Incidence of Late-Stage Age-Related Macular Degeneration in American Whites: Systematic Review and Meta-analysis

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• PURPOSE: To estimate incidence of age-related macular degeneration (AMD) by subtype in American whites aged ≥50 years.

• DESIGN: Systematic review and meta-analysis.

• METHODS: SETTING: Prospective cohort studies of AMD incidence in populations of white European ancestry published in MEDLINE, EMBASE, and Web of Science. STUDY POPULATION: Fourteen publications in 10 populations that examined AMD incident cases were identified. OBSERVATION PROCEDURE: Data on age-sex-specific incidence of late AMD, geographic atrophy (GA) and neovascular AMD (NVAMD), year of recruitment, AMD grading method, and continent were extracted. MAIN OUTCOME MEASURE(S): Annual incidence of late AMD, GA, and NVAMD by age-sex in American whites aged ≥50 years from a Bayesian meta-analysis of incidence studies was compared with incidence extrapolated from published prevalence estimates.

• RESULTS: Incidence rates from the review agreed with those derived from prevalence, but the latter were based on more data, especially at older ages and by AMD subtypes. Annual incidence (estimated from prevalence) of late AMD in American whites was 3.5 per 1000 aged ≥50 years (95% credible interval 2.5, 4.7 per 1000), equivalent to 293 000 new cases in American whites per year (95% credible interval 207 000, 400 000). Incidence rates approximately quadrupled per decade in age. Annual incidence GA rates were 1.9 per 1000 aged ≥50 years, NVAMD rates were 1.8 per 1000. Late AMD incidence was 38% higher in women vs men (95% credible interval 6%, 82%).

• CONCLUSIONS: Estimating AMD incidence from prevalence allows better characterization at older ages and by AMD subtype where longitudinal data from incidence studies are limited. (Am J Ophthalmol 2015;160(1):85–93. © 2015 The Authors. Published

ESTIMATING THE NUMBER IN A POPULATION WITH late age-related macular degeneration (AMD) is important for estimating health service need and provision, especially in the context of providing new treatments.[1] While prevalence measures the proportion with disease in the population, incidence is a key measure to examine new cases over time, allowing current demand for health services to be planned. Additionally, monitoring changes in incidence over time may relate to changes in potential risk factors, providing clues to etiology and pathways to prevention. While a large number of population-based studies have reported the prevalence of AMD in older people,[2–4] fewer have reported incidence, especially with long-term follow-up.[5–7] Disability, frailty owing to reduced vision and/or other morbidities, and mortality are factors leading to loss to follow-up and nonparticipation over time. Differences in duration of follow-up, especially at older ages, will impact on incidence and may explain variability in estimates of incidence between studies.[5,8–10] Low response rates, especially in the oldest age groups where AMD is more common, will lead to an underestimation of disease incidence. Moreover, when generalizing to a population at large, it is important that demographic characteristics of the entire population are taken into account. We have carried out a Bayesian meta-analysis of studies examining AMD incidence, allowing for differences in age and duration of follow-up. Incidence can also be estimated from age-specific prevalence.[11] We compare estimates of incidence from the meta-analysis of incidence studies with that derived from a meta-analysis of prevalence estimates[4] applied to the American white population demographics.

METHODS

• SYSTEMATIC REVIEW PROCESS: Eligible studies were those that reported on the prevalence and/or incidence of AMD. We searched MEDLINE (1950 onwards), EMBASE (1960 onwards), and Web of Science (1960 onwards) electronic databases; the search was updated to

October 2012.[4] A combination of text words for AMD (age-related macula$ degeneration/age related maculopathy/senile macula$ degeneration) and epidemiologic terms (inciden$/prevalen$/Population$/Survey$) were combined with related subject headings in MEDLINE and EMBASE only (in addition to MESH/subject headings for population study designs). Studies that quantified the incidence of late AMD, geographic atrophy (GA), and/or neovascular AMD (NVAMD) from a nondiseased state at baseline (in 1 or both eyes), in population-based samples of European ancestry, with detailed methods of sampling, were included. Studies were excluded if they were carried out in other racial groups, where nonspecific volunteers or those from particular professions (except for 1 study of American watermen)[12] were included, if they were hospital audits/surveys, or where self-reported diagnoses were made or clinical diagnosis was only ascertained in those with reduced vision (as these may represent a subgroup with disease). Papers reporting incidence rates based on counting eyes rather than individuals were also excluded. In total, 74 studies on incidence and prevalence were found and reviewed in detail (by A.R.R., Z.J., and C.G.O.), from which 14 publications based on 10 population studies contained relevant incidence data.

• DATA EXTRACTION: AMD incidence rates (and associated 95% confidence limits and/or standard errors) were extracted, or calculated from the number of new cases reported over time (person-years), by age and sex, if available. The reported mean (or median) age at baseline or midpoint of the age range reported was used for analysis. If the age group was specified as younger than x, older than x, or $x+$, then the age band was taken to be the same width as other age groups reported in the same study. The calendar year at baseline, period of follow-up, and number of participants were also recorded where available. Whether International Classification System or Wisconsin Age-Related Maculopathy Grading System (or other systems) were used was recorded,[13,14] as was whether 1 eye or both eyes were examined (with or without fundus imaging). The geographic location of the study was extracted and classified into 3 continental regions (America, Australasia, Europe). We recorded whether an individual was defined as a case of AMD on the basis of disease being present in either eye/worse eye/at least 1 eye/1 or both eyes or only in 1 eye randomly selected for ocular assessment. Late AMD refers to eyes with GA and/or NVAMD. Data on other potential confounders, such as smoking, were not routinely available. Data were extracted by 3 reviewers (Z.J., A.R.R., C.G.O.) with independent extraction on a subgroup of studies. Disagreements were resolved by discussion.

• META-ANALYSIS OF INCIDENCE STUDIES: Most of the studies reported cumulative incidence as a percentage; only 1 study reported rates by person-years of follow-up.[15]

Assuming incidence rates follow a Poisson distribution, a meta-analysis of incidence rates requires the number of cases of AMD along with the person-years of follow-up for each study. For the other studies either the person-years or the number of cases of AMD had to be derived from the published estimates of cumulative incidence and average duration of follow-up. If the number of new cases of AMD or person-years of follow-up were not reported, they were estimated from the reported cumulative incidence and average duration of follow-up. An assumption was made that cases of AMD occurred halfway through the follow-up period and that non-cases were followed-up for the entire duration of the study to give an approximation for person-years of follow-up for each study. Study-specific incidence rates were combined using Bayesian Poisson meta-regression, adjusting for age, year of recruitment (to examine trends in incidence over time), continent (to examine geographic variations in incidence among populations of the same ancestry), and AMD classification system, to produce mutually adjusted rate ratios. Our model took into account that some studies had incidence rates for more than 1 age group and 3 population-based studies reported incidence rates at different time points (eg, 5-, 10-, 15-year incidence).[5–7,10,15–17] As in our previous meta-analyses of prevalence,[4,18] within-study repeated measures of incidence were modeled by a Poisson multilevel Bayesian meta-regression using WinBUGS software (MRC Biostatistics Unit, Cambridge, UK). Our model simultaneously took account of the following study level confounders: average age, sex, year of survey (to examine trends in incidence over time), continent (to examine geographic variations in incidence among populations of the same ancestry), and AMD classification system, to produce mutually adjusted rate ratios.

• ESTIMATING AGE-RELATED MACULAR DEGENERATION INCIDENCE FROM AGE-RELATED MACULAR DEGENERATION PREVALENCE: We obtained the prevalence of late AMD, GA, NVAMD (for men, women, and sexes combined) for each year of age from 50 to 97 years (the oldest reported age in the studies included)[4] from our earlier meta-analysis of 31 prevalence surveys (with 51 173 participants, including 1571 cases of late AMD, 455 with GA, and 404 with NVAMD).[4] These prevalence estimates allow for study characteristics, such as age of the sample, examination methods, and definitions of disease (internationally recognized definitions being preferred),[13,14] and represent the most up-to-date meta-analysis of AMD prevalence in white populations, similar to the older white population of the US. Age-sex-specific estimates of prevalence standardized to studies using fundus imaging and either International Classification System or Wisconsin Age-Related Maculopathy Grading System were applied to 2011 American white population estimates[19] to give the prevalence of late AMD, GA, and NVAMD and absolute number of prevalent cases by 5-year age bands in men and women separately and

TABLE 1. Studies of Age-Related Macular Degeneration Incidence in White Populations

First Author, Year	Study Name/Location, Country	Age Range (Years)	Duration (Years)	Data by Sex			AMD Type			Grading System	AMD Assessment		No. Participants	Cumulative Incidence (%)
				M	F	All	Late	NV	GA		FI	EE		
Bressler, 1995[12]	Waterman Study, USA	≥70	5	✔				✔		WARM	✔		50	2.0
Chang, 2008[21]	Salisbury Eye Evaluation (SEE) Project, USA	65–86	2			✔	✔			SS	✔		1156	0.3
Coleman, 2010[22]	Oregon, Minneapolis, Baltimore, and Pennsylvania, USA	74–85+	5		✔		✔			WARM	✔		1493	6.2
Delcourt, 2005[25]	Pathologies Oculaires Liees a l'Age Study, France	65–85+	3			✔	✔			IC	✔		1424	0.5
Jonasson, 2005[24]	Reykjavik Eye Study, Iceland	50–80+	5	✔	✔	✔	✔			IC	✔		693	1.2
Klaver, 2001[17]	Rotterdam Study, Netherlands	55–85+	2	✔	✔	✔	✔			IC	✔		4953	0.24
van Leeuwen 2003[15]	Rotterdam Study, Netherlands	55–80+	6.5			✔	✔	✔	✔	WARM	✔		3636	1.8[a]
Klein, 1997[16]	Beaver Dam Eye Study, USA	43–86	5	✔	✔	✔	✔			WARM	✔		3502	0.9
Klein, 2002[10]	Beaver Dam Eye Study, USA	43–86	10	✔	✔	✔	✔			WARM	✔		3496	2.1
Klein, 2007[6]	Beaver Dam Eye Study, USA	43–86	15	✔	✔	✔	✔	✔	✔	WARM	✔		3830	3.1
Mitchell, 2002[5]	Blue Mountains Eye Study, Australia	<60–80+	5	✔	✔	✔	✔	✔	✔	WARM	✔		2312	1.1
Wang, 2007[7]	Blue Mountains Eye Study, Australia	<60–80+	10	✔	✔	✔	✔	✔	✔	WARM	✔		2395	3.7
Mukesh, 2004[26]	Melbourne Visual Impairment Project, Australia	40–80+	5	✔	✔	✔	✔			IC	✔	✔	1618	0.5
Sparrow, 1997[23]	Melton Mowbray, England	84–97	7			✔	✔	✔	✔	WARM	✔		82	4.9

AMD = age-related macular degeneration; EE = eye examination; FI = fundus imaging; GA = geographic atrophy/dry AMD; IC = International Classification System; NV = neovascular/exudative/wet AMD; SS = study specific; WARM = Wisconsin Age-Related Maculopathy Grading System.
[a]Incidence rate per 1000 person-years.

combined. We give the 95% credible intervals of prevalence, which represents the range of values within which the true prevalence is expected to lie with 95% probability.

Owing to the relatively small number of longitudinal studies reporting incidence by AMD subtype and by sex (especially at older ages), we also derived estimates of incidence from age-sex-specific prevalence (standardized to studies using fundus imaging and either International Classification System or Wisconsin Age-Related Maculopathy Grading System)[4] using a method previously reported for estimating incidence of major causes of eye disease (including "senile macular degeneration") from the Framingham Eye Study.[11] The method assumes that (1) the duration of disease is life-long after diagnosis, since the disease is considered to be irreversible; (2) mortality risk is the same in diseased and nondiseased individuals; and (3) disease incidence and population composition (in terms of risk factors for late AMD) remain stable over time. These assumptions refer to the population at large, not the study population. Calculation of incidence requires knowledge of the population at the beginning of a given age interval (available from the US Census Bureau[19]), the probability of dying (available from the National Centre for Health Statistics),[20] and the probability of AMD (estimated from prevalence) for the same age interval. We used this approach to estimate the annual incidence per 1000 by age for late AMD, GA, and NVAMD in men and women separately and combined.

Data presented on prevalence and incidence are based on "either eye" definitions (including at least 1 eye, worse eye, 1 or both eyes) using the International Classification System or Wisconsin Age-Related Maculopathy Grading System along with fundus imaging.

RESULTS

IN TOTAL, 14 PUBLICATIONS WITH DATA ON AMD INCIdence in 10 populations were identified (Table 1). Four of the populations were based in the US,[6,10,12,16,21,22] 4 in western Europe,[15,17,23–25] and 2 in Australia.[5,7,26] For late AMD this equates to approximately 135 000 person-years of follow-up with 361 incident cases of AMD. Twelve publications presented data for late AMD in men and women combined, and 10 publications provided data by sex.

• SYSTEMATIC REVIEW AND META-ANALYSIS OF INCIDENCE STUDIES: The incidence per 1000 person-years of late AMD, GA, and NVAMD by age for each population is shown in Figure 1. Incidence is plotted on a logarithmic scale and shows a linear increase with age. A meta-analysis of incidence studies showed that the incidence rate for late AMD triples per decade increase in age (rate ratio 2.9; 95% credible interval 2.6, 3.2, Table 2). There was no evidence of a trend in late AMD incidence rates over time. There
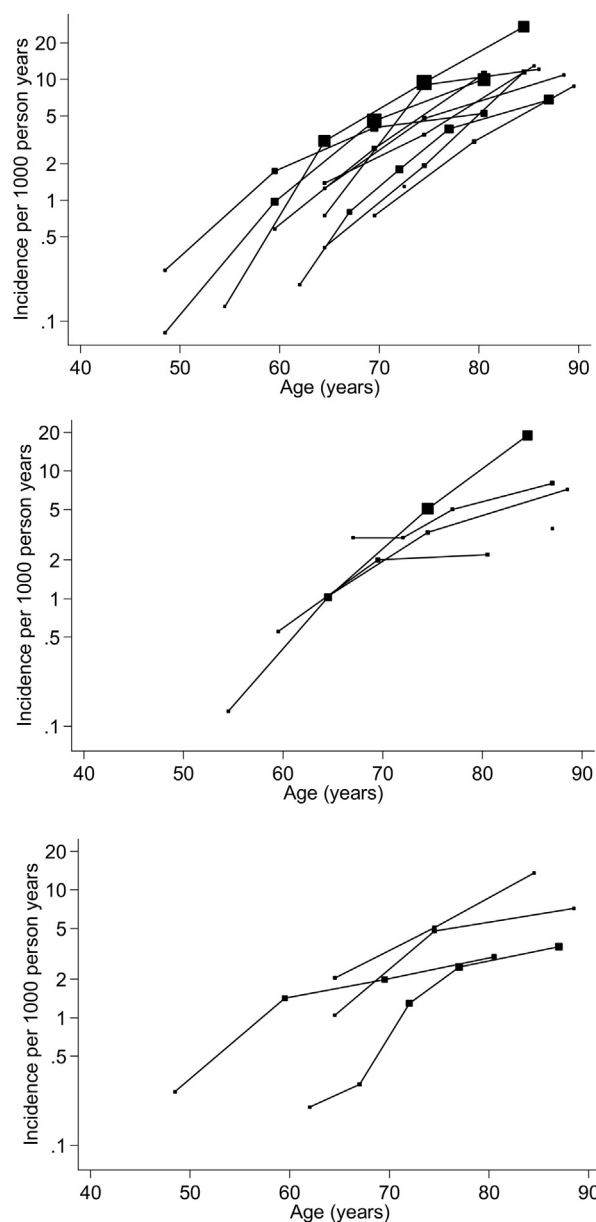

FIGURE 1. Incidence per 1000 person-years of late age-related macular degeneration (AMD), geographic atrophy (GA), and neovascular age related macular degeneration (NVAMD) by age for each population. Square symbols represent the estimated incidence per 1000 person-years of late AMD (Top), GA (Middle), and NVAMD (Bottom) at a given age for each study. Data points from the same study are joined by a straight line. The size of each symbol is inversely proportional to the standard error of the estimate of incidence. The vertical axis is plotted on a logarithmic scale.

was no evidence of a difference between studies using International Classification System or Wisconsin Age-Related Maculopathy Grading System (Table 2). While late AMD incidence rates appeared marginally higher in the US and Australia, compared to Europe (Table 2), there were only a small number of studies and credible intervals

TABLE 2. Mutually Adjusted Rate Ratios for Late Age-Related Macular Degeneration From Bayesian Meta-regression Model

Factor	No. of Study Populations	Adjusted Rate Ratio[a] (95% Cri)
Per decade increase in age	8	2.91 (2.63, 3.23)
Per calendar year	8	1.07 (0.99, 1.17)
Europe	4	1.00
United States	2	1.62 (0.73, 3.44)
Australia	2	1.72 (0.73, 3.01)
AMD grading system		
WARM	3	1.00
IC	5	0.76 (0.38, 1.40)
Women vs men[b]	7	1.38 (1.06, 1.82)

95% Cri = Bayesian 95% credible interval; IC = International Classification System; WARM = Wisconsin Age-Related Maculopathy Grading System.

[a]Rate ratios from analysis based on 8 population studies (sexes combined) adjusted for all factors listed in table except sex.

[b]The comparison of women vs men is from a separate meta-analysis in the subset of 7 studies that reported data stratified by sex, taking account of the other factors listed in the table.
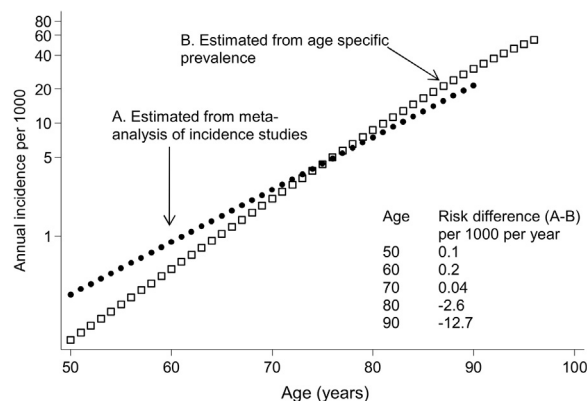

FIGURE 2. Annual incidence per 1000 of late age-related macular degeneration against age from a meta-analysis of incidence studies in populations of white European ancestry (solid circles) and as estimated from age-specific prevalence (open squares) applied to the demographics of the American white population. Incidence on the vertical axis is on a logarithmic scale.

were wide (and included the null value of 1). Hence, there was no strong evidence of geographic differences in late AMD incidence. However, while the same incident rates may apply, the age-sex structure of populations in these countries are heterogeneous; hence, the number of incident cases will differ markedly between countries. Incidence rates for late AMD were 38% higher in women than in men (rate ratio 1.4, 95% credible interval 1.1, 1.8). Exclusion of 1 small study carried out on American watermen, at the margins of the inclusion criteria, made no difference to the point estimate and marginally widened the confidence interval (odds ratio 1.38, 95% credible interval 1.08, 1.83). Incidence data for GA or NVAMD separately were available for 4 populations only. These data were insufficient to provide stable estimates of incidence by year of age by AMD subtypes.

• INCIDENCE OF AGE-RELATED MACULAR DEGENERATION IN THE AMERICAN WHITE POPULATION: Applying age-specific prevalence estimates from a recent meta-analysis[4] to the American white population aged 50–97 years gave an overall prevalence of late AMD of 2.3% (95% credible interval 1.7%, 3.2%). The Supplemental Table (available at AJO.com) gives estimates by age, sex, and AMD subtype. Figure 2 shows the 2 methods used to estimate annual incidence rate; A from the Bayesian meta-regression of incidence studies in populations of white European ancestry and B incidence estimated by applying age-specific prevalence[4] to the population demographics of the American white population. The 2 approaches yield similar rates (see

absolute rate differences given in Figure 2), with a steeper rise with age with method B (approximately quadrupling per decade; rate ratio 3.9, 95% credible interval 3.8, 4.0). Incidence estimated from age-specific prevalence yielded a tighter 95% credible interval and we were able to estimate it over a wider age range, as well as by AMD subtype and sex. Overall annual incidence in American whites estimated from prevalence is 3.5 per 1000 (95% credible interval 2.5, 4.7) for late AMD in those aged 50–97 years. The corresponding rates for GA and NVAMD are 1.9 per 1000 (95% credible interval 1.3, 2.8) and 1.8 per 1000 (95% credible interval 1.2, 2.5), respectively (Table 3). This corresponds to approximately 293 000 new cases of late AMD each year (95% credible interval 207 000, 400 000), and 160 000 (95% credible interval 107 000, 234 000) and 148 000 (95% credible interval 103 000, 207 000) for GA and NVAMD, respectively. The estimated total number of new cases rises rapidly from age 50 years to the mid-80s and then begins to drop (Figure 3). In those aged 65 years and older the annual incidence rate for late AMD is 7.8 per 1000 (95% credible interval 5.5, 10.6), 4.3 per 1000 for GA (95% credible interval 2.9, 6.2), and 3.9 per 1000 for NVAMD (95% credible interval 2.7, 5.5). In those aged 80 years and older the annual incidence rates per 1000 are 19.4 (95% credible interval 13.8, 26.2), 10.9 (95% credible interval 7.2, 16.1), and 9.9 (95% credible interval 6.8, 14.0), respectively. Under 70 years of age the number of incident cases is similar in men and women. Beyond 70 years of age the number of new cases of AMD is consistently higher in women than in men (Table 3, Figure 3). For all age groups (except the youngest), women have a slightly higher annual incidence rate of late AMD (4 per 1000, 95% credible interval 2.3, 6.6) than men (2.4 per 1000, 95% credible interval 1.4, 4.2; Table 3). Overall, women have a marginally higher rate of GA than men,

TABLE 3. Estimated Number of New Cases Each Year and Average Annual Incidence per 1000 of Age-Related Macular Degeneration (Late Age-Related Macular Degeneration, Geographic Atrophy, Neovascular Age-Related Macular Degeneration) by 5-Year Age Groups for Men and Women in the White American Population

Age Group (Years)	Number of New Cases per Year in 1000s (95% Cri)			Estimated Annual Incidence per 1000 (95% Cri)		
	Late AMD	GA	NVAMD	Late AMD	GA	NVAMD
Men						
50–54	1.4 (0.8, 2.6)	0.9 (0.5, 1.6)	0.8 (0.5, 1.5)	0.2 (0.1, 0.3)	0.1 (0.1, 0.2)	0.1 (0.1, 0.2)
55–59	2.5 (1.4, 4.6)	1.6 (1.0, 2.7)	1.4 (0.8, 2.5)	0.3 (0.2, 0.6)	0.2 (0.1, 0.3)	0.2 (0.1, 0.3)
60–64	4.4 (2.4, 8.0)	2.8 (1.7, 4.6)	2.5 (1.5, 4.2)	0.6 (0.3, 1.1)	0.4 (0.2, 0.7)	0.4 (0.2, 0.6)
65–69	6.4 (3.5, 11.5)	4.1 (2.6, 6.5)	3.5 (2.1, 5.8)	1.3 (0.7, 2.3)	0.8 (0.5, 1.3)	0.7 (0.4, 1.1)
70–74	9.0 (5.1, 16.4)	5.8 (3.7, 9.2)	4.8 (2.9, 8.2)	2.5 (1.4, 4.5)	1.6 (1.0, 2.5)	1.3 (0.8, 2.3)
75–79	13.3 (7.5, 23.7)	8.6 (5.4, 13.8)	6.9 (4.1, 12.0)	4.9 (2.8, 8.8)	3.2 (2.0, 5.1)	2.6 (1.5, 4.4)
80–84	18.8 (10.7, 32.7)	12.3 (7.6, 20.1)	9.7 (5.7, 17.0)	9.5 (5.4, 16.6)	6.2 (3.9, 10.2)	4.9 (2.9, 8.6)
85–89	20.5 (11.8, 34.6)	13.7 (8.2, 22.6)	10.6 (6.2, 18.7)	17.7 (10.2, 29.8)	11.8 (7.1, 19.5)	9.1 (5.3, 16.1)
90+	19.5 (11.9, 30.1)	13.6 (8.0, 22.4)	10.5 (6.1, 18.3)	33.4 (20.3, 51.5)	23.3 (13.7, 38.3)	18.0 (10.4, 31.4)
All ages	95.8 (55.1, 164.2)	63.3 (38.7, 103.5)	50.7 (29.8, 88.0)	2.4 (1.4, 4.2)	1.6 (1.0, 2.6)	1.3 (0.8, 2.2)
Women						
50–54	1.6 (0.9, 3.0)	0.9 (0.5, 1.6)	1.0 (0.6, 1.8)	0.2 (0.1, 0.3)	0.1 (0.1, 0.2)	0.1 (0.1, 0.2)
55–59	3.0 (1.6, 5.4)	1.7 (1.0, 2.8)	1.8 (1.1, 3.2)	0.4 (0.2, 0.6)	0.2 (0.1, 0.3)	0.2 (0.1, 0.4)
60–64	5.3 (2.9, 9.8)	3.0 (1.8, 4.9)	3.3 (1.9, 5.5)	0.7 (0.4, 1.3)	0.4 (0.2, 0.7)	0.4 (0.3, 0.7)
65–69	8.0 (4.5, 14.6)	4.5 (2.9, 7.3)	4.8 (2.9, 8.0)	1.4 (0.8, 2.6)	0.8 (0.5, 1.3)	0.8 (0.5, 1.4)
70–74	12.2 (6.8, 21.9)	6.9 (4.4, 10.9)	7.0 (4.3, 12.0)	2.8 (1.6, 5.1)	1.6 (1.0, 2.5)	1.6 (1.0, 2.8)
75–79	19.7 (11.2, 35.0)	11.2 (7.1, 17.9)	11.2 (6.8, 19.2)	5.6 (3.2, 9.9)	3.2 (2.0, 5.1)	3.2 (1.9, 5.4)
80–84	32.6 (18.5, 55.7)	18.7 (11.7, 30.5)	18.2 (10.9, 31.5)	10.8 (6.1, 18.5)	6.2 (3.9, 10.1)	6.0 (3.6, 10.5)
85–89	43.5 (25.3, 71.7)	25.8 (15.8, 42.6)	24.5 (14.5, 42.3)	19.9 (11.6, 32.8)	11.8 (7.2, 19.5)	11.2 (6.6, 19.3)
90+	53.5 (33.2, 80.9)	34.1 (20.7, 55.3)	31.7 (18.9, 53.5)	37.4 (23.2, 56.5)	23.8 (14.5, 38.6)	22.2 (13.2, 37.3)
All ages	179 (105, 298)	107 (66.0, 174)	104 (61.9, 177)	4.0 (2.3, 6.6)	2.4 (1.5, 3.8)	2.3 (1.4, 3.9)
Men and women						
50–54	3.0 (2.0, 4.3)	1.5 (0.9, 2.4)	1.6 (1.0, 2.3)	0.2 (0.1, 0.2)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)
55–59	5.5 (3.8, 7.9)	2.8 (1.8, 4.2)	2.8 (1.9, 4.0)	0.3 (0.2, 0.5)	0.2 (0.1, 0.3)	0.2 (0.1, 0.2)
60–64	10.1 (6.9, 14.1)	5.1 (3.4, 7.3)	5.1 (3.5, 7.0)	0.7 (0.5, 1.0)	0.3 (0.2, 0.5)	0.3 (0.2, 0.5)
65–69	15.1 (10.5, 21.2)	7.7 (5.2, 10.8)	7.5 (5.3, 10.1)	1.4 (1.0, 2.0)	0.7 (0.5, 1.0)	0.7 (0.5, 0.9)
70–74	22.7 (15.8, 31.6)	11.6 (8.1, 16.4)	11.1 (8.0, 14.9)	2.9 (2.0, 4.0)	1.5 (1.0, 2.1)	1.4 (1.0, 1.9)
75–79	35.8 (24.9, 49.7)	18.5 (12.8, 26.4)	17.4 (12.4, 23.7)	5.7 (4.0, 8.0)	3.0 (2.1, 4.2)	2.8 (2.0, 3.8)
80–84	56.2 (39.3, 77.8)	29.7 (20.1, 43.2)	27.5 (19.4, 38.0)	11.3 (7.9, 15.6)	6.0 (4.0, 8.7)	5.5 (3.9, 7.6)
85–89	70.4 (49.6, 95.7)	38.7 (25.8, 57.3)	35.2 (24.3, 50.1)	21.0 (14.8, 28.6)	11.6 (7.7, 17.1)	10.5 (7.3, 15.0)
90+	74.1 (54.2, 97.5)	44.3 (28.8, 65.9)	39.9 (26.9, 57.0)	36.7 (26.9, 48.4)	22.0 (14.3, 32.7)	19.8 (13.4, 28.3)
All ages	293 (207, 400)	160 (107, 234)	148 (103, 207)	3.5 (2.5, 4.7)	1.9 (1.3, 2.8)	1.8 (1.2, 2.5)

95% Cri = Bayesian 95% credible interval; AMD = age-related macular degeneration; GA = geographic atrophy/dry AMD; NV = neovascular/exudative/wet AMD.

Incidence estimated from prevalence for men and women combined is based on a meta-analysis of 30 prevalence studies, whereas estimates stratified by sex are from a meta-analysis of 19 studies that reported AMD prevalence by sex.

Absolute number of new cases per year is calculated by multiplying the numbers in the second, third, or fourth column by 1000, (eg, total number of cases of late AMD across all ages in men and women combined is 293 × 1000 = 293 000).

but within each 5-year age group incidence rates in Table 3 for GA appear similar in men and women and this is partly owing to rounding. In those aged 65 years and older the incidence rates of NVAMD within each 5-year age group are higher in women than in men.

We carried out sensitivity analyses to test the assumption of equal mortality in cases and non-cases of AMD in estimating incidence from prevalence. If we assume substantial differences in mortality of up to 20% higher or 20% lower in cases of AMD, the incidence estimates are contained within the 95% credible intervals presented in Table 3.

The Supplemental Figure (available at AJO.com) shows the effect of differences in mortality 5%, 10%, and 20% higher or lower on the age-sex-specific incidence rates. It is noteworthy that a 20% higher or lower mortality is substantial, and the estimated age-sex annual incidence is contained within the original 95% credible intervals.

If we restrict our previous meta-analysis of prevalence[4] to US studies only (13 prevalence studies), the point estimates are included within the 95% credible interval presented in tables based on all studies of white European ancestry (30 prevalence studies that included both men
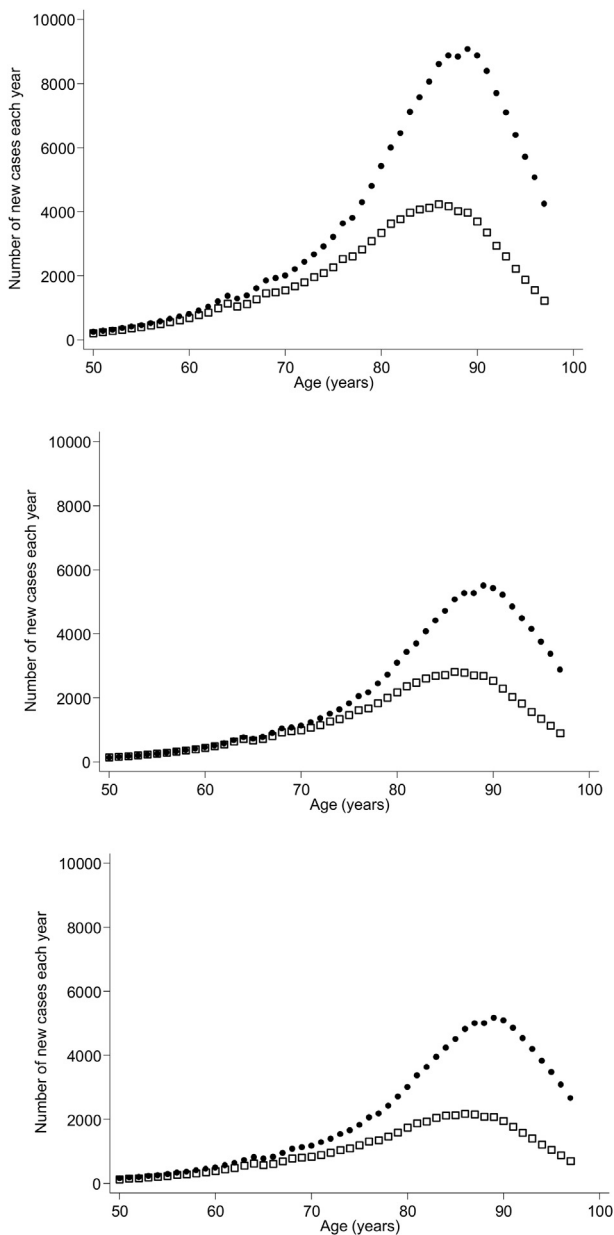
FIGURE 3. Graphs showing the annual incidence (estimated from age-specific prevalence) as the number of new cases per year in the American white population of late age-related macular degeneration (Top), geographic atrophy (Middle), and neovascular age-related macular degeneration (Bottom). Men are illustrated by open squares and women by solid circles.

and women); that is, estimates are in line with those already presented for all whites of European ancestry. However, the 95% credible intervals are much wider (ie, less precise) when the meta-analysis is restricted to US-only studies. This is what we would expect. Restricting the meta-analysis to US studies reduces the power, as the number of participants and cases of AMD contributing to the analysis is reduced.

DISCUSSION

WE PROVIDE THE MOST UP-TO-DATE ESTIMATES OF THE number of new cases of late AMD among American whites per year. We show an exponential rise in AMD incidence with age and that women have a higher annual incidence rate of late AMD compared to men. Although late AMD incidence increases log-linearly with age, the absolute number of incident cases of late AMD decreases beyond the age of about 85 years because of increased mortality.

Owing to the limited number of prospective studies that report incidence by age, sex, and AMD subtype, we chose to estimate incidence from age-specific prevalence. However, a key question is whether this is comparable to obtaining incidence rates directly from a meta-analysis of prospective studies. Unfortunately, incidence rates were not systematically reported in prospective studies and had to be estimated from cumulative incidence and average duration of follow-up (except for 1 study[17]). Approximating person-years of follow-up for each study from aggregated data (rather than individual data) may make rate estimates less accurate, especially with a disease that increases exponentially with age, in a population with high rates of other morbidities and mortality. In addition, follow-up in elderly prospective studies is challenging. There are a greater number of prevalence surveys that included data at older ages, allowing AMD incidence to be estimated over a wider age range by AMD subtype as well as in men and women separately. However, deriving incidence from prevalence requires a number of assumptions about the population: first, that disease remains incurable; second, that those with disease have similar mortality rates to those without; and third, that risk factors for disease remain stable. In terms of late AMD these assumptions are appropriate, as the first is correct, there is currently no evidence to argue against the second,[27–29] and while risk factors may have altered over time, particularly with reductions in cigarette smoking and improved diets,[30,31] occurrence of the disease appears to have remained stable among studies with preferred methodologies (ie, using fundus imaging and international classification of disease)[4,13,14] and our meta-analysis did not elicit any trends in AMD incidence over time (Table 2). Similarly, our meta-analysis of prevalence studies over an extended period of 30 years[4] did not show evidence of any trends in late AMD prevalence over time. This is consistent with recent evidence from serial data from the National Health and Nutrition Examination Survey (USA), which suggests that apparent declines in "any" AMD might be explained in part by methodological differences between successive surveys.[32] Figure 2 shows comparable estimates of incidence obtained directly from a meta-analysis of incidence studies and those estimated from age-specific prevalence obtained from a meta-analysis of prevalence estimates[4] standardized to the American white population demographics. Findings are further supported by our sensitivity analysis, presented as a Supplemental Figure,

illustrating that there would have to be stark differences in mortality between cases and non-cases of AMD to substantially alter incidence estimated from prevalence.

In proportionate terms, annual incidence rates from prevalent studies suggest a quadrupling in risk per decade, whereas the meta-analysis of incidence studies suggests a tripling. Shortage of data at older ages and selection effects associated with longer-term follow-up may explain the weaker increase in incidence with age among incidence studies, compared to estimates from prevalence. Previous reports from prospective studies have also found a proportionate rise in AMD incidence with age but with less certainty, as these are often reported by broad age groups[6,9,17,26] and are heavily dependent on the distribution of age within each study and duration of follow-up.

An individual participant meta-analysis could provide more accurate data on follow-up and exact age at event and adjust for individual environmental or genetic factors. Such an approach is preferable if these data can be obtained for all relevant studies. However, the difficulty with an individual patient data meta-analysis is that it is likely to represent a subset of well-resourced studies and may be biased if it is not representative of all studies. By adopting a more inclusive approach, we were able to include more studies, representing a wider age range of participants and increased sample size; this allowed more precise estimates of incidence for each year of age. We took account of study-level confounders including continent, AMD grading system, age, and sex and examined trends over time. We showed that there is no clear evidence of differences in late AMD incidence across the 3 continents. If we restrict the meta-analysis to studies conducted in the US alone the point estimates are contained within the 95% credible interval already presented in the paper. However, 95% credible interval based on studies conducted in the US only are less precise, with wider credible intervals, because they are based on fewer studies.

The higher incidence of late AMD observed in women, particularly for NVAMD, is supported by data published from prospective studies.[5–7,9,10,16,26] However, data from individual studies are often insufficiently powered to find a statistically significant difference between men and women. By applying our age-specific prevalence rate estimates to the US population we have been able to demonstrate and quantify the sex difference in AMD incidence rates and by AMD subtype. While these sex differences may have hormonal/menopausal etiologies,[33] there is increasing interest in whether this might be linked to sex difference in cerebrovascular events,[34] especially for NVAMD, where women have higher rates at older ages[35] (as cerebrovascular mortality may have already occurred in men). Although our overall estimates of NVAMD incidence are high (owing to the inclusion of those at older ages, especially in women), this does not reflect the number in need of treatment. The type of NVAMD on presentation cannot be estimated from these data, although some evidence suggests two thirds are likely to have classic forms of the disease that may benefit from treatment.[36] Of note, the inclusion of older ages in our estimates may include a large number who are unwilling or too frail to undergo treatment.

Findings from this study provide clear recommendations for the use and interpretation of study methods, particularly the ascertainment of AMD cases in the future. The review provides contemporary estimates of the number of incident cases of late AMD, GA, and NVAMD in the white older population of the US. Accurate prediction of the numbers of new cases of late AMD, by type, is needed in order to more accurately estimate the cost of AMD, which will inform current and future healthcare provision. It is important to give country-specific data, when the potential impact on clinical practice and social service provision is very country dependent. Approximately 89% of the US population aged 80 years and older is white.[19] Evidence suggests similar or lower rates of AMD in populations of non-European ancestry, but data are sparse.[2,37] These data demonstrate that late AMD is a significant public health problem, especially in an aging population. Although not all new cases of AMD would be eligible for treatment, they may require visual rehabilitation. As new therapies become available, the proportion of new cases that might benefit from treatment is likely to increase.

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Biosketch

Dr Alicja R. Rudnicka, PhD, is currently Reader in Medical Statistics in the Population Health Research Institute at St George's, University of London, UK. Dr Rudnicka trained in medical statistics at the London School of Hygiene and Tropical Medicine, UK, and prior to joining St George's in 2005, worked at the Wolfson of Institute of Preventive Medicine in London on a number of cardiovascular epidemiological projects, antenatal screening for Down Syndrome and Bayesian meta-analyses. Her current interests include lifecourse, cardiovascular and ophthalmic epidemiology, and in particular the application of meta-analytic techniques to assimilate evidence from observational studies.

Late AMD in men / **Late AMD in women**
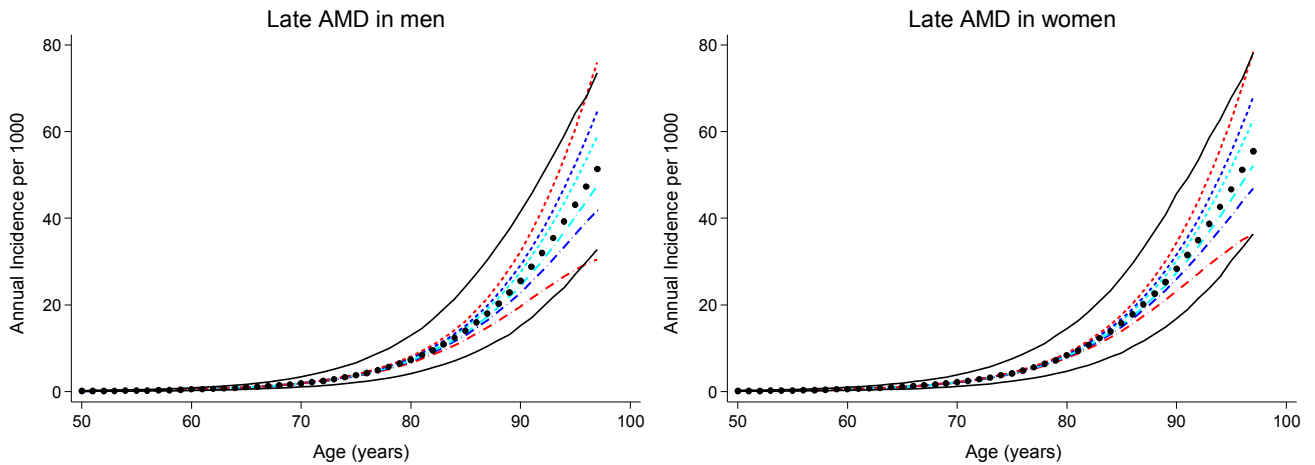
SUPPLEMENTAL FIGURE. The influence of differential mortality for individuals with late age-related macular degeneration (AMD) compared to those not affected by late AMD on the age-specific annual incidence of late AMD estimated from age-specific prevalence. The solid black round symbols are the point estimates already presented in the article, assuming that those with late AMD have the same mortality as those without late AMD. The corresponding 95% credible intervals are shown as solid black lines. The dashed lines assume that those with late AMD have a higher mortality and the dashed-dot lines assume that those with late AMD have a lower mortality. The line color corresponds to a difference in mortality of 5% for cyan, 10% for blue, and 20% for the red lines. A 20% higher or lower mortality is substantial, and even under these assumptions the estimated age-sex annual incidence is contained within the original 95% credible intervals, assuming nondifferential mortality between cases and non-cases of late AMD.

Age Group (Years)	Number of Prevalent Cases in 10 000s (95% Cri)			Estimated Prevalence as % (95%Cri)		
	Late AMD	GA	NVAMD	Late AMD	GA	NVAMD
Men						
50–54	1.0 (0.6, 2.0)	0.6 (0.3, 1.1)	0.7 (0.4, 1.3)	0.1 (0.1, 0.2)	0.1 (0.0, 0.1)	0.1 (0.0, 0.1)
55–59	1.9 (1.0, 3.5)	1.1 (0.6, 1.9)	1.2 (0.7, 2.2)	0.2 (0.1, 0.4)	0.1 (0.1, 0.2)	0.2 (0.1, 0.3)
60–64	3.3 (1.8, 6.1)	1.9 (1.1, 3.2)	2.1 (1.2, 3.7)	0.5 (0.3, 0.9)	0.3 (0.2, 0.5)	0.3 (0.2, 0.5)
65–69	4.8 (2.6, 8.7)	2.7 (1.6, 4.5)	3.0 (1.7, 5.1)	0.9 (0.5, 1.7)	0.5 (0.3, 0.9)	0.6 (0.3, 1.0)
70–74	6.8 (3.8, 12.3)	3.8 (2.4, 6.3)	4.1 (2.4, 7.0)	1.9 (1.0, 3.4)	1.1 (0.7, 1.7)	1.1 (0.7, 1.9)
75–79	10.0 (5.6, 17.7)	5.7 (3.6, 9.1)	5.9 (3.6, 10.0)	3.7 (2.1, 6.6)	2.1 (1.3, 3.4)	2.2 (1.3, 3.7)
80–84	14.2 (8.1, 24.5)	8.1 (5.2, 13.0)	8.3 (5.0, 14.0)	7.2 (4.1, 12.4)	4.1 (2.6, 6.6)	4.2 (2.5, 7.1)
85–89	15.4 (9.0, 25.5)	9.1 (5.8, 14.5)	9.0 (5.5, 15.1)	13.3 (7.8, 21.9)	7.9 (5.0, 12.5)	7.8 (4.7, 13.0)
90+	14.7 (9.1, 22.3)	9.2 (5.9, 14.3)	8.9 (5.5, 14.5)	25.2 (15.6, 38.3)	15.8 (10.1, 24.5)	15.3 (9.4, 24.8)
All ages	72.1 (41.4, 122.7)	42.2 (26.3, 67.9)	43.2 (26.0, 73.0)	1.8 (1.1, 3.1)	1.1 (0.7, 1.7)	1.1 (0.7, 1.9)
Women						
50–54	1.1 (0.6, 2.0)	0.6 (0.3, 1.2)	0.7 (0.4, 1.3)	0.1 (0.1, 0.2)	0.1 (0.0, 0.1)	0.1 (0.0, 0.1)
55–59	2.0 (1.0, 3.7)	1.1 (0.6, 2.0)	1.3 (0.7, 2.3)	0.2 (0.1, 0.4)	0.1 (0.1, 0.2)	0.2 (0.1, 0.3)
60–64	3.5 (1.9, 6.5)	2.0 (1.1, 3.5)	2.3 (1.3, 4.0)	0.5 (0.3, 0.9)	0.3 (0.2, 0.5)	0.3 (0.2, 0.5)
65–69	5.3 (2.9, 9.8)	3.0 (1.8, 5.0)	3.3 (1.9, 5.7)	0.9 (0.5, 1.7)	0.5 (0.3, 0.9)	0.6 (0.3, 1.0)
70–74	8.1 (4.5, 14.7)	4.6 (2.8, 7.5)	4.9 (2.9, 8.4)	1.9 (1.0, 3.4)	1.1 (0.7, 1.7)	1.1 (0.7, 1.9)
75–79	13.2 (7.4, 23.4)	7.5 (4.7, 12.0)	7.8 (4.7, 13.2)	3.7 (2.1, 6.6)	2.1 (1.3, 3.4)	2.2 (1.3, 3.7)
80–84	21.8 (12.4, 37.7)	12.5 (7.9, 20.0)	12.7 (7.7, 21.5)	7.2 (4.1, 12.5)	4.2 (2.6, 6.6)	4.2 (2.6, 7.1)
85–89	29.4 (17.1, 48.4)	17.4 (11.0, 27.5)	17.2 (10.5, 28.8)	13.4 (7.8, 22.1)	7.9 (5.0, 12.6)	7.9 (4.8, 13.2)
90+	37.0 (22.9, 55.9)	23.3 (14.9, 36.1)	22.5 (13.9, 36.4)	25.8 (16.0, 39.1)	16.3 (10.4, 25.2)	15.7 (9.7, 25.4)
All ages	121.3 (70.8, 202.1)	72.0 (45.2, 114.7)	72.7 (44.0, 121.6)	2.7 (1.6, 4.5)	1.6 (1.0, 2.5)	1.6 (1.0, 2.7)
Men and women						
50–54	1.9 (1.3, 2.9)	1.0 (0.5, 1.7)	1.0 (0.6, 1.7)	0.1 (0.1, 0.2)	0.1 (0.0, 0.1)	0.1 (0.0, 0.1)
55–59	3.6 (2.4, 5.2)	1.8 (1.1, 2.9)	1.9 (1.2, 2.9)	0.2 (0.1, 0.3)	0.1 (0.1, 0.2)	0.1 (0.1, 0.2)
60–64	6.5 (4.4, 9.3)	3.2 (2.0, 5.1)	3.3 (2.2, 4.9)	0.4 (0.3, 0.6)	0.2 (0.1, 0.3)	0.2 (0.2, 0.3)
65–69	9.7 (6.7, 13.8)	4.9 (3.2, 7.3)	4.9 (3.4, 7.0)	0.9 (0.6, 1.3)	0.5 (0.3, 0.7)	0.5 (0.3, 0.7)
70–74	14.7 (10.1, 20.6)	7.4 (5.0, 10.8)	7.4 (5.1, 10.1)	1.8 (1.3, 2.6)	0.9 (0.6, 1.4)	0.9 (0.6, 1.3)
75–79	23.2 (16.2, 32.2)	11.9 (8.2, 17.0)	11.5 (8.2, 15.7)	3.7 (2.6, 5.2)	1.9 (1.3, 2.7)	1.9 (1.3, 2.5)
80–84	36.6 (25.7, 50.3)	19.2 (13.2, 27.4)	18.3 (13.1, 24.9)	7.3 (5.2, 10.1)	3.9 (2.7, 5.5)	3.7 (2.6, 5.0)
85–89	46.3 (33.0, 62.4)	25.2 (17.3, 35.9)	23.6 (16.8, 32.2)	13.8 (9.9, 18.6)	7.5 (5.2, 10.7)	7.0 (5.0, 9.6)
90+	54.0 (39.9, 69.6)	31.8 (21.8, 45.0)	29.4 (20.8, 40.1)	26.8 (19.8, 34.6)	15.8 (10.8, 22.3)	14.6 (10.3, 19.9)
All ages	196 (140, 266)	106 (72.4, 153)	101 (71.4, 139)	2.3 (1.7, 3.2)	1.3 (0.9, 1.8)	1.2 (0.8, 1.7)

95% Cri = Bayesian 95% credible interval; AMD = age-related macular degeneration; GA = geographic atrophy/dry AMD; NV = neovascular/exudative/wet AMD.

Estimates for men and women combined are based on a meta-analysis of prevalence from 30 studies. Estimates for men and women separately are based on a meta-analysis of 19 studies that reported AMD prevalence by sex.

Absolute number of prevalent cases is calculated by multiplying the numbers in the second column by 10 000 (eg, total number of cases across all ages in men and women combined is 196 × 10 000 = 1 960 000).