Lifetime Exposure to Ambient Ultraviolet Radiation and the Risk for Cataract Extraction and Age-Related Macular Degeneration: The Alienor Study

Cécile Delcourt,[1,2] Audrey Cougnard-Grégoire,[1,2] Mathieu Boniol,[3] Isabelle Carrière,[4,5] Jean-François Doré,[6] Marie-Noëlle Delyfer,[1,2,7] Marie-Bénédicte Rougier,[7] Mélanie Le Goff,[1,2] Jean-François Dartigues,[1,2] Pascale Barberger-Gateau,[1,2] and Jean-François Korobelnik[1,2,7]

[1]Université de Bordeaux, Bordeaux, France
[2]INSERM, ISPED, Centre INSERM U897-Epidemiologie-Biostatistique, Bordeaux, France
[3]International Prevention Research Institute, Lyon, France
[4]Inserm, U1061, Montpellier, France
[5]University Montpellier I, Montpellier, France
[6]Centre de Recherche en Cancérologie de Lyon, UMR Inserm U1052 - CNRS U5286, Lyon, France
[7]CHU de Bordeaux, Service d'Ophtalmologie, Bordeaux, France

Correspondence: Cécile Delcourt, Inserm U897, ISPED, Université de Bordeaux, 146 rue Léo Saignat, 33076 Bordeaux Cedex, France; cecile.delcourt@isped.fr.

Submitted: March 28, 2014
Accepted: October 5, 2014

Citation: Delcourt C, Cougnard-Grégoire A, Boniol M, et al. Lifetime exposure to ambient ultraviolet radiation and the risk for cataract extraction and age-related macular degeneration: the Alienor Study. *Invest Ophthalmol Vis Sci*. 2014;55:7619–7627. DOI:10.1167/iovs.14-14471

Purpose. While exposure to ultraviolet radiation (UVR) is a recognized risk factor for cataract, its association is more controversial with age-related macular degeneration (AMD). We report the associations of lifetime exposure to ambient UVR with cataract extraction and AMD.

Methods. The Alienor Study is a population-based study of 963 residents of Bordeaux (France), aged 73 years or more. Lifetime exposure to ambient UVR was estimated from residential history and Eurosun satellite-based estimations of ground UVR. It was divided in three groups (lower quartile, intermediate quartiles, upper quartile), using the intermediate quartiles as the reference. Early and late AMD was classified from retinal color photographs. Cataract extraction was defined as absence of the natural lens at slit-lamp.

Results. After multivariate adjustment, subjects in the upper quartile of lifetime ambient UVR exposure were at increased risk for cataract extraction (odds ratio [OR] = 1.53; 95% confidence interval [CI], 1.04–2.26; $P = 0.03$) and for early AMD (OR = 1.59; 95% CI, 1.04–2.44; $P = 0.03$), by comparison with subjects in the intermediate quartiles. Subjects in the lower quartile of UVR exposure also were at increased risk for early AMD (OR = 1.69; 95% CI, 1.06–2.69; $P = 0.03$), by comparison with those with medium exposure. Associations of late AMD with UVR exposure was not statistically significant.

Conclusions. This study further confirms the increased risk for cataract extraction in subjects exposed to high ambient UVR. Moreover, it suggests that risk for early AMD is increased in subjects exposed to high UVR, but also to low UVR, by comparison with medium exposures.

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

Cataract and age-related macular degeneration (AMD) are leading causes of blindness and visual impairment worldwide.[1] Both of these diseases are multifactorial, involving nonmodifiable (e.g., age, sex, genetics) and modifiable factors.[2,3] The control of these modifiable factors may represent a preventive strategy for decreasing the incidence of these diseases and of the related visual impairment. Among other modifiable factors (in particular smoking and nutrition),[2,3] the potential role of sunlight exposure in the etiology of these diseases has been investigated.[4,5] The absorption of solar radiations by biological tissues results in photochemical reactions and the formation of reactive oxygen species (including singlet oxygen), which may damage all cellular components (lipids, proteins, DNA).[6] The part of solar radiations that interacts with the eye is known as "optical radiations" and includes wavelengths from ultraviolet (UV; 100–400 nm), visible light (400–760 nm), to infrared (760–10,000 nm). Ultraviolet radiations (UVR) represent the most energetic part of optical radiations, and, thus, are responsible for a large part of photochemical damage.

The crystalline lens is particularly exposed to phototoxic damage, because it absorbs most of UVR, together with the cornea. This has been confirmed by epidemiological studies, which have shown consistent associations of cataract (resulting from lens opacification) with sunlight exposure and, in particular, UVR exposure.[7–13] Ultraviolet exposure has been consistently associated with the risk for cataract in numerous studies, performed in different continents with different methodologies, showing dose-dependent relationships, and specific associations with cortical cataracts. It now is a recognized risk factor for cataract.[2]

By contrast, epidemiological data regarding the associations of light exposure with the risk for AMD remain scarce and inconsistent. Several studies have suggested an increased risk

for AMD in subjects highly exposed to sunlight,[14–17] but others showed no significant associations,[18–20] and some even suggested a decreased risk for AMD in the most exposed subjects.[21,22]

In the present study, we reported the associations of lifetime exposure to ambient UVR with the risk for cataract extraction and AMD, in the framework of a population-based cross-sectional study of elderly subjects from the South of France.

Subjects and Methods

Study Aims

The Alienor (Antioxydants, Lipides Essentiels, Nutrition et maladies OculaiRes) Study is a population-based prospective study aiming at assessing the associations of age-related eye diseases (AMD, glaucoma, cataract, dry eye syndrome) with nutritional factors (in particular antioxidants, macular pigment, and fatty acids).[23] It also takes into account other major determinants of eye diseases, including gene polymorphisms, lifestyle, and vascular factors.

Study Sample

Subjects of the Alienor Study were recruited from an ongoing population-based study on the vascular risk factors for dementia, the Three City (3C) Study.[24] The 3C Study included 9294 subjects aged 65 years or more from three French Cities (Bordeaux, Dijon, and Montpellier), among which 2104 were recruited in Bordeaux. Subjects were contacted individually from the electoral rolls. They were initially recruited between 1999 and 2001, and followed up approximately every 2 years since. The Alienor study consists of eye examinations, which are offered to all participants from the third follow-up (2006–2008) of the 3C cohort in Bordeaux. Among the 1450 participants re-examined between 2006 and 2008, 963 (66.4%) participated in the first eye examination of the Alienor Study.

This research followed the tenets of the Declaration of Helsinki. Participants gave written consent for the participation in the study. The design of this study was approved by the Ethical Committee of Bordeaux (Comité de Protection des Personnes Sud-Ouest et Outre-Mer III) in May 2006.

Eye Examination

The eye examination took place in the Department of Ophthalmology of the University Hospital of Bordeaux. It included a recording of ophthalmological history, measures of visual acuity, refraction, two 45° nonmydriatic color retinal photographs (one centered on the macula, the other centered on the optic disc), measures of IOP and central corneal thickness, and tear film break-up time test. A self-completed questionnaire on risk factors specific to the eye (including residential history for estimation of light exposure) and dry eye symptoms was filled at home and brought back on the day of the eye examination.

Retinal photographs were performed using a high-resolution digital nonmydriatic retinograph (TRC NW6S; Topcon, Tokyo, Japan). Photographs were interpreted in duplicate by two specially trained technicians. Inconsistencies between the two interpretations were adjudicated by a retina specialist for classification of AMD and other retinal diseases, or by a glaucoma specialist for classification of glaucoma. All cases of late AMD, other retinal diseases, and glaucoma were reviewed and confirmed by specialists. Graders had no access to light exposure variables, or any of the potential confounders.

Cataract Extraction

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

Classification of AMD

Retinal photographs were interpreted according to the international classification[25] and to a modification of the grading scheme used in the Multi-Ethnic Study of Atherosclerosis for drusen size, location, and area.[26] Eyes were classified according to one of the three exclusive groups: no AMD, early AMD, and late AMD.

Late AMD was defined by the presence of neovascular AMD or geographic atrophy within the grid (3000 μm from the foveola). Neovascular AMD included serous or hemorrhagic detachment of the RPE or sensory retina, subretinal or sub-RPE hemorrhages, and fibrous scar tissue. Geographic atrophy was defined as a discrete area of retinal depigmentation, 175 μm in diameter or larger, characterized by a sharp border and the presence of visible choroidal vessels. Five cases of late AMD had no gradable photographs, and were classified using ophthalmologic history of AMD and AMD therapy (in particular intravitreal antiangiogenic agents and photodynamic therapy), and confirmed by their treating ophthalmologist.

Early AMD was defined by the presence of soft distinct drusen and/or soft indistinct drusen and/or reticular drusen and/or pigmentary abnormalities. Soft distinct and indistinct drusen were larger than 125 m in diameter and with uniform density and sharp edges or decreasing density from the center outwards and fuzzy edges, respectively. Pigmentary abnormalities were defined as areas of hyperpigmentation and/or hypopigmentation (without visibility of choroidal vessels).

Ambient UVR Exposure

For each participant, average annual ambient UVR exposure was estimated using the residential history, by weighting annual ambient UVR at each location by the time spent at that location. Residential history from birth (locations, time spent at each location) was self-declared up to the first eye examination (2006–2008). In France, locations were divided in 101 geographical areas, corresponding to the 101 administrative departments (95 in metropolitan France and six overseas departments). Concerning foreign countries, ambient UVR generally was estimated for the capital of the country, except when the capital was very off-centered, in which case a more central location was chosen. Very large countries (United States, China, and so forth) were excluded from this analysis, since an estimation of solar radiation in a single geographic location is meaningless.

Average annual ambient solar radiation was assessed for the first 65 years of life, since almost all subjects (97.3%) lived in the Bordeaux area beyond this age.

Ultraviolet Radiation. In each location, UVR was extracted from the Eurosun UV database (available in the public domain at www.eurosun-project.org). Briefly, UV irradiation levels were initially extracted from surface solar irradiance derived from the Meteosat satellite's images. From these irradiation levels, the UV component was computed by a model that exploits the algorithm set up by the Royal Institute of Meteorology, Belgium (Brussels, Belgium) published in the European Solar Radiation Atlas (spectral model of Joukoff ESRA). The algorithm converts the total irradiance (E) into its spectral distribution E(λ), every 10 nm, and gives estimates for total UV (280–400 nm), UVA (315–400 nm), and UVB (280–315 nm). The calculation of individual exposure assumes that the irradiation levels in different regions remained constant over

the years. The information provided by Eurosun corresponds to the average of daily UVR over the period 1988 to 2007 for each location. We conducted analysis of change in UVR over the period 1988 to 2007 in Eurosun maps and found only minor changes of less than 1% yearly change. These observations were in line with the results obtained from COST 726, which also reported a stability of UV irradiation in Europe for a period of 50 years of data up to 2002 (the project COST 726 report and details are available in the public domain at http://www-med-physik.vu-wien.ac.at/uv/cost726/cost726.htm). So, these analyses from Eurosun data and observation from COST 726 action are suggesting a stability of UV, which let us assume no change over time. These estimates were available for European and North African countries, with a resolution of 5 km. However, they are not available for other countries (Americas, Sub-Saharan Africa, Asia, Oceania).

Estimation of Missing UVR Data Using Global Solar Radiation (GSR). In each location, global ambient annual solar radiation (a measure of solar energy including all wavelengths) was estimated using astronomical equations and the statistics of sunshine hours, using the same methodology as in the POLA Study.[13] Overall, global ambient annual solar radiation estimates were available in 116 locations (101 French departments, 7 European countries, 3 North African countries, 5 other countries). In 105 locations (95 French departments, 7 European countries, 3 North African countries), UVR and GSR estimates were available. Pearson's correlation coefficient between these two variables was 0.952. For the 11 areas with missing UVR, but available solar radiation (six French overseas departments and five countries), we, thus, estimated ambient UVR from GSR, using linear regression modeling. The regression equation derived from the 105 locations with UVR and GSR was: UVR = 5613.105 + 0.0729 × GSR ($r^2 = 0.91$). The same analyses were performed for UVA and UVB, leading to the following equations: UVA = 5467.398 + 0.0710 × GSR; UVB = 145.708 + 0.00189 × GSR.

Finally, estimates of UVR exposure still could not be estimated for some countries. When, for a given subject, the number of years spent in such countries was less than or equal to 3 years, these countries were eliminated from the calculations. Therefore, for 71 subjects, average ambient UVR was calculated on 62, 63, or 64 years instead of 65. In addition, 113 subjects were excluded from the analyses because they had spent more than 3 years in countries where UVR could not be estimated.

Other Variables

The following potential confounders have been selected, based on literature results reporting significant associations of AMD and/or cataract and/or light exposure with age, sex, educational level, diabetes, hypertension, asthma, oral corticosteroid use, smoking, physical activity, body mass index (BMI), plasma glucose and lipids, dietary intake of energy, antioxidants, lutein, and zeaxanthin, and omega3 fatty acids.[2,3] We also included the two major genetic polymorphisms associated with AMD: Complement Factor H (*CFH*) Y402H (rs1061170) and Age-Related Maculopathy Susceptibility 2 (*ARMS2*) A69S (rs10490924) polymorphisms.[27–29] These genetic polymorphisms also were strongly associated with AMD in the Alienor study.[30,31] By comparison with subjects homozygous for the most frequent allele (TT for *CFH* Y402H and GG for *ARMS2* A69S), subjects homozygous for the less frequent allele (CC for *CFH* Y402H, TT for *ARMS2* A69S) exhibit 5- to 15-fold increased risk for AMD. Heterozygous subjects (TC for *CFH* Y402H and GT for *ARM2* A69S) exhibit intermediate risks (2- to 5-fold increased risks). Indeed, all of these factors may represent confounders in the relationship of AMD with lifetime ambient UVR, since lifestyle (smoking, physical activity, diet), health conditions, and genetic characteristics have been reported to vary according to geographical location, and, thus, with lifetime ambient UVR.[32–34]

Data were collected during a face-to-face interview using a standardized questionnaire administered by a trained psychologist or nurse. At baseline (1999–2000), general data included demographic characteristics, educational level, and smoking. The BMI (kg/m^2) was calculated as weight/height^2. Physical activity was assessed by two questions: "Do you practice sports?" (yes/no) and "Do you perspire when you practice sports?" (Never/sometimes/most of the time/always). A 3-level variable was computed to describe intensity of physical activity, as already published.[35] Plasma glucose and lipids were measured at the Biochemistry Laboratory of the University Hospital of Dijon from baseline fasting blood samples. Dietary intake of energy, antioxidants, lutein, and zeaxanthin, and omega3 fatty acids were estimated from a 24-hour recall performed through face-to-face interview by specifically trained dietitians from 2001 to 2002.[35,36] Genetic polymorphisms were determined by the Lille Génopôle, from the DNA samples collected at baseline (1999–2001).

Statistical Methods

First, associations of ambient solar radiation with sociodemographic factors, lifestyle, and biological and dietary parameters were assessed using χ^2 test or ANOVA.

Associations of cataract extraction and AMD with ambient UVR were estimated using logistic Generalized Estimating Equations (GEE) models,[37] which allow taking into account the data from both eyes and their intraindividual correlations. Adjusted odds ratios (ORs) were estimated using cataract extraction or AMD as the dependent variable, and ambient UVR and potential confounders as the independent variables. Ambient UVR was divided in three groups (lower quartile, intermediate quartiles, upper quartile), the medium category being the reference. With regard to AMD, two models were performed (for early and late AMD, respectively), subjects without any AMD being the reference in both models. With regard to cataract, subjects without cataract extraction were the reference group.

With regard to cataract extraction, potential confounders retained in the analysis were known risk factors for cataract[2] (age, sex, smoking, diabetes, oral corticosteroid use, and asthma) and factors significantly associated with ambient UVR (at $P < 0.05$). Similarly, with regard to AMD, potential confounders retained in the analysis were well known risk factors, which are associated strongly with AMD in our cohort (age, sex, smoking,[30] *CFH*,[30] and *ARMS2*[31] polymorphisms, dietary intake of omega3 fatty acids[36]) and factors significantly associated with ambient UVR (at $P < 0.05$). No collinearity was detected between the variables included in the final models. No major confounding was detected (variation by more than 10% of the estimates of the ORs when deleting one confounder from the models). All statistical analyses were performed using statistical software (SAS, version 9.1; SAS Institute, Inc., Cary, NC, USA).

Results

The Figure presents the distribution of annual ambient UVR exposures (total UV, UVA, and UVB), estimated from residential history. These variables showed important interindividual variability, ranging, respectively, from 32.39 to 50.93, 31.55 to 49.61, and 0.81 to 1.32 kJ/cm^2. The central peaks correspond to subjects who spent all their life in the Bordeaux

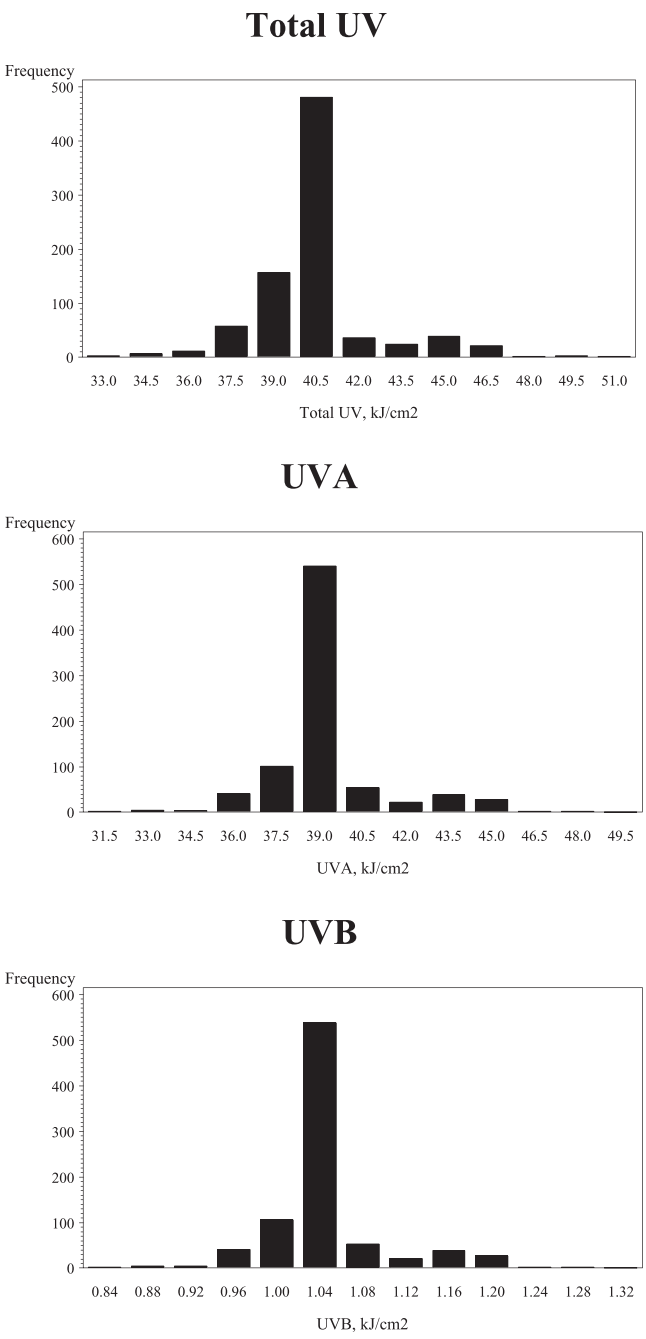

Figure. Distribution of lifetime ambient total UV, UVA, and UVB radiations exposure in participants of the Alienor Study (Bordeaux, 2006–2008).

area. As shown in Table 1 for total UVR, these subjects constituted the middle group (intermediate quartiles), who were born and lived all their life in the South of France. By contrast, two thirds of subjects from the lower quartile of ambient solar radiation were born in Central or Northern France, where they spent approximately 23 years on average. Among subjects from the upper quartile, more than a quarter were born in Northern Africa and remained there for 32 years on average (corresponding to the independence of these countries in the 1960s) and 8.13% were born in Southern Europe. Although the definition of the intermediate quartiles is narrow (39.649–40.173 kJ/cm2), there is significant variability, with a mean of 38.375 kJ/cm^2 in the lower quartile, compared to 42.718 kJ/cm^2 in the upper quartile. Similar findings were found for UVA and UVB (data not shown).

Sociodemographic, lifestyle, and biological characteristics of participants appeared different according to their lifetime solar exposure. As shown in Table 2, compared to subjects from the middle quartiles, subjects in the higher quartile more often were males (42.58% vs. 31.74%) and tended to have a higher frequency of the TC genotype of *CFH* Y402H (47.12% vs. 37.43%) and lower frequency of TT genotype of *CFH* Y402H (45.03% vs. 49.21%), while subjects from the lower quartiles had a higher educational level (48.80% with University degree versus 26.97%) and tended to have a higher frequency of the TC genotype of *CFH* Y402H (47.15% vs. 37.43%) and lower frequency of TT genotype of *CFH* Y402H (40.93% vs. 49.21%). As shown in Table 3, subjects from the upper and lower quartiles had smoked more during their life (18.36% and 22.93% having smoked more than 20 pack-years, respectively), by comparison with intermediate exposures (12.50%). Subjects in the upper quartile also had higher total energy intake (1835.7 vs. 1678.2 Kcal/d). Therefore, these variables (education, smoking, *CFH* Y402H genotypes, and total energy intakes) were considered as potential confounders in the analyses of association of solar radiation with cataract extraction and AMD.

Cataract extraction status was available in at least one eye of 958 subjects (99.5%). Of those, 837 had complete data for light exposure variables. In addition, 143 subjects had missing values in potential confounders, leaving 694 subjects in the fully adjusted models, representing 1388 eyes, among which 542 had undergone cataract surgery. Participants with missing data were not significantly different from those without missing data, with regard to age, sex, ambient UVR, or genetic polymorphisms (data not shown). As shown in Table 4, after adjustment for confounders, by comparison with participants exposed to medium ambient total UVR, participants exposed to high ambient total UVR were at increased risk for cataract extraction (OR = 1.53; 95% confidence interval [CI], 1.04–2.26; $P = 0.03$), while participants with low exposure had similar risk as those with medium exposures (OR = 0.75; 95% CI, 0.51–1.12). Similar results were observed for UVA and UVB. Among the potential confounders included in the multivariate models, those significantly associated with cataract surgery were age (OR = 1.18 for 1-year increase; 95% CI, 1.13–1.22; $P < 0.0001$), sex (OR = 1.86 for females versus males; 95% CI, 1.23–2.80; $P = 0.003$), having smoked 20 pack-years or more (OR = 2.23; 95% CI, 1.37–3.64; $P = 0.001$), and history of asthma (OR = 1.99; 95% CI, 1.15–3.42; $P = 0.01$).

The AMD status was available in at least one eye of 875 subjects (91%). Of those, 769 had complete data for light exposure variables. In addition, 172 subjects had missing values in potential confounders, leaving 597 subjects in the fully adjusted models, representing 1154 eyes among which were 238 with early AMD and 49 with late AMD. Participants with missing data were not significantly different from those without missing data, with regard to age, sex, ambient UVR, or genetic polymorphisms (data not shown). Participants exposed to high ambient total UVR tended to be at increased risk for early AMD (OR = 1.59; 95% CI, 1.04–2.44; $P = 0.03$), by comparison with participants with medium exposures (Table 5). In addition, participants exposed to low ambient solar radiation were at increased risk for early AMD (OR = 1.69; 95% CI, 1.06–2.69; $P = 0.03$), by comparison with medium exposures. By contrast, no statistically significant associations of late AMD with UVR exposures were found. Overall, results were very similar for total UV, UVA, and UVB exposures. Among the potential confounders included in the multivariate models, those significantly associated with early AMD were age

Table 1. Light Exposure–Related Characteristics of 837 Participants According to Lifetime Ambient Total UVR Exposure of the Alienor Study (Bordeaux, France, 2006–2008)

	Total UVR, kJ/cm²			
	≤39.649, *n* = 209	39.649–40.173, *n* = 419	≥40.173, *n* = 209	*P* Value
Mean total UVR, kJ/cm² (SD)	38.375 (1.26)	39.887 (0.08)	42.718 (2.29)	
Place of birth, 837 subjects, *n* (%)				
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, *n* = 837, median y (range)				
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

(OR = 1.06 for 1-year increase; 95% CI, 1.02–1.10; $P = 0.008$), sex (OR = 1.95 for females versus males; 95% CI, 1.19–3.21; $P = 0.01$), *ARMS2* A69S GT genotype (OR = 1.62; 95% CI, 1.12–2.35; $P = 0.01$), *ARMS2* A69S TT genotype (OR = 12.09; 95% CI, 4.63–31.55; $P < 0.0001$), and *CFH* Y402H CC genotype (OR = 1.89; 95% CI, 1.13–3.16; $P = 0.01$). The factors significantly associated with late AMD were age (OR = 1.24; 95% CI, 1.14–1.35; $P < 0.0001$), sex (OR = 2.93; 95% CI, 1.16–7.43; $P = 0.02$), *ARMS2* A69S TT genotype (OR = 59.71; 95% CI, 15.53–229.57; $P < 0.0001$), *CFH* Y402H TC genotype (OR = 3.49; 95% CI, 1.31–9.30; $P = 0.009$), *CFH* Y402H CC genotype (OR = 6.68; 95% CI, 2.05–21.77; $P = 0.001$), dietary omega3 fatty acids intake (OR = 0.63; 95% CI, 0.41–0.96; $P = 0.03$), and secondary education (OR = 7.46; 95% CI, 1.63–34.05; $P = 0.01$). We detected no significant interactions of genetic polymorphisms with UVR exposure.

Discussion

While confirming the well-known association of cataract with high ambient UVR,[7–13] the present study suggested a U-shaped association of early AMD with ambient UVR, with increased risk in low- and high-UVR exposures. The effects of UVR on human health generally follows such a U-shaped (or J-shaped) relationship.[38] Indeed, on one hand, high exposures have well-documented effects on skin diseases (skin cancers, sunburns, and chronic sun damage) and several eye diseases (acute

Table 2. Sociodemographic, Medical, and Genetic Characteristics of 837 Participants According to Lifetime Ambient Total UVR Exposure of the Alienor Study (Bordeaux, France, 2006–2008)

	Ambient Total UVR, kJ/cm²			
	≤39.649, *n* = 209	39.649–40.173, *n* = 419	≥40.173, *n* = 209	*P* Value
Age, 837 subjects, mean y (SD)	80.50 (4.42)	80.21 (4.49)	79.96 (4.44)	0.46
Male sex, 837 subjects, *n* (%)	87 (41.63)	133 (31.74)	89 (42.58)	0.008
Education, 837 subjects, *n* (%)				
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, 763 subjects, *n* (%)	23 (12.17)	53 (13.80)	21 (11.05)	0.63
Hypertension, 837 subjects, *n* (%)	161 (77.03)	318 (75.89)	152 (72.73)	0.56
Asthma, 828 subjects, *n* (%)	21 (10.14)	36 (8.67)	14 (6.80)	0.47
Oral corticosteroid use, 837 subjects, *n* (%)	3 (1.44)	2 (0.48)	4 (1.91)	0.22
CFH Y402 H, 766 subjects, *n* (%)				
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, 703 subjects, *n* (%)				
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 837 Participants According to Lifetime Ambient Total UVR Exposure of the Alienor Study (Bordeaux, France, 2006–2008)

	Ambient Total UVR, kJ/cm²			
	≤39.649, *n* = 209	39.649–40.173, *n* = 419	≥40.173, *n* = 209	*P* Value
Smoking, 828 subjects, *n* (%)				
Nonsmoker	111 (54.15)	296 (71.15)	138 (66.67)	0.0005
<20 pack-y	47 (22.93)	68 (16.35)	31 (14.98)	
≥20 pack-y	47 (22.93)	52 (12.50)	38 (18.36)	
Physical activity, 837 subjects, *n* (%)				
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)	
BMI, 829 subjects, mean kg/m² (SD)	25.90 (4.00)	26.17 (3.97)	26.61 (3.65)	0.17
Fasting plasma measurements, mean mmol/L (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/d, *n* = 797	1835.7 (574.1)	1678.2 (513.4)	1704.5 (535.3)	0.003
Vitamin C, mg/d, *n* = 797	89.62 (56.98)	81.95 (60.96)	92.10 (82.66)	0.15
Vitamin E, mg/d, *n* = 797	6.72 (4.72)	6.30 (4.51)	6.70 (4.43)	0.45
Lutein and zeaxanthin, mg/d, *n* = 781	0.60 (0.92)	0.55 (0.91)	0.71 (0.90)	0.14
Omega3 fatty acids, mg/d, *n* = 797	0.48 (1.20)	0.43 (1.00)	0.41 (1.16)	0.79

photokeratitis and conjunctivitis, acute solar retinopathy, pterygium, cortical cataract).[38] On the other hand, cutaneous UVR exposure is necessary for endogenous production of vitamin D, so that low UVR exposures are associated with an increased risk for osteomuscular diseases and possibly of other diseases related to vitamin D deficiency (in particular several cancers, cardiovascular disease, autoimmune diseases).[38–40] Indeed, besides its effects on bone health, vitamin D has many cellular effects, including regulation of cellular differentiation, proliferation, apoptosis, and angiogenesis,[40] and anti-inflammatory properties.[41] Many of these processes are implicated in the physiopathology of AMD and some studies have suggested that low vitamin D status may be associated with an increased risk for AMD.[42–45] Whether vitamin D deficiency may explain the higher risk for AMD observed with low sunlight exposure in the present study will need to be determined in future studies.

Only few epidemiological studies have addressed the potential link of AMD with UVR exposure, with inconsistent results. This probably is due to major methodological

Table 4. Associations of Cataract Extraction With Lifetime Ambient UVR Exposure in the Alienor Study (Bordeaux, France, 2006–2008), OR and 95% CI

	Cataract Surgery					
	No, 846 Eyes		Yes, 542 Eyes			
	n	%	*n*	%	OR*	*P*
Total UV, kJ/cm²						
≤39.649, 350 eyes	230	65.71	120	34.29	0.75 (0.51–1.12)	0.16
39.649–40.173 696 eyes	430	61.78	266	38.22	1.00 (ref)	
≥40.173, 342 eyes	186	54.39	156	45.61	1.53 (1.04–2.26)	0.03
UVA, kJ/cm²						
≤38.617, 350 eyes	230	65.71	120	34.29	0.75 (0.51–1.12)	0.16
38.617–39.131, 696 eyes	430	61.78	266	38.22	1.00 (ref)	
≥39.131, 342 eyes	186	54.39	156	45.61	1.53 (1.04–2.26)	0.03
UVB, kJ/cm²						
≤1.028, 350 eyes	230	65.71	120	34.29	0.75 (0.51–1.10)	0.14
1.028–1.042, 696 eyes	430	61.78	266	38.22	1.00 (ref)	
≥1.042, 342 eyes	186	54.39	156	45.61	1.53 (1.04–2.26)	0.03

* Estimated using multivariate GEE logistic regression models, adjusted for age, sex, educational level, smoking, diabetes, oral corticosteroid, asthma, total energy intake and *CFH* Y402H. ref, reference.

Investigative Ophthalmology & Visual Science

Table 5. Associations of AMD With Lifetime Ambient UVR Exposure in the Alienor Study (Bordeaux, France, 2006–2008), OR and 95% CI

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

* Estimated using multivariate GEE logistic regression models, age, sex, educational level, smoking, *CFH* Y402H, and *ARMS2* A69S polymorphisms, cataract extraction, and dietary intake of total energy and omega3 fatty acids.

difficulties in the assessment of UVR exposure. Indeed, UVR exposure and its health effects result from distal factors (such as latitude, season, cloud cover, stratospheric ozone levels, and lower atmospheric pollution), conditioning ambient UVR, in addition to proximal factors (in particular occupational and leisure exposures to sunlight, use of hats and sunglasses, skin pigmentation, and sun sensitivity),[46] conditioning individual exposure and response to exposure. Moreover, previous studies have shown that health effects of UVR exposure are cumulative over the lifetime. Thus, estimation of lifetime ocular UVR exposure requires detailed questionnaires on lifetime distal and proximal factors, combined with complex modeling of their effects on ocular UVR exposure. Since most epidemiological studies in the field of AMD, including the present study, addressed not only the effect of sunlight exposure, but also of many other factors (smoking, cardiovascular risk factors, genetics, nutrition), only partial information on distal and/or proximal factors was collected, limiting the validity of the estimates of UVR exposure, and the comparability of studies.

The Maryland Watermen Study included detailed questionnaires of ocular exposures, combined with field and laboratory data, to assess ocular UVR exposure. In this study, ocular UVR exposure was not significantly associated with prevalent AMD.[47] In the Beaver Dam Eye Study, ambient UVB exposure, estimated from residential history, was not significantly associated with prevalent[15] or incident[16,17] AMD, but subjects having spent more than 5 hours/day outside during summer in their youth were more likely to have prevalent[15] and incident AMD.[16,17] In the POLA Study,[22] performed in the South of France, the risk for prevalent early AMD was higher in subjects exposed to low ambient solar radiation. In the Blue Mountains Eye Study, prevalent AMD was associated with high and low sun sensitivity index, by comparison with medium sun sensitivity index,[48] although this was not confirmed in the prospective analysis of the same cohort.[20] Finally, in an Australian case-control study, AMD was associated with poorer tanning ability and lower time of ocular sunlight exposure.[21]

In the present study, only estimates of ambient UVR exposure were available, based on residential history and satellite-based estimates of UVR, while no data were available on sun-related behaviors, skin pigmentation, or sun sensitivity. This may have led to significant misclassification of exposures, since actual ocular UVR exposure may be quite different from ambient UVR exposure in those subjects with very low time spent outdoors. However, it seems most likely that misclassification was unrelated to ambient UVR (i.e., that there would be similar proportions of people with low/high outdoors activities in areas with different ambient UVR), and, thus, was unlikely to have biased the associations of eye diseases with UVR exposure. Moreover, the well known association of UVR exposure with cataract was confirmed in the present study, suggesting that our measure of UVR exposure had some validity.

While the lack of information on proximal factors is clearly a limitation, the use of satellite-based estimates of UVR is a strength. Indeed, most previous studies relied on formulas, estimating UVR mainly from latitude and altitude. While these are major determinants of UVR, weather conditions also contribute to actual ground UVR, in particular because of attenuation by cloud cover. The UVR estimations in the present study rely on Meteosat satellite measurements of total solar irradiance by the earth's surface by reflection, over 30 years.

Using detailed estimation of ocular lifetime exposure, the Maryland Watermen study and the EUREYE study have suggested that AMD risk may be associated with blue light exposure,[14,49] which also is supported by animal and laboratory studies.[6,50] In the present study, we could only estimate ambient UVR, since no data on blue light currently are available in the Eurosun project. However, it is difficult to distinguish the effect of the different wavelengths, since they are naturally highly correlated. For instance, in the present study, GSR (a measure of solar energy including all wavelengths) showed a correlation coefficient of 0.95 with UV radiation, measured in 105 geographical areas.

The present study has several limitations. One limitation of our study could come from the representativeness of the sample. The Alienor subsample tends to over-represent younger subjects and high socioeconomic status, among subjects participating to the 3C Study.[23] Therefore, the individuals included in this study may be healthier and have different lifestyles, particularly concerning sunlight exposure, than the general population. These differences may have affected the distribution of sunlight exposure or the prevalence of eye diseases. However, subjects participating in the 3C study and included in the Alienor study were not different from those who were not included for most parameters of interest in our study.[23] Furthermore, as described previously,[23] the age–

sex-specific prevalence rates of AMD in the Alienor study were similar to those observed in other studies performed in Europe[51,52] and other industrialized countries.[53] Data collection was performed in the same way in all individuals regardless of their AMD stage and photograph graders had no access to sunlight exposure data. Therefore, we can assume that the error was not differential and was unlikely to have biased the estimation of any of the associations of AMD with ambient solar radiation.

In observational studies, confounding always is a concern. Therefore, we adjusted for potential confounders, including all known risk factors for cataract and AMD. However, we cannot totally exclude residual confounding. In the present study, it is particularly striking that not only sociodemographic and lifestyle variables varied with ambient UVR exposure, but also genetic background (mainly *CFH* Y402H). While there are major differences in distribution of *CFH* Y402H alleles among ethnic groups (with low frequency of the at-risk C allele in non-Europeans[54,55]), to our knowledge, no data are available on its geographical distribution within the European continent (where most of the Alienor participants were born). However, large variations of allele frequencies between European countries have been reported, in particular for Apolipoprotein E.[33] Since AMD has a strong genetic component, and there may be geographical variation in the distribution of gene polymorphisms, gene polymorphisms may be confounders in the relationship of AMD with any factor affected by geographical variation (including UVR exposure, but also lifestyle and diet). This underlines the importance of taking into account environmental and genetic confounders in studies of associations of eye diseases with sunlight exposure. None of the previously published studies took potential genetic confounders into account. In the present study, although we took into account the two major genetic risk factors for AMD (*CFH* Y402H and *ARMS2* A69S), we cannot exclude that these groups of subjects differ for other genetic factors related to AMD (complement factors *CF1*, *C2*, *C3*, and *CFB*, *LIPC*, *CETP*[3]).

Since this study was cross-sectional, recall bias may have affected the results. However, only few prospective studies are available in this field. Our study included only a small number of cases of late AMD, which induced low statistical power for detecting associations with ambient solar radiation and of interactions of genetic polymorphisms with UVR exposure. Finally, cataract status was determined only on the basis of cataract surgery, rather than on the presence of lens opacities, which were not available in our study because of lack of pupil dilation. This may have caused misclassification of cataract status and, therefore, may have biased the estimates.

In conclusion, our study confirmed the high risk for cataract in subjects exposed to high ambient solar radiation. It also suggested a U-shaped association of early AMD with UVR exposure, with an increased risk for low- and high-exposures. This will need to be confirmed in future, possibly prospective, studies. The reasons for a potentially increased risk for early AMD with low solar radiation remain unclear and must be studied further.

Acknowledgments

Supported by Laboratoires Théa (Clermont-Ferrand, France) and Fondation Voir et Entendre (Paris, France), and by the European Union's Public Health Executive Agency under Grant Agreement No. 2006320 (EUROSUN project). The authors alone are responsible for the content and writing of the paper.

Disclosure: **C. Delcourt**, Allergan (C), Bayer (C), Bausch&Lomb (C), Laboratoires Thea (C), Novartis (C); **A. Cougnard-Grégoire**, None; **M. Boniol**, None; **I. Carrière**, None; **J.-F. Doré**, None; **M.-N. Delyfer**, Laboratoires Thea (C); **M.-B. Rougier**, Allergan (C), Bausch&Lomb (C), Laboratoires Thea (C); **M. Le Goff**, None; **J.-F. Dartigues**, Novartis (C); **P. Barberger-Gateau**, Aprifel (C), Danone (C), Groupe Lipides Nutrition (C); **J.-F. Korobelnik**, Alcon (C), Allergan (C), Bayer (C), Laboratoires Thea (C), Novartis (C)

References

1. Resnikoff S, Pascolini D, Etya'ale D, et al. Global data on visual impairment in the year 2002. *Bull World Health Organ*. 2004; 82:844–851.
2. Asbell PA, Dualan I, Mindel J, Brocks D, Ahmad M, Epstein S. Age-related cataract. *Lancet*. 2005;365:599–609.
3. Lim LS, Mitchell P, Seddon JM, Holz FG, Wong TY. Age-related macular degeneration. *Lancet*. 2012;379:1728–1738.
4. Sui GY, Liu GC, Liu GY, et al. Is sunlight exposure a risk factor for age-related macular degeneration? A systematic review and meta-analysis. *Br J Ophthalmol*. 2013;97:389–394.
5. McCarty CA, Taylor HR. A review of the epidemiologic evidence linking ultraviolet radiation and cataracts. *Dev Ophthalmol*. 2002;35:21–31.
6. Wu J, Seregard S, Algvere PV. Photochemical damage of the retina. *Surv Ophthalmol*. 2006;51:461–481.
7. Brilliant LB, Grasset NC, Pokhrel RP, et al. Associations among cataract prevalence, sunlight hours, and altitude in the Himalayas. *Am J Epidemiol*. 1983;118:250–264.
8. Hiller R, Sperduto RD, Ederer F. Epidemiologic associations with cataract in the 1971–1972 National Health and Nutrition Examination Survey. *Am J Epidemiol*. 1983;118:239–249.
9. Taylor HR, West SK, Rosenthal FS, et al. Effect of ultraviolet radiation on cataract formation. *N Engl J Med*. 1988;319:1429–1433.
10. Rosmini F, Stazi MA, Milton RC, Sperduto RD, Pasquini P, Maraini G. A dose-response effect between a sunlight index and age-related cataracts. Italian-American Cataract Study Group. *Ann Epidemiol*. 1994;4:266–270.
11. West SK, Duncan DD, Munoz B, et al. Sunlight exposure and risk of lens opacities in a population-based study: The Salisbury Eye Evaluation Project. *JAMA*. 1998;280:714–718.
12. Sreenivas V, Prabhakar AK, Badrinath SS, et al. A rural population based case-control study of senile cataract in India. *J Epidemiol*. 1999;9:327–336.
13. Delcourt C, Carriere I, Ponton Sanchez A, et al. Light exposure and the risk of cortical, nuclear, and posterior subcapsular cataracts: the Pathologies Oculaires Liées à l'Age (POLA) Study. *Arch Ophthalmol*. 2000;118:385–392.
14. Taylor HR, Munoz B, West S, Bressler NM, Bressler SB, Rosenthal FS. Visible light and risk of age-related macular degeneration. *Trans Am Ophthalmol Soc*. 1990;88:163–173.
15. Cruickshanks KJ, Klein R, Klein BE. Sunlight and age-related macular degeneration. The Beaver Dam Eye Study. *Arch Ophthalmol*. 1993;111:514–518.
16. Cruickshanks KJ, Klein R, Klein BE, Nondahl DM. Sunlight and the 5-year incidence of early age-related maculopathy: the beaver dam eye study. *Arch Ophthalmol*. 2001;119:246–250.
17. Tomany SC, Cruickshanks KJ, Klein R, Klein BE, Knudtson MD. Sunlight and the 10-year incidence of age-related maculopathy: the Beaver Dam Eye Study. *Arch Ophthalmol*. 2004;122:750–757.
18. Eye Disease Case-Control Study Group. Risk factors for neovascular age-related macular degeneration. The Eye Disease Case-Control Study Group. *Arch Ophthalmol*. 1992;110: 1701–1708.
19. Khan JC, Shahid H, Thurlby DA, et al. Age related macular degeneration and sun exposure, iris colour, and skin sensitivity to sunlight. *Br J Ophthalmol*. 2006;90:29–32.

20. Pham TQ, Rochtchina E, Mitchell P, Smith W, Wang JJ. Sunlight-related factors and the 10-year incidence of age-related maculopathy. *Ophthalmic Epidemiol*. 2009;16:136–141.
21. Darzins P, Mitchell P, Heller RF. Sun exposure and age-related macular degeneration. An Australian case-control study. *Ophthalmology*. 1997;104:770–776.
22. Delcourt C, Carriere I, Ponton Sanchez A, Fourrey S, Lacroux A, Papoz L. Light exposure and the risk of age-related macular degeneration: the Pathologies Oculaires Liees a l'Age (POLA) study. *Arch Ophthalmol*. 2001;119:1463–1468.
23. Delcourt C, Korobelnik JF, Barberger-Gateau P, et al. Nutrition and age-related eye diseases: The ALIENOR (Antioxydants, Lipides Essentiels, Nutrition et Maladies Oculaires) Study. *J Nutr Health Aging*. 2010;14:854–861.
24. The 3C Study Group. Vascular factors and risk of dementia: design of the Three-City Study and baseline characteristics of the study population. *Neuroepidemiology*. 2003;22:316–325.
25. Bird AC, Bressler NM, Bressler SB, et al. An international classification and grading system for age-related maculopathy and age-related macular degeneration. The International ARM Epidemiological Study Group. *Surv Ophthalmol*. 1995;39:367–374.
26. Klein R, Klein BE, Knudtson MD, et al. Prevalence of age-related macular degeneration in 4 racial/ethnic groups in the multi-ethnic study of atherosclerosis. *Ophthalmology*. 2006;113:373–380.
27. Chakravarthy U, McKay GJ, de Jong PT, et al. ARMS2 increases the risk of early and late age-related macular degeneration in the European Eye Study. *Ophthalmology*. 2013;120:342–348.
28. Despriet DD, Klaver CC, Witteman JC, et al. Complement factor H polymorphism, complement activators, and risk of age-related macular degeneration. *JAMA*. 2006;296:301–309.
29. Seddon JM, Gensler G, Rosner B. C-reactive protein and CFH, ARMS2/HTRA1 gene variants are independently associated with risk of macular degeneration. *Ophthalmology*. 2010;117:1560–1566.
30. Delcourt C, Delyfer MN, Rougier MB, et al. Associations of complement factor H and smoking with early age-related macular degeneration: The ALIENOR Study. *Invest Ophthalmol Vis Sci*. 2011;52:5955–5962.
31. Delcourt C, Delyfer MN, Rougier MB, et al. ARMS2 A69S polymorphism and the risk for age-related maculopathy: The ALIENOR Study. *Arch Ophthalmol*. 2012;130:1077–1078.
32. Czernichow S, Bruckert E, Oppert JM, et al. Intake of added oils and fats among middle-aged French adults: relationships with educational level and region of residence. *J Am Diet Assoc*. 2005;105:1889–1894.
33. Ewbank DC. The APOE gene and differences in life expectancy in Europe. *J Gerontol A Biol Sci Med Sci*. 2004;59:16–20.
34. Al Delaimy WK, Van Kappel AL, Ferrari P, et al. Plasma levels of six carotenoids in nine European countries: report from the European Prospective Investigation into Cancer and Nutrition (EPIC). *Public Health Nutr*. 2004;7:713–722.
35. Feart C, Jutand MA, Larrieu S, et al. Energy, macronutrient and fatty acid intake of French elderly community dwellers and association with socio-demographic characteristics: data from the Bordeaux sample of the Three-City Study. *Br J Nutr*. 2007;98:1046–1057.
36. Merle B, Delyfer MN, Korobelnik JF, et al. Dietary omega-3 fatty acids and the risk for age-related maculopathy: the Alienor study. *Invest Ophthalmol Vis Sci*. 2011;52:6004–6011.
37. Zeger SL, Liang KY Albert PS. Models for longitudinal data: a generalized estimating equation approach. *Biometrics*. 1988;44:1049–1060.
38. Lucas RM, McMichael AJ, Armstrong BK, Smith WT. Estimating the global disease burden due to ultraviolet radiation exposure. *Int J Epidemiol*. 2008;37:654–667.
39. Chowdhury R, Kunutsor S, Vitezova A, et al. Vitamin D and risk of cause specific death: systematic review and meta-analysis of observational cohort and randomised intervention studies. *BMJ*. 2014;348:g1903.
40. Holick MF. Vitamin D deficiency. *N Engl J Med*. 2007;357:266–281.
41. Mora JR, Iwata M, von Andrian UH. Vitamin effects on the immune system: vitamins A and D take centre stage. *Nat Rev Immunol*. 2008;8:685–698.
42. Parekh N, Chappell RJ, Millen AE, Albert DM, Mares JA. Association between vitamin D and age-related macular degeneration in the Third National Health and Nutrition Examination Survey, 1988 through 1994. *Arch Ophthalmol*. 2007;125:661–669.
43. Millen AE, Voland R, Sondel SA, et al. Vitamin D status and early age-related macular degeneration in postmenopausal women. *Arch Ophthalmol*. 2011;129:481–489.
44. Morrison MA, Silveira AC, Huynh N, et al. Systems biology-based analysis implicates a novel role for vitamin D metabolism in the pathogenesis of age-related macular degeneration. *Hum Genomics*. 2011;5:538–568.
45. Seddon JM, Reynolds R, Shah HR Rosner B. Smoking, dietary betaine, methionine, and vitamin d in monozygotic twins with discordant macular degeneration: epigenetic implications. *Ophthalmology*. 2011;118:1386–1394.
46. Lucas R, McMichael T, Smith W, Armstrong B. *Solar Ultraviolet Radiation - Global Burden of Disease From Solar Ultraviolet Radiation*. Geneva, Switzerland: WHO; 2006.
47. West SK, Rosenthal FS, Bressler NM, et al. Exposure to sunlight and other risk factors for age-related macular degeneration see comments. *Arch Ophthalmol*. 1989;107:875–879.
48. Mitchell P, Smith W, Wang JJ. Iris color, skin sun sensitivity, and age-related maculopathy: The Blue Mountains Eye Study. *Ophthalmology*. 1998;105:1359–1363.
49. Fletcher AE, Bentham GC, Agnew M, et al. Sunlight exposure, antioxidants, and age-related macular degeneration. *Arch Ophthalmol*. 2008;126:1396–1403.
50. Sparrow JR, Boulton M. RPE lipofuscin and its role in retinal pathobiology. *Exp Eye Res*. 2005;80:595–606.
51. Augood CA, Vingerling JR, de Jong PT, et al. Prevalence of age-related maculopathy in older Europeans: the European Eye Study (EUREYE). *Arch Ophthalmol*. 2006;124:529–535.
52. Vingerling JR, Dielemans I, Hofman A, et al. The prevalence of age-related maculopathy in the Rotterdam Study. *Ophthalmology*. 1995;102:205–210.
53. Friedman DS, O'Colmain BJ, Munoz B, et al. Prevalence of age-related macular degeneration in the United States. *Arch Ophthalmol*. 2004;122:564–572.
54. Kim NR, Kang JH, Kwon OW, Lee SJ, Oh JH, Chin HS. Association between complement factor H gene polymorphisms and neovascular age-related macular degeneration in Koreans. *Invest Ophthalmol Vis Sci*. 2008;49:2071–2076.
55. Sofat R, Casas JP, Webster AR, et al. Complement factor H genetic variant and age-related macular degeneration: effect size, modifiers and relationship to disease subtype. *Int J Epidemiol*. 2012;41:250–262.

Investigative Ophthalmology & Visual Science