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Prevalence of Age-Related Macular Degeneration in Europe

The Past and the Future

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Purpose: Age-related macular degeneration (AMD) is a frequent, complex disorder in elderly of European ancestry. Risk profiles and treatment options have changed considerably over the years, which may have affected disease prevalence and outcome. We determined the prevalence of early and late AMD in Europe from 1990 to 2013 using the European Eye Epidemiology (E3) consortium, and made projections for the future.

Design: Meta-analysis of prevalence data.

Participants: A total of 42 080 individuals 40 years of age and older participating in 14 population-based cohorts from 10 countries in Europe.

Methods: AMD was diagnosed based on fundus photographs using the Rotterdam Classification. Prevalence of early and late AMD was calculated using random-effects meta-analysis stratified for age, birth cohort, gender, geographic region, and time period of the study. Best-corrected visual acuity (BCVA) was compared between late AMD subtypes; geographic atrophy (GA) and choroidal neovascularization (CNV).

Main Outcome Measures: Prevalence of early and late AMD, BCVA, and number of AMD cases.

Results: Prevalence of early AMD increased from 3.5% (95% confidence interval [CI] 2.1%–5.0%) in those aged 55–59 years to 17.6% (95% CI 13.6%–21.5%) in those aged ≥85 years; for late AMD these figures were 0.1% (95% CI 0.04%–0.3%) and 9.8% (95% CI 6.3%–13.3%), respectively. We observed a decreasing prevalence of late AMD after 2006, which became most prominent after age 70. Prevalences were similar for gender across all age groups except for late AMD in the oldest age category, and a trend was found showing a higher prevalence of CNV in Northern Europe. After 2006, fewer eyes and fewer ≥80-year-old subjects with CNV were visually impaired ($P = 0.016$). Projections of AMD showed an almost doubling of affected persons despite a decreasing prevalence. By 2040, the number of individuals in Europe with early AMD will range between 14.9 and 21.5 million, and for late AMD between 3.9 and 4.8 million.

Conclusion: We observed a decreasing prevalence of AMD and an improvement in visual acuity in CNV occuring over the past 2 decades in Europe. Healthier lifestyles and implementation of anti–vascular endothelial growth factor treatment are the most likely explanations. Nevertheless, the numbers of affected subjects will increase considerably in the next 2 decades. AMD continues to remain a significant public health problem among Europeans. *Ophthalmology 2017;124:1753-1763 © 2017 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

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Age-related macular degeneration (AMD) can cause irreversible blindness and is the leading cause of visual impairment in the elderly of European ancestry.[1] Two stages are known for this disease: early AMD, which is characterized by drusen and pigmentary changes, and late AMD, which can be distinguished in 2 subtypes—geographic atrophy (GA) and choroidal neovascularization (CNV).[2]

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Worldwide estimates approximated that 30−50 million people are affected by AMD,[3,4] and these numbers are expected to increase over time because of the aging population.[1,5−9] Although multiple small studies have assessed the prevalence of AMD and its relation to visual decline at various places in Europe,[10−12] a clear overview for Europe as a whole is lacking.[13] Comprehensive epidemiologic figures on AMD in Europe would help proper planning for public health and eye care policy makers.

Recent studies report a decrease in AMD-associated blindness and visual impairment,[14,15] which are likely to be attributable to improved diagnostic procedures and hence earlier diagnosis, and the introduction of anti−vascular endothelial growth factor (VEGF) therapy.[14−16] Anti-VEGF therapy for CNV was introduced in 2004 and, since 2006, it has been widely used for clinical care in Europe.[17,18] However, the impact of anti-VEGF therapy on general visual function of persons with AMD in Europe has not been sufficiently studied.[1,16]

In this study, we investigated the prevalence of both early and late AMD in Europe using summary data of population-based cohort studies from the European Eye Epidemiology (E3) consortium. We analyzed changes in prevalence over time, compared geographic regions, and studied differences between men and women. Moreover, we analyzed the visual acuity of affected individuals before and after the introduction of anti-VEGF therapy and predicted the number of persons with AMD by 2040 in Europe.

Methods

Study Population

Fourteen population-based cohort studies participating in the E3 consortium contributed to this analysis. This consortium consists of European studies with epidemiologic data on common eye disorders; a detailed description on the included studies has been published elsewhere.[16] For the current analysis, studies with gradable macular fundus photographs (n = 42 080 participants) and participants aged 40 years and over provided summary data. Participants were recruited between 1990 and 2013 from the following countries: Estonia, France, Germany, Greece, Italy, Northern Ireland, Norway, Netherlands, Spain, Portugal,[19,20] and the United Kingdom (UK)[16] (Table 1). The composition of AMD in each cohort is shown in Figure 1 (available at www.aaojournal.org). The study was performed in accordance with the Declaration of Helsinki for research involving human subjects and the good epidemiologic practice guideline.

Grading of Age-Related Macular Degeneration

Both eyes of each participant were graded and classified separately by experienced graders or clinicians, and the most severe AMD grade of the worse eye was used for classification of the person. To harmonize classification of AMD, studies were graded or reclassified according to the Rotterdam Classification, as previously described.[21] Main outcomes of this study were early AMD (grade 2 or 3 of the Rotterdam Classification) and late AMD (grade 4 of the Rotterdam Classification). Persons with late AMD were stratified as GA and CNV or mixed (both GA and CNV present in one person, either both types in the same eye or one type per eye), which is henceforth in this article referred to as CNV. The Tromsø Eye Study, the Thessaloniki Eye Study, and the European Prospective Investigation into Cancer and Nutrition (EPIC) study had fundus photograph grading that could not be converted to match the definition of early AMD of the Rotterdam Classification. Therefore, these 3 studies only participated in the late AMD analysis.

Visual Impairment

Visual acuity was measured for each eye separately as best-corrected visual acuity in 2 categories: $\geq$0.3 and <0.3. When best-corrected visual acuity differed in the 2 eyes, visual acuity of the best eye was used to classify the person. Low vision and blindness were defined as visual acuity <0.3 and further referred to as visually impaired.

Projection of Age-Related Macular Degeneration

The projection of AMD cases in Europe from 2013 to 2040 was calculated using the prevalence data for 5-year age categories obtained from the meta-analysis. Two different scenarios were used to calculate the projection. In the first scenario, it was assumed that the prevalence of both early and late AMD will remain stable until 2040. This scenario accounted for changes in population structure only. The second scenario followed the trend of decreasing prevalence based on data from the meta-analysis of the E3 consortium regarding the period 2006−2013. We calculated the rate of decline, with 2013 as the starting point and 2040 as the end point, and made the assumption that the rate of decline was decelerating and zero at the end point. For each projected year, prevalences were calculated for every 5-year age group, for early AMD from 45 years of age and onward and for late AMD 65 years and onward. The projected prevalences were then multiplied by the predicted European population estimates obtained from Eurostat for all 28 countries in Europe, and the sum of individuals from all age groups was calculated.[22]

Statistical Analysis

The crude prevalence of early and late AMD were calculated per study for each 5-year age group. A random-effects meta-analysis was performed by weighing the studies according to sample size, for early and late AMD separately for 5-year age groups and for people aged 70 years and older. In case of reported zero prevalence, the Haldane correction was used.[23] In the case of 100% prevalence, 0.01 was subtracted to prevent exclusion from the analysis. This analysis was repeated, stratified for the midpoint year of the study recruitment period, before and after the year 2006 and for 10-year birth cohorts. Furthermore, it was repeated for gender, and for geographical area in Europe based on the United Nations Geoscheme.[24] A chi-square test was used to compare time trends.

In addition, a meta-analysis was performed for eyes with visual impairment owing to late AMD, and per subtype of late AMD. Subsequently, the analysis was stratified for studies conducted before and after 2006, for which the midpoint year of the study recruitment period was used. The number of visually impaired people was calculated before and after 2006. Meta-analysis was performed with Stata software (release 13, version 13.1; StataCorp LP, College Station, TX) using metaprop. Graphical outputs were constructed with GraphPad Prism 7 (for Windows; GraphPad Software, La Jolla, CA; www.graphpad.com).

Table 1. Description of the European Eye Epidemiology Consortium Studies Included in the Meta-analysis

Region	Study	Data Collection Period	Total Participants (n)	Age Range (yrs)	Median Age (yrs)	Male Gender (%)	European Ethnicity (%)	Crude Prevalence of Early AMD (%)	Crude Prevalence of Late AMD (%)
North	United Kingdom EPIC	2004–2011	5344	45–85+	60–64	43.1	99.7	–	0.5
	Norway Tromsø	2007–2008	2631	65–85+	65–69	42.5	91	–	3.5
West	France ALIENOR-3C	2006–2008	879	70–85+	75–79	37.7	–	16.8	5.6
	Germany GHS	2007–2012	3839	40–74	50–54	50.2	–	2.3	0.2
	Netherlands RS-I	1990–1993	6419	55–85+	60–64	40.7	98.9	7.5	1.7
	Netherlands RS-II	2000–2002	2545	55–85+	55–59	45.4	97.8	6	0.7
	Netherlands RS-III	2005–2008	3449	45–85+	55–59	43.4	96.4	4.6	0.4
	France Montrachet-3C	2009–2013	1069	75–85+	80–84	37	100	9.2	2.2
	France POLA	1995–1997	2196	60–85+	65–69	43.5	–	8.7	1.9
South	Portugal Lousa	2012–2013	3021	55–85+	60–64	43.9	99.3	15.4	1.3
	Portugal Mira	2009–2011	2975	55–85+	65–69	43.4	99.7	6.9	0.7
	Thessaloniki Thessaloniki Eye Study	2000–2005	2107	60–85+	65–69	55.6	97.7	–	2.7
	Italy PAMDI	2005–2006	853	60–85+	65–69	45.8	100	13.5	2.1
Multiple	EUREYE	2000–2002	4753	65–85+	65–69	44.8	–	12.6	3.3

ALIENOR = Antioxydants, Lipids Essentials, Nutrition et maladies OculaiRes Study; AMD = age-related macular degeneration; EPIC = European Prospective Investigation into Cancer; EUREYE = European Eye Study; GHS = Gutenberg Health Study; PAMDI = Prevalence of Age-Related Macular Degeneration in Italy; POLA = Pathologies Oculaires Liées à l'Age Study; RS = Rotterdam Study; – = data not available.

Results

The total study population included in this analysis consisted of 42 080 individuals from 14 studies with a median age of 65–69 years and a slight female predominance (55.8%). The prevalence of all age groups together varied per study between 2.3% and 16.8% for early AMD (total N = 2703) and between 0.2% and 5.6% for late AMD (total N = 664) (Fig 2A and B, available at www.aaojournal.org; to avoid biased estimates only groups larger than 30 individuals are shown; this applied only to the Rotterdam Study 3 age category ≥85 years). Owing to moderate to high heterogeneity (I^2 ≥75% in 73 of 141 analyses), which was not related to time trends, we applied a random-effects model for each meta-analysis. This provided a prevalence of early AMD increasing with age from 3.5% (95% confidence interval [CI] 2.1%–5.0%) at 55–59 years to 17.6% (95% CI 13.6%–21.5%) in persons aged ≥85 (Fig 3A, and Table 2, available at www.aaojournal.org). The prevalence of late AMD rose from virtually zero in the youngest age group to 9.8% (95% CI 6.3%–13.3%) for those in the highest age group (Fig 3B). Taking together all people aged ≥70 years, the overall prevalence was 13.2% (95% CI 11.2%–15.1%) for early AMD and 3.0% (95% CI 2.2%–3.9%) for late AMD. We investigated prevalence changes over time by dividing the E3 consortium into studies conducted before and after 2006. The prevalence of early AMD before and after 2006 seemed to rise with age in a similar fashion. For late AMD, a trend of decreasing prevalence was observed for the higher age categories after 2006 (Fig 3C and D). Even after exclusion of the 2 cohorts (Rotterdam Study [RS]-II and European Eye Study [EUREYE]) with the highest prevalences in the highest age category before 2006, results remained similar (data not shown). When we analyzed prevalence data as a function of birth cohort, a relatively stable prevalence of early AMD was visible across all birth cohorts, whereas a decreasing prevalence of late AMD was seen for the more recent birth cohorts (Fig 4A and B).

Gender and Geographic Region

We studied the relation with gender and found no differences in the prevalence of early and late AMD between men and women except for the age category of 85 years and older for late AMD (Fig 5A and B, available at www.aaojournal.org). This category shows a trend for a higher prevalence in women compared to men, although CIs overlap.

To address differential distribution of AMD in Europe, we stratified studies according to 3 regions defined by the United Nations.[24] In older individuals, we observed a trend toward a higher prevalence of early AMD in the North (16% in those ≥70 years; 95% CI 14%–17%) compared to the West (12%; 95% CI 10%–14%) and South (14%; 95% CI 10%–17%) (Fig 6A, available at www.aaojournal.org). Likewise, late AMD had the highest prevalence in the North (4.2%; 95% CI 2%–6%) compared to the West (3.1%; 95% CI 2%–4%) and South (3.1%; 95% CI 2%–4%) (Fig 6B, available at www.aaojournal.org). More detailed analyses showed that a frequency difference was only present for CNV (Fig 6C and D, available at www.aaojournal.org); however, CIs of the regional differences overlapped.

Visual Consequences

As most countries implemented anti-VEGF therapy for CNV from 2006 onward, we compared visual impairment from AMD in studies carried out before and after this year. Before 2006,

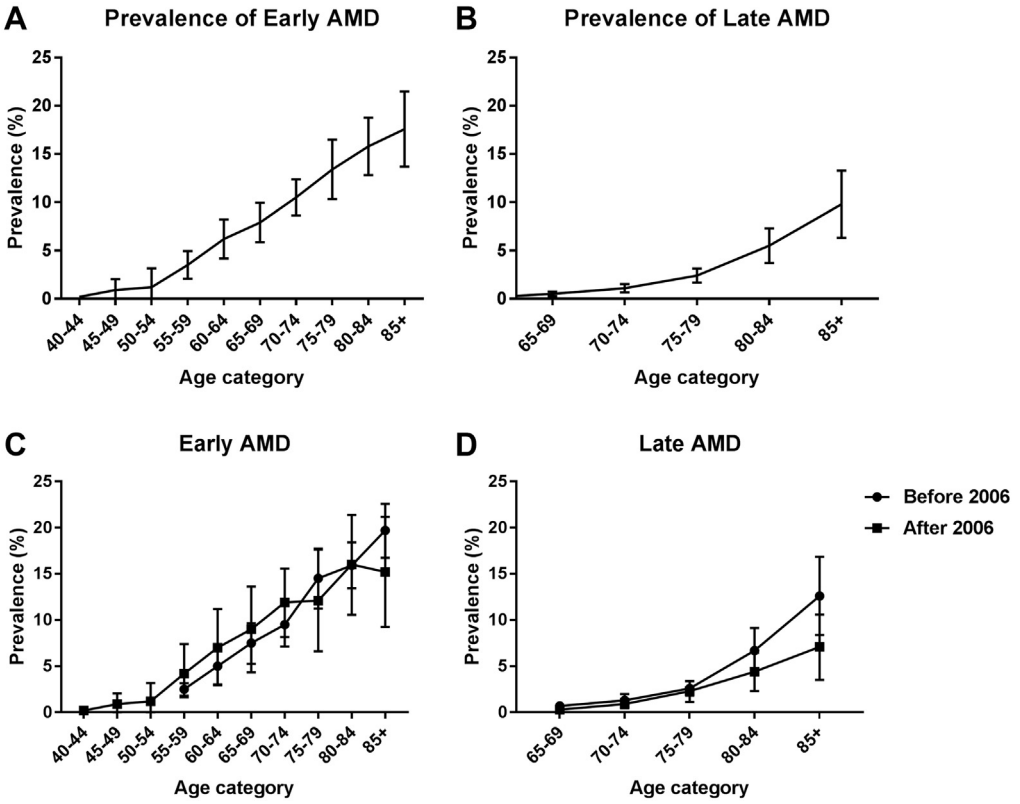

Figure 3. Meta-analysis of (**A**) early and (**B**) late age-related macular degeneration (AMD) in Europe per age category for the participating studies. Meta-analysis of the prevalence of (**C**) early and (**D**) late AMD before and after 2006.

54.2% of eyes with GA were visually impaired, and 79.8% of eyes suffering from CNV were visually impaired. From 2006 onward, the proportion of visually impaired eyes remained the same for GA (47.6%; $P = 0.40$), but dropped to 66.2% ($P = 0.026$) for CNV (Fig 7A). This improvement was also observed for the number of bilaterally visually impaired persons; 120 of 345 (34.8%) before 2006 to 75 of 259 (28.9%; $P = 0.13$) after 2006. The largest drop was seen for people aged 80 years and older; 85 of 175 (48.6%) before 2006 to 46 of 132 (34.8%; $P = 0.016$) after 2006 (Fig 7B).

Projections of Age-Related Macular Degeneration in Europe for 2040

Assuming that the prevalence of early and late AMD will remain stable over time, an increase from 15.0 million in 2013 to 21.5 million for early AMD can be expected by 2040. The number of people with late AMD will almost double during this time period, from 2.7 million in 2013 to 4.8 million in 2040.

Assuming a more realistic scenario for which E3 historic data and a decelerating slope were used, we found that the prevalence of

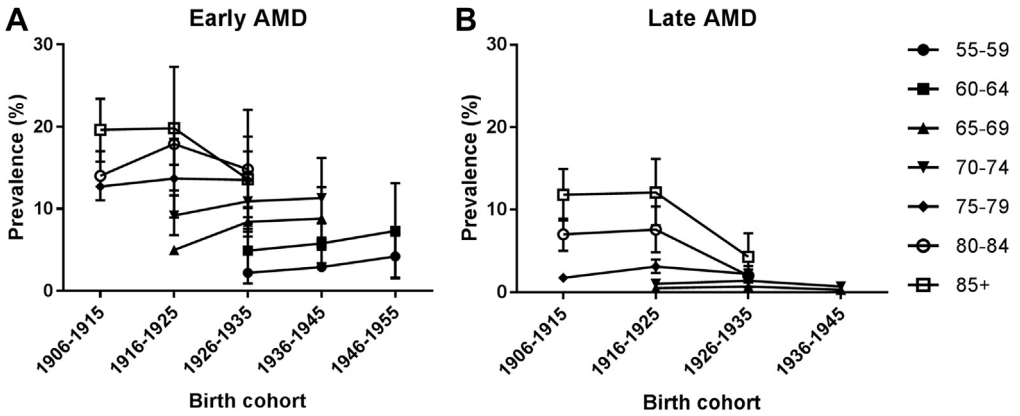

Figure 4. Meta-analysis of early (**A**) and late (**B**) age-related macular degeneration in Europe by 10-year birth cohorts.

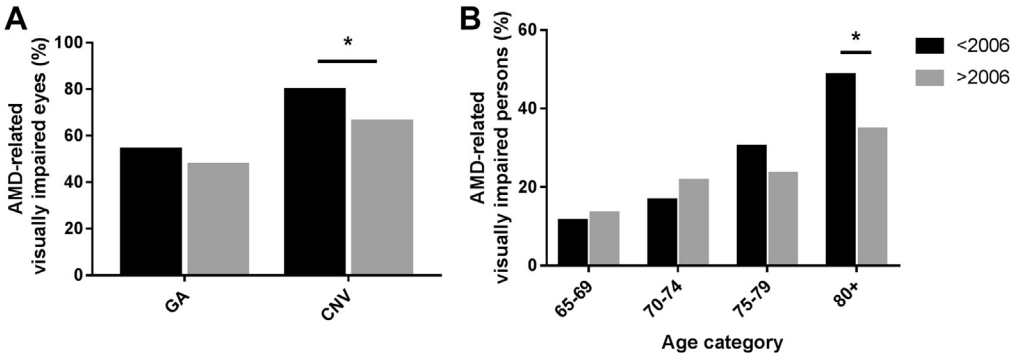

Figure 7. **A**, Proportion of visually impaired eyes within each subgroup of late age-related macular degeneration (AMD). The proportion of visually impaired eyes remained the same for geographic atrophy (47.6%; $P = 0.4$), but dropped to 66.2% ($P = 0.026$) for choroidal neovascularization after 2006. **B**, Proportion of persons with late AMD with bilateral visual impairment before and after 2006 ($P = 0.016$). *$P < 0.05$.

early AMD will first decrease and then slightly increase between 2013 and 2040. The model estimated that the number of people with early AMD would remain almost the same: from 15.0 million in 2013 to 14.9 million in 2040. This model also displayed that the number of people with late AMD in Europe will increase from 2.7 million in 2013 to 3.9 million by 2040 (Fig 8).

Discussion

Age-Related Macular Degeneration Prevalence and Its Time Trends

Our study provides insight into the prevalence of both early and late AMD in Europe. Based on meta-analyzed data from 14 population-based cohort studies included in the E3 consortium, the overall prevalence of early and late AMD was 13.2% and 3.0%, respectively, in the age category ≥70 years. These estimates are comparable to those among persons of European descent living in other continents.[4,25]

Our data show a trend toward a slightly decreasing prevalence of AMD in the older age categories. It is unlikely that this is explained by differential mortality in AMD patients before and after 2006, although studies have shown conflicting results on death as a competing risk factor for AMD, and we cannot exclude that this plays a role.[26–28] The decreasing trend in time has also been observed in the Beaver Dam Eye Study, indicating that these trends are not confined to Europe.[29] Decreasing rates have also been observed for other aging disorders such as cardiovascular disease and dementia,[30–33] and may be related to improved lifestyle among the elderly[34–36]; for example, the number of smokers declined by 30.5% from 1990 to 2010 in Europe.[37] Taken together, the decline in prevalence suggests that the increases in the number of AMD patients may not be as substantial as previous prediction studies suggested.[38]

Gender and Geographic Regions

Our data showed no difference in the prevalence of early and late AMD with respect to gender. In the oldest age category of 85 years and older, women seemed to have a higher prevalence of late AMD, but detailed analysis showed that this was mostly owing to imprecision of the estimate in men, caused by a lower number of men in this age group (Fig 9, available at www.aaojournal.org). This has also been observed in other studies.[7,39]

As for regional differences, we noticed that the northern region of Europe showed a slightly higher prevalence of early and late AMD. This trend was the result of a higher prevalence of CNV in the north. Our findings are in concordance with the results previously published by the Tromsø Eye Study[40] but are in contrast with other studies performed in the north of Europe finding a higher prevalence of GA (EUREYE, Reykjavik Eye Study, and Oslo Macular Study).[41–43] Considering the larger sample size and high response rate of the Tromsø Eye Study compared with the other studies, these findings might be more legitimate. No consistent differences were observed for the western and southern regions of Europe.

Visual Consequences

The proportion of eyes affected by CNV that were visually impaired was reduced after the year 2006. Unfortunately, our study lacked actual data on interventions for CNV, but it is likely that the reduction is attributable to the use of anti-VEGF injections, which were introduced as a therapy for CNV in Europe from 2006 onward.[18] This notion is supported by findings from clinical trials[44,45] and other studies, which show an up to 2-fold decrease in legal blindness due to AMD after 2006.[14,15,46,47] The public campaigns that were initiated after the introduction of anti-VEGF have undoubtedly contributed to the reduction of visual loss, as they made elderly persons more aware of the symptoms and stimulated prompt therapy.[48,49]

Projections of Age-Related Macular Degeneration in Europe

It is unclear whether the prevalence of AMD will decrease even more in the coming years, but an increase is not likely to be expected. Therefore, we projected the estimated number of AMD-affected persons until the year 2040 based on 2 different scenarios: 1 based on stable prevalence and 1

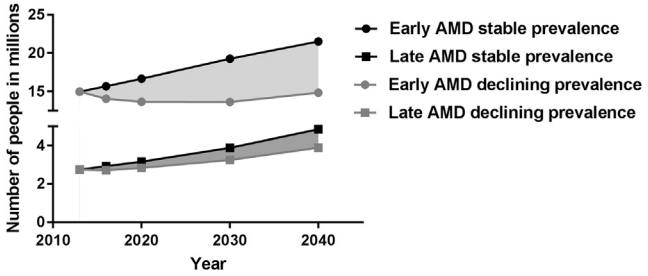

Figure 8. Predicted number of persons with age-related macular degeneration (AMD) in years 2013–2040 as a function of 2 prevalence scenarios.

following the trend of declining prevalences. The results of the first scenario suggests that the absolute number of persons with late AMD will increase by 2.1 million, a 1.5-times increase. A Norwegian study predicted, under the assumption of a stable prevalence, the same relative increase of affected subjects, with a total of 328 000 cases of late AMD in Scandinavia by 2040.[5,8] A study in the United States calculated a 2.2-times increase in absolute numbers and estimated a total number of affected subjects to be 3.8 million by 2050.[5,8] Worldwide projections have shown a doubling of late AMD and an increase of 9 million cases by 2040.[4]

The second scenario was based on declining rates, and showed a small increase in the number of people with early AMD, from 14 million in 2016 to 14.9 million by 2040, and a larger relative increase in the number of people with late AMD, from 2.7 million in 2016 to 3.9 million by 2040. Considering the declining rates of smoking and implementation of healthier diets in elderly persons, the second projection may be more legitimate.

Study Limitations

A limitation to this E3 consortium meta-analysis is the heterogeneity across studies regarding study design and inclusion criteria. For example, age at inclusion and method of recruitment varied between studies. Although in every study AMD was classified according to the Rotterdam Classification, studies differed in AMD grading, especially for pigmentary changes and drusen size. Given the heterogeneity, we therefore performed a random-effects meta-analysis for both early and late AMD. Furthermore, patient management and access to health care may have differed between study sites, resulting in differences in preventive and treatment options.[50,51]

When data collection started in 1990, fundus photography was the gold standard for grading AMD. Since 1990, imaging techniques evolved rapidly, greatly improving the diagnosis of AMD features with non-invasive techniques such as optical coherence tomography, autofluorescence, and near-infrared photographs. In addition, multimodal imaging better visualizes edema and subtle changes resulting from CNV, which may not be so apparent when the patient was treated with anti-VEGF therapy.[52,53] Although macular edema due to subretinal neovascularization often coincides with prominent retinal changes such as hemorrhages or hard exudates, our data may have underestimated the true prevalence of CNV.[53]

In summary, this study estimates the prevalence of early and late AMD per age category in Europe over the past two decades. Prevalence of both these forms remained stable or decreased slightly. Nevertheless, we observed a significant reduction in the proportion of visually impaired eyes attributable to CNV after 2006. Unfortunately, due to the aging population, the number of people with AMD will increase during the next decades, indicating a continuous need to develop comprehensive modalities for prevention and treatment of AMD.

Appendix

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Abbreviations and Acronyms:
AMD = age-related macular degeneration; **CI** = confidence interval; **CNV** = choroidal neovascularization; **E3** = European Eye Epidemiology (consortium); **EPIC** = European Prospective Investigation into Cancer and Nutrition; **EUREYE** = European Eye Study; **GA** = geographic atrophy; **RS** = Rotterdam Study; **UK** = United Kingdom; **VEGF** = vascular endothelial growth factor.

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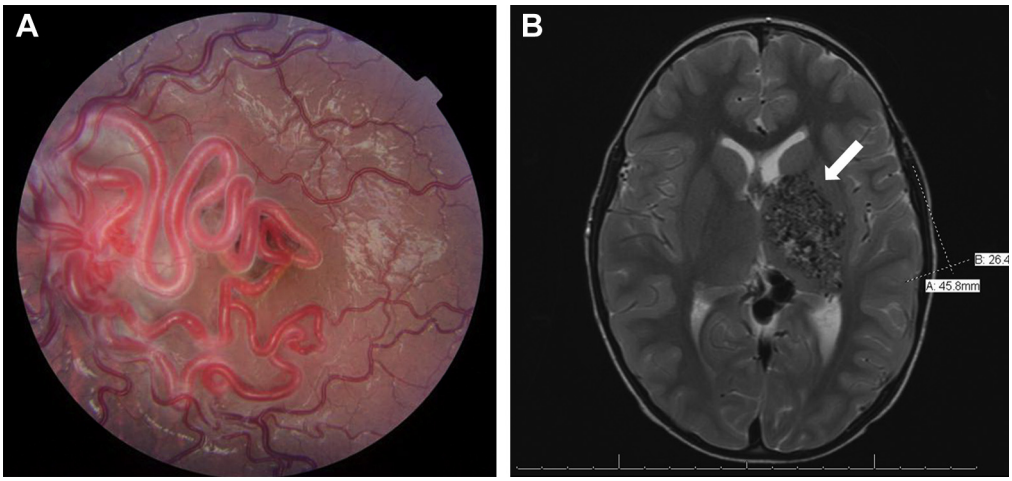
Pictures & Perspectives



Wyburn-Mason Incidentally Diagnosed on Evaluation of Eye Redness

A 10-year-old boy presented with a 1-week history of painless left eye injection without visual changes. He also acknowledged intermittent headaches and right-sided weakness. Dilated examination of the left eye revealed dilated, tortuous retinal vasculature (Fig 1**A**). T2-weighted brain magnetic resonance imaging (MRI) with contrast demonstrated a large left arteriovenous malformation (*arrow*) centered on the posterior limb of the internal capsule with involvement of the left basal ganglia and thalamus (Fig **1B**). These collective findings are consistent with a diagnosis of Wyburn-Mason syndrome. The patient's left eye injection was likely unrelated because there was no evidence of a carotid-cavernous fistula or venous outflow obstruction. (Magnified version of Fig 1**A-B** is available online at www.aaojournal.org).

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