Supplementary Online Content

Saunier V, Merle BMJ, Delyfer M-N, et al. Incidence of and risk factors associated with age-related macular degeneration: four-year follow-up from the ALIENOR Study. *JAMA Ophthalmol*. Published online March 29, 2018. doi:10.1001/jamaophthalmol.2018.0504

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods 1. Classification of age-related macular degeneration (AMD)

Advanced AMD was defined by the presence of neovascular AMD or atrophic AMD within the grid (3000 μm from the foveal center). Neovascular AMD included serous or hemorrhagic detachment of the retinal pigment epithelium (RPE) or sensory retina, subretinal or sub-RPE hemorrhages and fibrous scar tissue visualized on retinal photograph. Atrophic AMD 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 on retinal photographs, within 3 000 μm from the foveal center. Atrophic AMD was defined as the presence of geographic atrophy in absence of neovascular AMD (pure atrophic AMD). In addition, at waves 2 and 3, SD-OCT macular scans (vertical and horizontal lines, macular volume) were interpreted for signs of retinal atrophy and neovascular AMD (subretinal fluid, subretinal tissue, pigment epithelium detachment, intra-retinal fluid). Finally, classification of atrophic and neovascular AMD at waves 2 and 3 were based on all available information (ophthalmological history and treatments, retinal photographs, SD-OCT scans). All cases of AMD were confirmed by a retina specialist.

Early AMD was classified in two groups (in the absence of advanced AMD): early AMD 1 (soft distinct drusen without pigmentary abnormalities or pigmentary abnormalities without large drusen (>125 μm)); early AMD 2 (soft indistinct drusen and/or reticular pseudodrusen and/or soft distinct drusen associated with pigmentary abnormalities (hyper- or hypopigmentation)). Soft distinct and indistinct drusen were larger than 125 μm in diameter and with uniform density and sharp edges or decreasing density from the centre outwards and fuzzy edges, respectively. Pigmentary abnormalities were defined as areas of hyperpigmentation and/or hypopigmentation (without visibility of choroidal vessels).

At each examination, eyes were classified into one of the five exclusive groups: no AMD, early AMD 1, early AMD 2, atrophic AMD or neovascular AMD. These definitions of AMD are similar to those used in other large epidemiological studies of AMD, such as the Blue Mountains Eye Study, [1] the Rotterdam Study, [2] or the EUREYE Study, [3] in order to facilitate comparisons with these studies. Definition of intermediate AMD according to the Macular Research Classification Committee[4] was similar to early AMD (stages 1 or 2) in the present study.

In addition, as described previously,[5] detailed characteristics of early AMD abnormalities were studied. We also assessed the risk of incident advanced AMD associated with the Age- related Eye Disease Study (AREDS) Simplified Severity Scale,[6] in which presence of large drusen and presence of any pigmentary abnormality in an eye or presence of intermediate drusen in both eyes, were each counted as one risk factor and the sum of factors across the two eyes provided a five-step (0-4) person-based scale.

At the eye level, incident advanced AMD was defined as the presence of advanced AMD at any follow-up examination, in eyes without advanced AMD at baseline. Incident early AMD was defined as the presence of early AMD at any follow-up examination, in eyes without any AMD (early or advanced) at baseline. At the person level, incident advanced AMD was defined as the presence of advanced AMD in at least one eye at any follow-up examination, in participants without advanced AMD in both eyes at baseline. Incident early AMD was defined as the presence of early AMD in at least one eye at any follow-up examination, in participants without any AMD (early or advanced) in both eyes at baseline. Similar definitions of incidence were used for other AMD endpoints (subtypes

of drusen and pigmentary abnormalities). Finally, progression from early to advanced AMD was defined as the presence of advanced AMD at any follow-up examination, in eyes with early AMD at baseline.

eMethods 2. Statistical analysis

The date of occurrence of AMD was calculated as the midpoint of the interval between the last visit without AMD and the first visit with AMD. Follow-up ended at the date of occurrence of AMD when the subject progressed to AMD or the date of the last gradable examination otherwise. Regarding analyses per age categories, the number of person-years was calculated by adding each person's contribution of the follow-up time to successive age categories. So, one participant could contribute person-years to different age categories (for instance, if aged 78 years at baseline, a participant would contribute 2 years to the 73-79 years category, and then 2 years to the 80 years or more category). Similar methodology was used for incidence rates per eye. In particular, time of AMD incidence (which may be different for the two eyes in cases with bilateral incident AMD) and time of follow-up (which may be different for the two eyes in cases of ungradable examinations in one eye but not the other) were calculated for each eye.

eTable 1. Comparison of characteristics between participants with and without follow-up in the ALIENOR Study, 2006-2012

	With follow-up (n=659 subjects)		**Without follow-up (n=170 subjects)**		**P**
	N=659		N=170		
Age (y), mean (SD)	79.7	(4.4)	80.6	(4.1)	*.01*
Female Gender, n (%)	413	(62.7)	102	(60.0)	*.52*
Smoking, n (%)	N=654		N=167		*.88*
Never	427	(65.3)	106	(63.5)	
<20 pack-years	112	(17.1)	33	(19.7)	
≥20 pack-years	115	(17.6)	28	(16.8)	
Hypertension, n (%)	N=659		N=170		*.60*
Yes	495	(75.1)	131	(77.1)	
Diabetes, n (%)	N=610		N=160		*.45*
Yes	46	(7.5)	15	(9.4)	
BMI (kg/m²), n (%)					*.26*
≤25	261	(39.9)	53	(31.4)	
25-30	293	(44.7)	93	(55.0)	
>30	101	(15.4)	23	(13.6)	
Plasma lipids (mg/dL), mean (SD)					
HDL-cholesterol	N=614		N=164		*.48*
	61.24	(22.43)	62.19	(32.10)	
LDL-cholesterol	N=613		N=164		*.35*
	141.72	(53.38)	139.03	(63.44)	
Total cholesterol	N=615		N=164		*.60*
	224.50	(103.66)	222.79	(133.06)	
Triglycerides	N=614		N=164		*.97*
	108.47	(32.77)	108.63	(34.54)	
***CFH* Y402H**	N=597		N=161		*.28*
TT	279	(46.7)	68	(42.2)	
TC	252	(42.2)	72	(44.7)	
CC	66	(11.1)	21	(13.1)	
***ARMS2* A69S**	N=543		N=149		*.03*
GG	369	(68.0)	85	(57.0)	
GT	158	(29.1)	60	(40.3)	

TT	16	(2.9)	4	(2.7)	

eTable 2. Incidence of early and late age-related macular degeneration (AMD) in population-based studies performed in individuals of European ancestry

Study	Country	Duration (y)	Age (y)	Early AMD Incidence (%)			Late AMD Incidence (%)		
				All subjects	70-79	≥ 80	All subjects	70-79	≥ 80
Beaver Dam Eye Study[7]	USA	5	≥ 45	8.2	16.1*	22.8**	0.9	1.3*	5.4**
Blue Mountain Eye Study[1]	Australia	5	≥ 49	8.7	18.3	14.8	1.1	2.4	5.4
Melbourne Visual Impairment Project[8]	Australia	5	≥ 40	17.3	29.8	20.0	0.5	1.7	6.3
Rotterdam Study[9]	Netherlands	6.5	≥ 55	7.9	14.7***	22.5	1.8	1.9***	3.4
Reykjavik Eye Study[10]	Iceland	5	≥ 50	-	43.9	50.0	1.2	4.4	5.9
Pathologies Oculaires Liée à l'Age[11]	France	3	≥ 65	-	-		0.5	0.6	3.4
Alienor	France	5	≥ 73	32.9	28.0	37.4	6.8	5.9****	11.2
Alienor	Retinal photographs only						4.9	4.1	8.8

*Range 65-74 years
** ≥ 75 years
***Range 75-79 years
**** Range 73-79 years

eReferences.

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