Prevalence of Age-related Macular Degeneration in Europe: the past and the future

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Abbreviations:

AMD = Age-related macular degeneration; **E3** = European Eye Epidemiology consortium; **BCVA** = Best-corrected visual acuity; **GA**=Geographic Atrophy; **CNV** = Choroidal neovascularization; **anti-VEGF therapy** = anti-Vascular Endothelial Growth Factor therapy**; EPIC** = European Prospective Investigation into Cancer and Nutrition; **USA** = United States of America; **ALIENOR** = Antioxydants, Lipids Essentiels, Nutrition et maladies OculaiRes Study; **EUREYE** = European Eye Study; **GHS**= Gutenberg Health Study; **POLA**= Pathologies Oculaires Liées à l'Age Study; **RS**= Rotterdam Study

This article contains additional online-only material. The following should appear online-only: Figures 1,2, 5, 6 and 9 and Table 2.

ABSTRACT

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 prevalence of Early and Late AMD in Europe from 1990-2013 using the European Eye Epidemiology (E3) consortium, and made projections for the future.

Design: Meta-analysis of prevalence data.

Participants: 42,080 individuals aged 40+ participating in fourteen population-based cohorts from ten countries in Europe.

Methods: AMD was diagnosed 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 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 Early and 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 almost doubling of affected persons despite a decreasing prevalence. By 2040, the number of individuals in Europe with Early AMD will range between 14.9-21.5 million, for Late AMD between 3.9-4.8 million.

Conclusion: Over the last two decades in Europe, we observed a decreasing prevalence of AMD and an improvement in visual acuity in CNV. Healthier lifestyles and implementation of anti-VEGF treatment are the most likely explanations. Nevertheless, the numbers of affected subjects will increase considerably in the next two decades. AMD continues to remain a significant public health problem among Europeans.

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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 two subtypes; geographic atrophy (GA) and choroidal neovascularization (CNV).[2]

Worldwide estimates approximated that 30 to 50 million people are affected by AMD[3], and these numbers are expected to increase over time due to the aging population.[1, 4-8] Although multiple small studies have assessed the prevalence of AMD and its relation to visual decline at various places in Europe[9-11], a clear overview for Europe as a whole is lacking[12]. 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[13, 14], which are likely to be due to improved diagnostic procedures and hence earlier diagnosis, and the introduction of anti-Vascular Endothelial Growth Factor (anti-VEGF) therapy.[13-15] Anti-VEGF therapy for CNV was introduced in 2004 and, from 2006 onwards, it has been widely used for clinical care in Europe.[16, 17] However, the impact of anti-VEGF therapy on general visual function of persons with AMD in Europe has not been sufficiently studied.[1, 15]

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[15]. For the current analysis, studies with gradable macular fundus photographs (n=42,080 participants) with 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 and Portugal[18, 19], United Kingdom, see Table 1.[15] The composition of AMD in each cohort is shown in Figure 1 (available at External link http://www.aaojournal.org). The study was performed in accordance with the Declaration of Helsinki for research involving human subjects and the good epidemiological 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 worst eye was used for classification of the person. To harmonize classification of AMD, studies were graded or re-classified according to the Rotterdam Classification as previously described.[20] 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 in 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 further in this article referred to as CNV. The Tromsø Eye Study, Thessaloniki Eye Study and European Prospective Investigation into Cancer and Nutrition (EPIC) study had fundus photo grading that could not be converted to match the definition of Early AMD of the Rotterdam grading. Therefore, these three studies only participated in the Late AMD analysis.

Visual impairment

Visual acuity was measured for each eye separately as best corrected visual acuity (BCVA) in two categories; ≥0.3 and <0.3. When BCVA differed in the two eyes, visual acuity of the best eye was used for classification of the person. Low vision and blindness were defined as visual acuity of <0.3 and further referred to as visually impaired.

Projection of AMD

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 for calculation of 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 endpoint, and made the assumption that the rate of decline was linear 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 onwards and for Late AMD 65 years and onwards. 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.[21]

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-years age groups and for people aged 70 years and older. In case of reported zero prevalence, the Haldane correction was used.[22] In 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, for ten-year birth cohorts, for gender, and geographical area in Europe based on the United Nations Geoscheme.[23] A chi-square test was used to compare time-trends.

In addition, a meta-analysis was performed for eyes with visual impairment due 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 (StataCorp. 2013. Stata Statistical Software: Release 13, version 13.1. College Station, TX: StataCorp LP.) using metaprop. Graphical outputs were constructed with GraphPad Prism 7 (GraphPad Prism version 7.00 for Windows, GraphPad Software, La Jolla California USA, www.graphpad.com").

RESULTS

The total study population included in this analysis comprised of 42,080 individuals from 14 studies with a median age group 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= 2,703) and between 0.2% and 5.6% for Late AMD (total N= 664) (Figure 2a and b available at external link

http://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+). Due to moderate to high heterogeneity (I^2: >= 75% in 73/141 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+ (Figure 3a and Table 2, available at External link http://www.aaojournal.org). The prevalence of Late AMD rose from virtually naught in the youngest age group to 9.8% [95% CI 6.3-13.3] for those in the highest age group (Figure 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 (85+ age group p= 0.16) (Figure 3c and d). Even after exclusion of the two cohorts (RS-II and EUREYE) with the highest prevalences in the highest age category before 2006, results remained similar (data not shown). When analyzing prevalence data as a function of birth cohort, a relatively stable prevalence of Early AMD was visible across all birth cohorts, while a decreasing prevalence of Late AMD was seen for the more recent birth cohorts (Figure 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 (Figure 5a and b, available at External link http://www.aaojournal.org). This category shows a trend for a higher prevalence in women compared to men, although confidence intervals overlap.

To address differential distribution of AMD in Europe, we stratified studies according to three regions defined by the United Nations.[23] In older individuals, we observed a trend towards a higher prevalence of Early AMD in the North (16% in 70+ years; [95%CI 14-17]) compared to the West (12%; [95% CI 10-14]) and South (14%; [95% CI 10-17]) (Figure 6a, available at External link http://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]) (Figure 6b). More detailed analyses showed that a frequency difference was only present for CNV (Figure 6c and d), however, confidence intervals of the regional differences overlapped.

Visual consequences

As most countries implemented anti-VEGF therapy for CNV from 2006 onwards, we compared visual impairment from AMD in studies carried out before and after this year. Before 2006, 54.2% of eyes with GA were visually impaired, and 79.8% of eyes suffering from CNV were visually impaired. From 2006 onwards, the proportion of visually impaired eyes remained the same for GA (47.6%, p-value= 0.40), but dropped to 66.2% (p-value= 0.026) for CNV (Figure 7a). This improvement was also observed for the number of bilaterally visually impaired persons; 120 out of 345 (34.8%) before 2006 to 75 out of 259 (28.9%, p=0.13) after 2006. The largest drop was seen for people aged 80 years and older; 85 out of 175 (48.6%) before 2006 to 46 out of 132 (34.8%, p-value=0.016) after 2006 (Figure 7b).

Projections of AMD in Europe for 2040

When 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 Early AMD will first decrease and then slightly rise 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 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 by 2040 (Figure 8).

DISCUSSION

AMD prevalence and its time trends

Our study provides insight in the prevalence of both Early and Late AMD in Europe. Based on meta-analyzed data from fourteen population-based cohort studies included in the European Eye Epidemiology Consortium (E3), 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 persons from European descent living in other continents.[3, 24]

Our data show a trend towards 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 this plays a role.[25-27] The decreasing trend in time has also been observed in the Beaver Dam Eye Study, indicating that these trends are not confined to Europe.[28] Decreasing rates have also been observed for other aging disorders such as cardiovascular disease and dementia[29-32], and may to be related to improved lifestyle among the elderly[33-35], e.g. the number of smokers declined by 30.5% from 1990 to 2010 in Europe[36]. Taken together, the decline in prevalence suggests that the increases in number of AMD patients may not be as substantial as previous prediction studies suggested[37].

Gender and Geographic regions

Our data showed no difference in 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 due to imprecision of the estimate in men, caused by a lower number of men in this age group. (Figure 9, available at External link http://www.aaojournal.org). This has also been observed in other studies.[6,38]

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 earlier published by the Tromsø Eye Study[39], but 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).[40-42] Considering the larger sample size and high response rate of the Tromsø Eye Study compared to the other studies, these findings might be more legitimate. No consistent differences were observed for West and South 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 due to the use of anti-VEGF injections, which was introduced as a therapy for CNV in Europe from 2006 onwards.[17] This notion is supported by findings from clinical trials[43, 44] and other studies, which show an up to 2-fold decrease in legal blindness due to AMD after 2006.[13, 14, 45, 46] The public campaigns which were initiated after the introduction of anti-VEGF have undoubtedly contributed to the reduction of visual loss, as they made elderly more aware of the symptoms and stimulated prompt therapy.[47, 48]

Projections of AMD in Europe

It is unclear whether the prevalence rates of AMD will decrease even more in the coming years, but an increase is not likely to be expected. Therefore, we performed projections of the estimated number of AMD affected persons until the year 2040 based on two different scenarios; i.e., one based on stable prevalence and one based on linear 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 thousand cases of Late AMD in Scandinavia by 2040.[4, 7] A study in the USA calculated a 2.2 times increase in absolute numbers and estimated a total number of affected subjects to be 3.8 million by 2050.[4, 7] Worldwide projections have shown a doubling of Late AMD and an increase of 9 million cases by 2040.[3]

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 diet in elderly, 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 of 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 healthcare may have differed between study sites, resulting in differences in preventative and treatment options.[49, 50]

When data collection started in 1990, fundus photography was the golden 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, auto-fluorescence 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.[51,52] 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.[52]

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 showed a slight decrease. Nevertheless, we observed a significant reduction in the proportion of visually impaired eyes due 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.

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FIGURE LEGENDS

Figure 3 a, b, c and d Meta-analysis of Early (A) and Late (B) AMD in Europe per age category for the participating studies**.** Meta-analysis of the prevalence of Early (A) and Late (B) AMD before and after 2006.

Figure 4 a and b Meta-analysis of Early (A) and Late (B) AMD in Europe by ten year birth cohorts.

Figure 7 a and b (A) Proportion of visually impaired eyes within each subgroup of Late AMD. The proportion of visually impaired eyes remained the same for GA (47.6%, p-value= 0.4), but dropped to 66.2% (p-value= 0.026) for CNV after 2006. (B) Proportion of persons with Late AMD with bilateral visual impairment before and after 2006, p-value=0.016.

Figure 8 Predicted number of persons with AMD in years 2013-2040 as a function of two prevalence scenarios.

Précis: (max 35 words)

The prevalence of AMD in Europe showed a slight decline during the past decades, however, the number of affected persons will continue to increase in the next two decades.

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