<0.0001
Central France	22 (2-58)	13 (1-34)	20 (4-37)	P=0.11
Northern France	23.5 (3-69)	3.5 (1-42)	12.5 (1-31)	0.001
Southern Europe		2.5 (1-6)	17 (2-31)	0.03
Northern Africa		1 (1-1)	32 (17-48)	P<0.0001
Other	3 (1-6)	3 (3-3)	18 (1-30)	0.13

Table 2. Socio-demographic, medical and genetic characteristics of participants according to lifetime ambient total UVR exposure of the Alienor Study (Bordeaux, France, 2006-2008) (N=837)

	Ambient total UVR, kJ/cm^2			
	≤ 39.649 (N=209)	]39.649-40.173[(N=419)	≥40.173 (N=209)	p-value
Age, years (mean (sd)) (N=837)	80.50 (4.42)	80.21 (4.49)	79.96 (4.44)	0.46
Male gender (n (%)) (N=837)	87 (41.63)	133 (31.74)	89 (42.58)	0.008
Education (n (%)) (N=837)				
None or primary school	48 (22.97)	130 (31.00)	54 (25.84)	P<0.0001
Secondary school	34 (16.27)	137 (32.70)	63 (30.14)	(global)
High school	25 (11.96)	39 (9.31)	23 (11.00)	
University	102 (48.80)	113 (26.97)	69 (33.01)	
Diabetes (n (%)) (N=763)	23 (12.17)	53 (13.80)	21 (11.05)	0.63
Hypertension (n (%)) (N=837)	161 (77.03)	318 (75.89)	152 (72.73)	0.56
Asthma (n (%)) (N=828)	21 (10.14)	36 (8.67)	14 (6.80)	0.47
Oral corticosteroid use (n (%)) (N=837)	3 (1.44)	2 (0.48)	4 (1.91)	0.22
CFH Y402 H (n (%)) (N=766)				
TT (low AMD risk)	79 (40.93)	188 (49.21)	86 (45.03)	0.05
TC (intermediate AMD risk)	91 (47.15)	143 (37.43)	90 (47.12)	(global)
CC (high AMD risk)	23 (11.92)	51 (13.35)	15 (7.85)	
ARMS2 A69S (n (%)) (N=703)				
GG (low AMD risk)	118 (66.67)	232 (66.48)	112 (63.28)	0.91
GT (intermediate AMD risk)	53 (29.94)	103 (29.51)	59 (33.33)	(global)
TT (high AMD risk)	6 (3.39)	14 (4.01)	6 (3.39)	

Table 3. Lifestyle and nutritional characteristics of participants according to lifetime ambient total UVR exposure of the Alienor Study (Bordeaux, France, 2006-2008) (N=837)

	Ambient total UVR, kJ/cm^2			
	≤ 39.649 (N=209)	]39.649-40.173[(N=419)	≥40.173 (N=209)	p-value
Smoking (n (%)) (N=828)				
Non smoker	111 (54.15)	296 (71.15)	138 (66.67)	0.0005
< 20 pack-years	47 (22.93)	68 (16.35)	31 (14.98)	
≥ 20 pack-years	47 (22.93)	52 (12.50)	38 (18.36)	
Physical activity (n (%)) (N=837)				
Low	29 (13.88)	83 (19.81)	31 (14.83)	0.20
Medium	112 (53.59)	226 (53.94)	108 (51.67)	
High	47 (22.49)	76 (18.14)	43 (20.57)	
No answer	21 (10.05)	34 (8.11)	27 (12.92)	
Body mass index, kg/m^2 (mean (sd)) (N=829)	25.90 (4.00)	26.17 (3.97)	26.61 (3.65)	0.17
Fasting plasma measurements, mmol/l (mean (sd)) :				
Glucose (N=759)	5.16 (1.03)	5.13 (1.12)	5.13 (1.22)	0.96
Total cholesterol (N=787)	5.83 (0.91)	5.83 (1.03)	5.72 (0.92)	0.37
HDL- cholesterol (N=786)	1.60 (0.40)	1.61 (0.39)	1.57 (0.39)	0.66
LDL- cholesterol (N=785)	3.66 (0.80)	3.67 (0.91)	3.61 (0.79)	0.73
Triglycerides (N=786)	1.25 (0.61)	1.23 (0.60)	1.18 (0.48)	0.37
Dietary intake (mean (sd)):				
Total energy Kcal/day (N=797)	1835.7 (574.1)	1678.2 (513.4)	1704.5 (535.3)	0.003
Vitamin C, mg/day (N=797)	89.62 (56.98)	81.95 (60.96)	92.10 (82.66)	0.15
Vitamin E, mg/day (N=797)	6.72 (4.72)	6.30 (4.51)	6.70 (4.43)	0.45
Lutein and zeaxanthin, mg/day (N=781)	0.60 (0.92)	0.55 (0.91)	0.71 (0.90)	0.14
Omega 3 fatty acids, mg/day (N=797)	0.48 (1.20)	0.43 (1.00)	0.41 (1.16)	0.79

Table 4. Associations of cataract extraction with lifetime ambient UVR exposure in the Alienor Study (Bordeaux, France, 2006-2008) (Odds-ratios (OR) and 95 % confidence intervals (CI))

|	Cataract surgery				Odds-ratio*	P
	No		Yes			
	(N=846 eyes)		(N=542 eyes)			
	N	%	N	%		
Total UV (kJ/cm^2)						
≤39.649 (n=350 eyes)	230	65.71	120	34.29	0.75 (0.51-1.12)	0.16
]39.649-40.173[(n=696 eyes)	430	61.78	266	38.22	1.00 (ref)	
≥40.173 (n=342 eyes)	186	54.39	156	45.61	1.53 (1.04-2.26)	0.03
UVA (kJ/cm2)						
≤38.617 (n=350 eyes)	230	65.71	120	34.29	0.75 (0.51-1.12)	0.16
]38.617-39.131[(n=696 eyes)	430	61.78	266	38.22	1.00 (ref)	
≥39.131 (n=342 eyes)	186	54.39	156	45.61	1.53 (1.04-2.26)	0.03
UVB (kJ/cm2)						
≤1.028 (n=350 eyes)	230	65.71	120	34.29	0.75 (0.51-1.10)	0.14
]1.028 -1.042[(n=696 eyes)	430	61.78	266	38.22	1.00 (ref)	
≥1.042 (n=342 eyes)	186	54.39	156	45.61	1.53 (1.04-2.26)	0.03

* estimated using multivariate Generalized Estimating Equations (GEE) logistic regression models, adjusted for age, gender, educational level, smoking, diabetes, oral corticosteroid, asthma, total energy intake and CFH Y402H.

Table 5. Associations of AMD with lifetime ambient UVR exposure in the Alienor Study (Bordeaux, France, 2006-2008) (Odds-ratios (OR) and 95 % confidence intervals (CI))

	Early AMD OR (CI)* (N=238 eyes)	P	Late AMD OR (CI)* (N=49 eyes)	P
Total UV (kJ/cm^2)				
≤39.649 (n=300 eyes)	1.69 (1.06-2.69)	0.03	1.03 (0.33-3.26)	0.95
]39.649-40,173[(n=559 eyes)	1.00 (ref)		1.00 (ref)	
≥40.173 (n=295 eyes)	1.59 (1.04-2.44)	0.03	1.11 (0.36-3.36)	0.86
UVA (kJ/cm2)				
≤38.617 (n=300 eyes)	1.69 (1.06-2.69)	0.03	1.03 (0.33-3.26)	0.95
]38.617-39.131[(n=559 eyes)	1.00 (ref)		1.00 (ref)	
≥39.131 (n=295 eyes)	1.59 (1.04-2.44)	0.03	1.11 (0.36-3.36)	0.86
UVB (kJ/cm2)				
≤1.028 (n=302 eyes)	1.66 (1.04-2.64)	0.03	1.03 (0.33-3.25)	0.96
]1.028 -1.042[(n=557 eyes)	1.00 (ref)		1.00 (ref)	
≥1.042 (n=295 eyes)	1.58 (1.03-2.42)	0.04	1.11 (0.36-3.36)	0.86

* estimated using multivariate Generalized Estimating Equations (GEE) logistic regression models, age, gender, educational level, smoking, CFH Y402H and ARMS2 A69S polymorphisms, cataract extraction, dietary intake of total energy and of omega3 fatty acids.
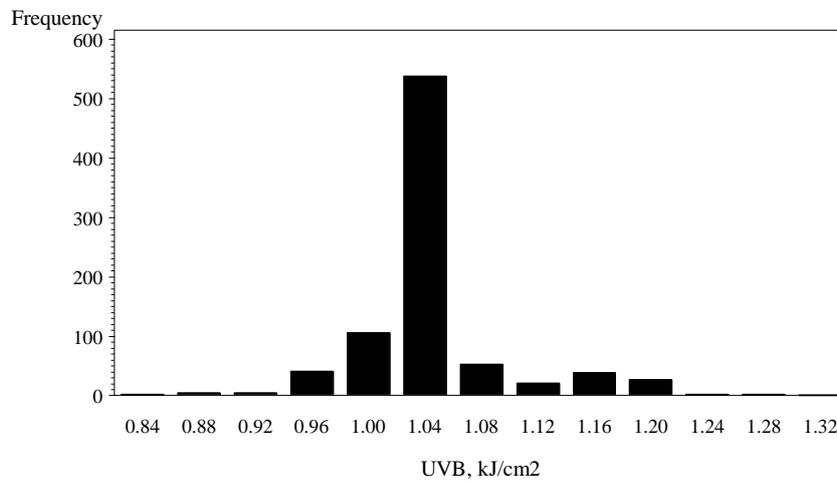
Total UV
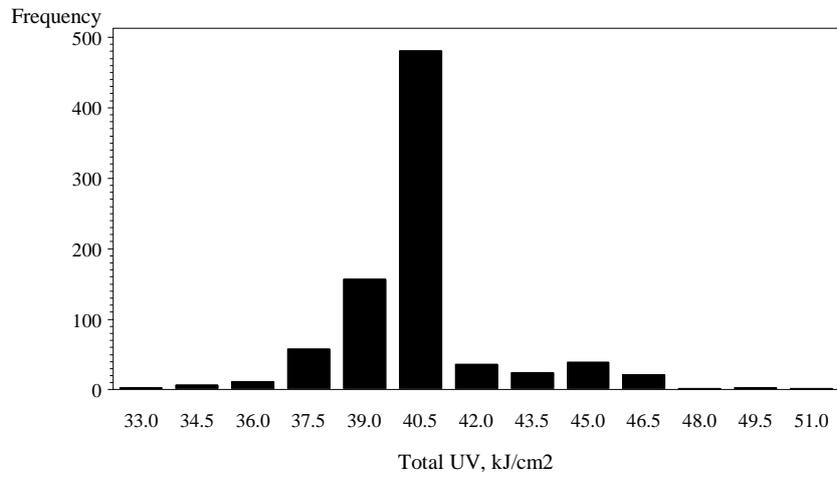
UVA
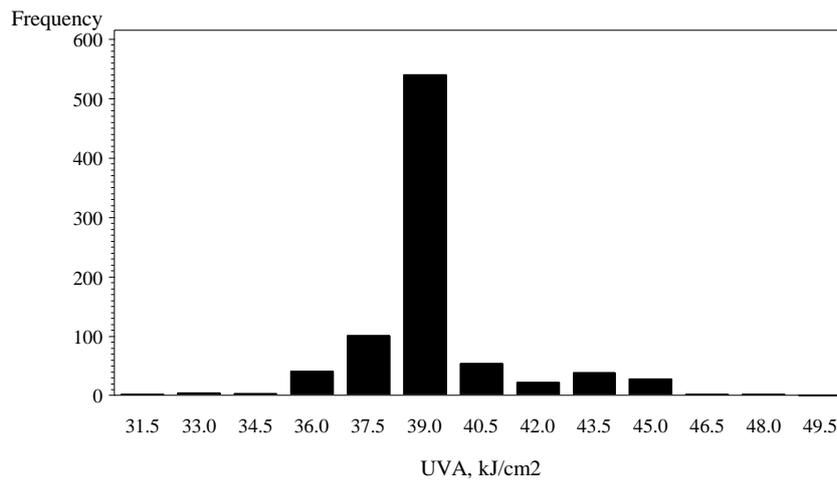
UVB

Figure 1. Distribution of lifetime ambient total UV, UVA and UVB radiations exposure in participants of the Alienor Study (Bordeaux, 2006-2008)