Prevalence and incidence of age-related macular degeneration in Europe: a systematic review and meta-analysis

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ABSTRACT

Background/Aims Age-related macular degeneration (AMD) is the main cause of visual impairment and blindness in Europe. A further increase in the number of affected persons is expected and current European data are needed for healthcare resource planning.

Methods We performed a systematic review on the prevalence and incidence of AMD based on the meta-analysis of observational studies in epidemiology guideline. Meta-analysis and meta-regression on time-trends, age, countries, regions, sex and classification systems for AMD were performed. Based on Eurostat population projections, the pooled prevalence estimates were extrapolated to the year 2050.

Results Twenty-two prevalence and four incidence studies published since 1996 were included. Our pooled prevalence estimate of early or intermediate AMD and any late AMD in those 60 years and older was 25.3% (95% CI 18.0% to 34.4%) and 2.4% (95% CI 1.8% to 3.3%), respectively. A significant increase in prevalence was seen in older populations. In the meta-analysis of incidence, the pooled annual incidence of any late AMD was 1.4 per 1 000 individuals (95% CI 0.8 to 2.6). Overall, the number of EU inhabitants with any AMD is expected to increase from 67 to 77 million until 2050. Incident late AMD is estimated to increase from 400 000 per year today to 700 000 per year in 2050.

Conclusions Approximately 67 million people in the EU are currently affected by any AMD and, due to population ageing, this number is expected to increase by 15% until 2050. Monitoring and treatment of people with advanced disease stages will require additional healthcare resources and thorough healthcare planning in the years and decades to come.special-featurepress-release

INTRODUCTION

Europe is facing intense demographic changes due to population ageing leading to increasing healthcare demands caused by age-related diseases.[1] This includes age-related macular degeneration (AMD), which already today represents the main cause of severe visual impairment and blindness in Europe. Even though the introduction of antivascular endothelial growth factor therapy has revolutionised treatment for neovascular AMD (nAMD), it requires considerable healthcare resources. Increasing nAMD treatment and monitoring demand will intensify the considerable burden on European healthcare systems even more. Hence, in order to face this challenge,

appropriate data are needed to perform careful healthcare planning in the future.

In a systematic review and meta-analysis by Wong *et al*, the global prevalence of any type of AMD has been reported to be 8.7%.[2] However, the pooled prevalence rates for people of European ancestry and the geographical European region were higher (12.3% and 18.3%, respectively) as compared with the global estimate. This underscores the need for regional data and analyses. A recent study by the European Eye Epidemiology (E3) Consortium[3] collated prevalence data of 14 European population studies and reported the prevalence of any AMD among adults aged 70 years and older to be 16.2% based on the Rotterdam classification. The authors extrapolated the number of Europeans with early and late AMD and predicted almost a doubling of AMD prevalence in Europe until 2040. Yet, until today, we lack pooled European estimates on AMD incidence.

The aim of this study was to assess the prevalence and incidence of AMD as well as to provide population-based estimates of future burden until the year 2050 in the European population.

MATERIALS AND METHODS
Literature search and data extraction
Based on the international guideline for systematic literature searches and meta-analysis of observational studies in epidemiology (MOOSE) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement,[4 5] we performed a systematic review to identify all relevant European publications on prevalence and incidence of AMD in the databases Medline (PubMed), Embase (Ovid) and Web of Science (WoS) (search query: box 1).

We included European studies published in the last 20 years starting from 1 January 1996 onwards. The primary search was performed on 1 August 2016 and was repeated on 10 August 2018 to identify more recent publications. Reference lists of identified articles were hand searched and results were merged using the reference management software Citavi (V.5.3.1.0, Swiss Academic Software GmbH).[6] Abstracts were examined and, if eligible, full texts and associated reference lists underwent further evaluation for eligibility by the main reviewer (JQL). When other reviews were identified, the included studies and reference lists were also screened for accordance to

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Box 1 Search query formatted for PubMed (analogous for Embase and WoS)

(("macular degeneration" [(MeSH Terms)) OR "macular degeneration" [(All Fields)) OR "macular degeneration/epidemiology" [(MeSH Terms)) OR "maculopathies" [(All Fields)) OR "maculopathy" [(All Fields)) OR "AMD" [(All Fields)) OR "ARMD" [(All Fields))) AND ("epidemiology" [(MeSH Terms)) OR "epidemiology" [(All Fields)) OR "epidemiological" [(All Fields)) OR "epidemiologic methods" [(MeSH Terms)) OR "censuses" [(MeSH Terms)) OR "topography, medical" [(MeSH Terms)) OR "prevalence" [(All Fields)) OR "incidence" [(All Fields)) OR "observational" [(All Fields)) OR "cross-sectional" [(All Fields)) OR "longitudinal" [(All Fields)) OR "cohort study" [(All Fields)) OR "cohort studies" [(All Fields)) OR "population-based" [(All Fields)) OR "statistics" [(All Fields))) AND ("Europe/epidemiology" [(MeSH Terms)) OR "europe" [(MeSH Terms)) OR "europe" [Title/Abstract] OR "European Union" [(MeSH Terms)) OR "European Union" [Title/Abstract] OR European [Title/Abstract] OR "germany" [(MeSH Terms)) OR "germany" [Title/Abstract] OR "german" [Title/Abstract] OR "france" [(MeSH Terms)) OR "france" [Title/Abstract] OR "french" [Title/Abstract] OR "Great Britain" [(MeSH Terms)) OR "Great Britain" [Title/Abstract] OR "UK" [Title/Abstract] OR British [Title/Abstract] OR "wales" [Title/Abstract] OR "welsh" [Title/Abstract] OR "scotland" [Title/Abstract] OR "Scottish" [Title/Abstract] OR "Northern Ireland" [Title/Abstract] OR "northern irish" [Title/Abstract] OR "spain" [(MeSH Terms)) OR "spain" [Title/Abstract] OR "spanish" [Title/Abstract] OR "italy" [(MeSH Terms)) OR "italy" [Title/Abstract] OR "Italian" [Title/Abstract])) AND ("1996/01/01" [(PDAT)) : "2016/" [(PDAT)))

our inclusion criteria. Respective studies were included in our review. Authors were contacted when necessary. A random sample of 5% of all publications was reassessed by a second reviewer (CW). According to Cohen's Kappa, interrater agreement was excellent (κ=1). AMD stage-specific prevalence data were recategorised according to the Clinical Classification System by the Beckman Initiative for Macular Research Classification Committee.[7] We included European population-based observational studies (national or multinational) reporting prevalence or incidence. Occurrence of nAMD and geographic atrophy (GA) in the same eye ('mixed' late AMD) was attributed to nAMD to reflect treatment related healthcare utilisation. For incidence data, longitudinal studies reporting the incidence of any late AMD in a defined observation period of individuals with no evidence of late AMD at the initial screening were included. Even though we did not exclude non-English publications a priori to minimise language bias, all publications meeting our inclusion criteria were in English.

To assess risk of bias and quality of primary studies or systematic reviews identified from database searches, full-texts of eligible publications were examined using a previously published checklist.[8] Risk of bias was scored by the main reviewer and rechecked by a second reviewer (κ=0.80). According to the review protocol, studies with high risk of bias were discussed with the senior reviewer (RPF) and potentially excluded.

As AMD is a retinal disease affecting elderly individuals, the lower age limit of more than half of the included studies was 65–75 years. In studies with a younger population or a broader age spectrum, we only included the older subsample in the meta-analyses (Gutenberg Health Study, GHS: 65–74 years;

Kooperative Gesundheitsforschung in der Region Augsburg, KORA and Crete: ≥60 years).[9–11]

Data analysis

Reported cumulative incidences were converted to mean annual incidences. For prevalence and incidence data, we performed both random-effects meta-analyses and meta-regressions. All analyses were performed using the statistical software R (V.3.5.3, R Foundation for Statistical Computing, Vienna, Austria) with the add-on packages meta (V.4.8–2) and metaphor (V.2.0–0).[12–14] Between-study heterogeneity was assessed with Higgins and Thompson's I^2 measure and tested by Cochran's Q-test for heterogeneity.[15 16] Summaries of results are presented using forest plots with exact binomial CIs.[17] Possible small-study effects were analysed using funnel plots and Peter's test.[18] Meta-regression was performed by age, sex, time-trends (starting year of each study's examinations), region (northern and southern Europe, determined by the orientation to the 45th parallel north), the five most populous countries (Germany, France, the UK, Italy and Spain) and study characteristics (use of fundus photographs, classification system, rate of gradable photographs, response rate). The latter variables were included in our meta-regression models because a review of AMD in populations of European ancestry showed that approximately 50% of the variance between studies may be attributed to study characteristics.[19] The main classification systems used in the included studies were: International Age-related Maculopathy Epidemiology Study Group (IARMESG), Multi-Ethnic Study of Atherosclerosis (MESA) and the Harmonized Three Continent AMD Consortium Severity Scale (3CACSS) or Rotterdam Classification (RC). Since some of the above-mentioned variables were not available in all of the analysed studies, it proved to be infeasible to analyse all variables together in one meta-regression model. We therefore fitted separate meta-regression models for various combinations of country, region, sex, time-trends, age and study characteristics, as indicated in online supplementary table 1. Rudnicka et al also showed that part of the variability between studies may be due to the definition of AMD (which could be based on either eye, at least one eye, one or both eyes or one randomly selected eye).[19] Since all of the studies included in our analysis based their definition of AMD on the worse eye, we did not further investigate this aspect in our meta-regression models.

Estimates of the number of persons affected by AMD in the European Union (EU, referring to EU-28 as of 2018) now and until 2050 were calculated using our age-stratified prevalence and incidence estimates and Eurostat population statistics.[20] Prevalence and incidence projections were calculated under the assumption that prevalence and incidence will remain stable and that mortality is already taken into account in the Eurostat population projections. Age-stratified prevalence data were applied to the population data to calculate the estimated prevalent cases for each calendar year. The number at risk for every calendar year was calculated by subtracting the prevalent cases from the overall population older than 55 years. We then used our age-stratified incidence estimates to calculate the total annual number of incident cases at 10-year intervals until 2050.

RESULTS

Prevalence of AMD in Europe

Twenty-two studies met the inclusion criteria for quantitative synthesis, of which one study was multinational (EUREYE) (figure 1, table 1). These contained data of 55 323 European
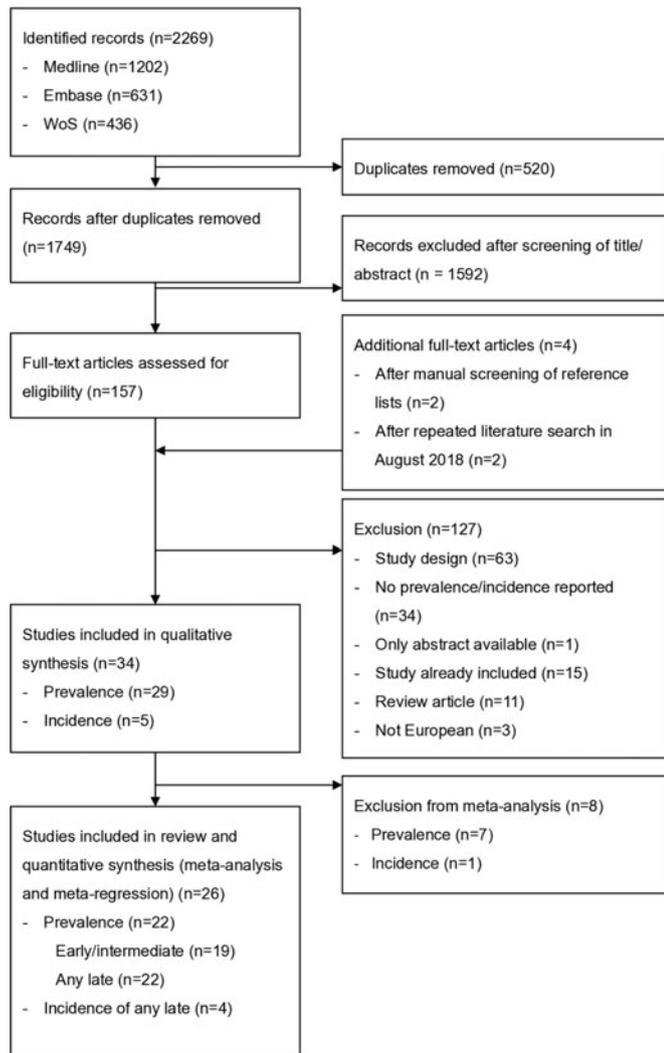
Figure 1 Flowchart of the systematic review process.

individuals with a mean age range of 60–81 years. In the Montrachet study, prevalence data could only be obtained from a conference abstract. However, methodology was previously described in detail. For the Rotterdam Eye study, we used the 3CACCS-harmonised data for better comparability.

All studies used fundus photography to diagnose AMD with two exceptions: the Thessaloniki Eye study performed clinical assessment of AMD lesions and Krasnik *et al* assessed AMD lesions using a combination of fundus photographs and spectral-domain optical coherence tomography (SD-OCT). The majority of studies used the classification by the IARMESG, (table 1). Seven studies were not included in the meta-analysis due to high risk of bias or diverging study design (online supplementary tables 2-4).

For early and intermediate AMD, the pooled prevalence estimates ranged from 9.3% (95% CI 4.4% to 18.5%) in those ≤64 years to 26.9% (95% CI 16.7% to 40.3%) in those 75+, with a prevalence of 25.3% (95% CI 18.0% to 34.4%) in all age groups combined (table 2, online supplementary figure 1). For any late AMD pooled prevalence ranged from 0.3% (95% CI 0.1% to 0.5%) to 6.4% (95% CI 5.2% to 8.0%), with a prevalence of 2.4% (95% CI 1.8% to 3.3%) in all age groups combined (table 2, online supplementary figure 2). Prevalence of nAMD was 1.4 times higher than for GA (1.4%; 95% CI 1.0% to 1.9%, vs 1.0%; 95% CI 0.7% to 1.5%). No asymmetry was observed in the funnel plots (online supplementary figures 3-4).

The date or year of study initiation was reported by 15 early or intermediate AMD studies and 16 studies of any late AMD. Regarding time-trends, we found a stable reported prevalence of any AMD. After meta-regression by country and age, the heterogeneity was strongly reduced for any late AMD (I^2=20.3%), nAMD and GA (both I^2=0%, table 2 and online supplementary table 6). Comparing sex, northern to southern European countries and different classification systems (IARMESG, MESA, 3CACSS/RC, other), no significant differences were found. Fundus photography for diagnosis of AMD was used in 21 out of 22 studies. In three studies, additional clinical examination was performed. Heterogeneity was only slightly reduced after meta-regression by study characteristics. Diagnosis of early AMD was more likely with additional clinical examination (OR: 2.2; 95% CI 1.0 to 5.3; p=0.08) and Beckman (OR 6.3; 95% CI 1.9 to 20.4; p<0.01), MESA (OR 4.3; 95% CI 1.7 to 10.3; p<0.01) or IARMESG classification (OR: 3.0; 95% CI 1.5 to 6.0; p<0.01) compared to 3CACSS/RC. No significant trends (at the 5% type-I error level) were seen for any late AMD. The heterogeneity could not be reduced by meta-regression by response rate and rate of gradable photographs. The results of the meta-regression are presented in table 2 and online supplementary table 7A-B.

Incidence of any late AMD
Included studies with incidence data of any late AMD in a population with no, early or intermediate AMD at baseline were fewer and differed widely in study design and diagnostic criteria. We identified five studies reporting cumulative incidences of late AMD, but excluded The Copenhagen City Eye Study due to the much longer observation period compared with the other studies. The Copenhagen City Eye Study assessed the 14-year cumulative incidence of early and late AMD (31.5% and 14.8%, n=359),[21] while the Rotterdam Eye Study, the AGES-R study, the POLA study and the recently published ALIENOR incidence study included only a mean of 3.3 years follow-up time (range 2–5 years).[22–25] The first three studies used the IARMESG classification and minimum age at baseline was 50–60 years (table 1). In contrast, as the ALIENOR study population was considerably older (≥73 years), we included this study in the meta-regression for age, but not in the meta-analysis. Furthermore, the ALIENOR study reported cumulative incidence data for two diagnostic modalities separately: based on fundus photography and SD-OCT. For better comparability in our analysis, we only included the incidence rate based on grading of fundus photography.

Subsequently, we pooled data of 7223 study participants and estimated an annual incidence of any late AMD of 1.4 per 1000 individuals in a population 50+ (online supplementary figure 5), corresponding to an approximate 5 year incidence of 0.7%. After meta-regression for age, I^2 was 31.6% and pseudo-R^2 was 79.4%, indicating that heterogeneity was considerably reduced through meta-regression (table 2). The annual incidence of any late AMD was 0.5 per 1000 in the age group <70 years and 6.7 per 1000 in the age group 70+.

Future projections
For the year 2050, we estimated more than 77 million individuals in the EU to be affected by any AMD as compared with 67 million in the year 2015 (figure 2 and online supplementary table 8). The largest increase of 15% is expected in individuals aged 75 years and older (from 50 to 57.6 millions) due to population ageing. For any late AMD, the increase is estimated at 20% from 10 to 12 million until 2050. Incident late AMD is estimated to increase from 400 000 European inhabitants per year today to 700 000 per year in

Table 1 Overview of included studies

Study	Country	North/south	Year of publication	Age (years)	Mean age (years)	% female	N	I/II	III	IIIa	IIIb	IARMESG	MESA	3CACSS/RES	Other	fp	clin	OCT	Risk of bias
Prevalence studies																			
EUREYE[29]	Multi		2006	≥65	73.2	61.0	4753	×	×	×	×	×				×			Low
AugUR†[26 30]	Germany	N	2015	≥70	77.5	45.8	1040	×	×					×	×	×			Low
GHS[9]	Germany	N	2014	65–75*	55.5	49.6	834*	×	×	×	×			×		×			Low
KORA[10]	Germany	N	2016	60–74*	47.5	49.8	608*	×	×	×	×				×	×			Low
POLA[31]	France	S	1998	≥60	70.4	56.5	2196		×	×	×	×				×			Low
ALIENOR[32]	France	S	2010	≥73	79.7	61.9	879	×	×	×	×		×			×			Low
Montrachet†[33 34]	France	S	2015	≥75	82.2	63	1069	×	×				×		×	×			Medium
BEAP[35]	UK	N	2017	≥65	75.0	55.8	3475	×	×	×	×			×		×			Low
EPIC-Norfolk[36]	UK	N	2015	48–92	67.4	56.9	5182	×	×	×	×	×				×			Low
Salandra[37]	Italy	S	1997	≥60	69.5	55.7	366	×	×	×	×				×	×	×		Medium
PAMDI[38]	Italy	S	2011	≥61	71.5	54.1	845	×	×	×	×	×				×			Low
SEE[39]	Spain	S	2011	≥65	n.r.	60.6	2132	×	×	×	×	×				×	×		Low
AGES-R[40]	Iceland	N	2011	≥66	76.6	58	5272	×	×	×	×		×			×			Low
Coimbra[41]	Portugal	S	2016	≥55	68.2	56.3	5996	×	×	×	×	×				×			Low
Crete[11]	Greece	S	1999	≥60*	68.4	59.5	627*		×	×	×			×	×	×	×		Medium
Oslo Macular[42]	Norway	N	2006	≥51	66.3	51.4	459	×	×	×	×	×				×			Low
Oulu[43]	Finland	N	1996	≥70	n.r.	67.2	478	×	×	×	×				×	×	×		Medium
RES[44–46]	Netherlands	N	2014	≥55	69	58.5	6251	×	×	×	×			×		×			Low
Slovakia[47]	Slovakia	N	2017	≥55	66.6	65.6	2924	×	×	×	×	×	×			×		×	Low
Thessaloniki[48]	Greece	S	2009	≥60	70	47.1	2554		×			×					×		Medium
TILDA[49]	Ireland	N	2015	≥50	61.6	54.3	4751	×	×	×	×	×				×			Low
Tromso[50]	Norway	N	2012	≥65	57.5	27.7	2631	×	×	×	×	×				×			Low
Incidence studies																			
POLA[22]	France	S	2005, baseline examination: 1995–1997, mean follow-up interval: 3 years				1424	35‡				×				×			Medium
ALIENOR[23]	France	S	2018, baseline examination: 2006–2008, mean follow-up interval: 4 years				659	24‡				×	×			×		(×)	Low
AGES-R[24]	Iceland	N	2005, baseline examination: 1996, mean follow-up interval: 5 years				846	37‡				×				×			Low
RES[25]	Netherlands	N	2001, baseline examination: 1990–1993, mean follow-up interval: 2 years				4953	35‡				×				×			Low

Reported AMD stages: I: early AMD, II: intermediate AMD, III: late AMD, IIIa: nAMD, IIIb: GA, according to Beckman classification. *Assessment:* clin: clinical, fp: fundus photography, OCT: optical coherence tomography; n.r.=not reported. *Studies:* EUREYE: European Eye Study (France, Italy, Spain, UK, Estonia, Greece), AugUR: Augenstudie an der Universität Regensburg, GHS: Gutenberg Health Study (subgroup 65–74 years, total sample size: 4340), KORA: Kooperative Gesundheitsforschung in der Region Augsburg (subgroup ≥60 years, total sample size: 2536), POLA: Pathologies Oculaires Liées à l'Age, ALIENOR: Antioxydants, Lipides Essentiels, Nutrition et maladies OculaiRes Study, Montrachet: Maculopathy Optic Nerve nutrition neurovAsCular and HEarT diseases, BEAP: Bridlington Eye Assessment Project, EPIC-Norfolk, European Prospective Investigation of Cancer, Norfolk, Salandra: Salandra Eye Study, PAMDI: Prevalence of Age-Related Macular Degeneration in Italy, SEE: Spanish Eyes Epidemiology Study, AGES-R: Age, Gene/Environment Susceptibility–Reykjavik Study, Coimbra: Coimbra Eye Study, Crete (subgroup ≥60 years, total sample size: 777), Oslo Macular: Oslo Macular Study, Rotterdam: Rotterdam Eye Study, Slovakia: Prevalence of AMD in Slovakia Study, Thessaloniki: Thessaloniki Eye Study, TILDA: The Irish Longitudinal Study on Ageing, Tromso: Tromso Eye Study; Classification systems: IARMESG: International ARM Epidemiology Study group,[51] MESA: Multi-ethnic Study of Atherosclerosis (modified Wisconsin Are-related maculopathy (ARM) grading system[52]), 3CACSS: harmonized Three Continent AMD Consortium severity scale,[44] RES: Rotterdam Eye Study,[45] other classification systems: see online supplementary table 5.
*Age subgroup (mean age refers to original study cohort).
†Prevalence data extracted from abstract
‡incidence studies: % of patients with early or intermediate AMD at baseline

Table 2 Random-effects meta-analysis and meta-regression of AMD prevalence and incidence

		N	Early/intermediate AMD	N	Any late AMD	N	nAMD	N	GA
Meta-analysis: Pooled prevalence, 60+ (%, 95% CI)									
Total		19	25.3 (18.6 to 34.4)	22	2.4 (1.8 to 3.3)	15	1.4 (1.0 to 1.9)	15	1.0 (0.7 to 1.5)
P (Q-het)			<0.01		<0.01		<0.01		<0.01
I^2 (%)			100		97		94		93
Meta-regression by age: Pooled prevalence of AMD (%), 95% CI									
≤64 years		6	9.3 (4.4 to 18.5)	8	0.3 (0.1 to 0.5)	5	0.1 (0.1 to 0.3)	5	0.1 (0.0 to 0.2)
65–74 years		11	18.5 (11.3 to 28.9)	15	1.5 (1.1 to 1.9)	11	0.8 (0.6 to 1.0)	11	0.6 (0.4 to 0.9)
≥75 years		10	26.9 (16.7 to 40.3)	14	6.4 (5.2 to 8.0)	11	3.3 (2.5 to 4.2)	11	3.2 (2.3 to 4.3)
P (Q-het)			<0.01		<0.01		<0.01		<0.01
P (Q-mod)			0.04		<0.01		<0.01		<0.01
I^2 (%)			99.2		82.0		0		0
Pseudo-R^2 (%)			18.4		79.8		81.7		64.6
Meta-regression by country and age combined: Pooled prevalence of AMD (%), 95% CI									
Germany	≤64		13.2 (8.7 to 19.6)		0.4 (0.2 to 0.8)		0.1 (0.0 to 0.3)		0.1 (0.0 to 0.2)
	65 to 75		22.9 (16.7 to 30.7)		1.5 (1.1 to 2.1)		0.3 (0.1 to 0.8)		0.3 (0.1 to 0.8)
	≥75		34.2 (24.6 to 45.3)		6.7 (5.0 to 8.9)		1.1 (0.4 to 3.3)		1.2 (0.4 to 3.3)
France	≤64		8.8 (3.5 to 20.3)		0.4 (0.2 to 0.8)		0.4 (0.2 to 0.8)		0.2 (0.1 to 0.4)
	65 to 75		15.8 (6.9 to 32.2)		1.4 (0.9 to 2.1)		1.4 (0.9 to 2.1)		0.7 (0.4 to 1.1)
	≥75		24.7 (12.4 to 43.2)		6.0 (4.1 to 8.7)		6.0 (4.1 to 8.7)		2.8 (1.8 to 4.3)
UK	≤64		34.1 (19.9 to 52.0)		0.5 (0.3 to 1.0)		0.3 (0.1 to 0.6)		0.2 (0.1 to 0.6)
	65 to 75		50.3 (35.4 to 65.2)		1.9 (1.4 to 2.5)		0.8 (0.6 to 1.0)		1.0 (0.8 to 1.3)
	≥75		63.9 (48.9 to 76.6)		8.1 (6.3 to 10.3)		3.2 (2.5 to 4.1)		4.3 (3.4 to 5.3)
Italy	≤64		–		0.6 (0.3 to 1.1)		–		–
	65 to 75		–		2.1 (1.4 to 3.2)		–		–
	≥75		–		9.1 (6.2 to 13.1)		–		–
Spain	≤64		4.2 (2.0 to 8.4)		0.4 (0.2 to 0.7)		0.3 (0.1 to 0.6)		0.2 (0.1 to 0.4)
	65 to 75		7.8 (4.3 to 13.7)		1.3 (0.9 to 1.8)		0.7 (0.5 to 1.0)		0.7 (0.5 to 1.0)
	≥75		12.9 (7.3 to 21.7)		5.8 (4.3 to 7.7)		3.0 (2.2 to 4.1)		2.8 (2.1 to 3.9)
p (Q-het)			<0.01		0.20		0.62		0.57
P (Q-mod)			<0.01		<0.01		<0.01		<0.01
I^2 (%)			95.1		20.3		0		0
Pseudo-R^2 (%)			84.9		97.8		100		100
Pooled annual incidence of any late AMD by age (per 1000), 95% CI									
Total			–	3	1.4 (0.8 to 2.6)		–		–
P (Q-het)					<0.01				
I^2 (%)			–		57.3		–		–
Meta-regression by age: Pooled annual incidence of any late AMD (per 1000), 95% CI									
<70 years			–	3	0.5 (0.1 to 2.7)		–		–
≥70 years			–	4	6.7 (3.2 to 14.1)		–		–
P (Q-het)					0.20				
P (Q-mod)					<0.01				
I^2 (%)					31.6				
Pseudo-R^2 (%)					79.4				

AMD, age-related macular degeneration; GA, geographic atrophy;
I^2, measure of heterogeneity; n, number of studies with available data; nAMD, neovascular AMD; pseudo-R^2, coefficient of determination in regression model; Q-het, Cochran's Q-test for heterogeneity; Q-mod, Q test for moderators.

2050, with the highest number of incident cases expected in Germany (120 000 in 2015 to 1 80 000 in 2050; figure 2, online supplementary table 8).

DISCUSSION

We found the prevalence and incidence of AMD to steadily increase in older Europeans, with a projected increase by 15% in prevalence and 75% in incidence until 2050. This has

considerable implications for healthcare planning and resource allocation.

Compared with pooled prevalence rates of other international and European studies, we found a higher any AMD prevalence rate (27.7%). Wong *et al* reported a pooled global prevalence of AMD of 12.3% in populations of European ancestry and 18.3% in Europe.[2] After correcting for age, the reported prevalence increased to 16% in the age group 60–69 years, 25.0% in those
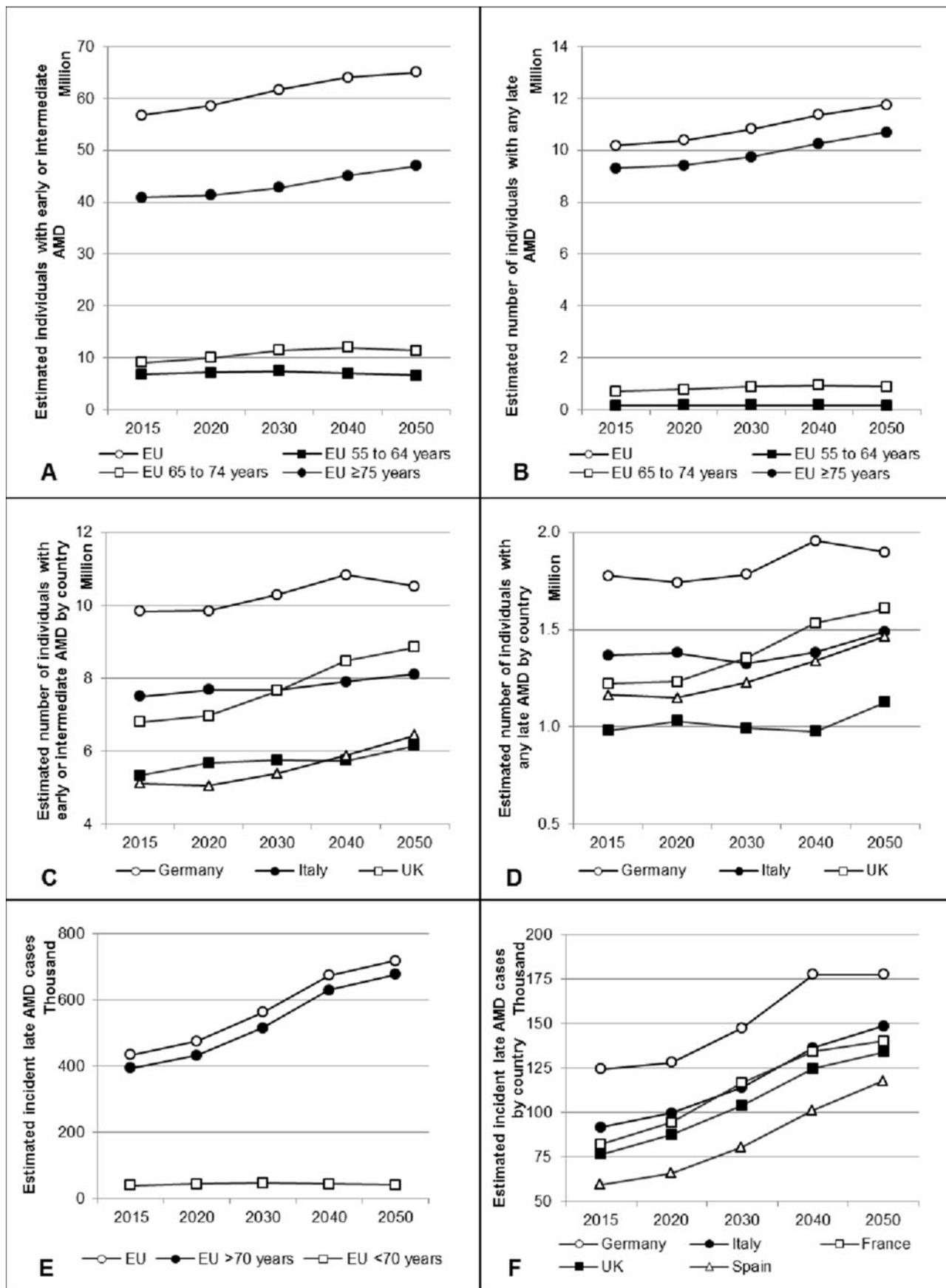
Figure 2 Extrapolation of AMD cases in Europe. (A)–(D) Extrapolation of the estimated number of individuals in the EU (55+) with early and intermediate or any late AMD. (A) Early and intermediate AMD (EU and by age group); (B) any late AMD (EU and by age group); (C) early and intermediate AMD by country; (D) any late AMD by country; (E,F) extrapolation of the estimated number of incident late AMD cases in the EU, (E) by age group, (F) by country. AMD, age-related macular degeneration.

aged 70–79 years and 33.2% in those aged 80–84 years, which is closer to our estimates. The prevalence rates reported by the E3 consortium were also lower than ours, which is likely due to the use of different AMD classification systems and included studies. Moreover, the authors pooled original data did not perform a meta-analysis of published data and regraded all images according to the Rotterdam classification. Recently, Brandl *et al* compared the Beckman Classification and the 3CACSS, which is more comparable to the Rotterdam classification and found substantial differences.[26] The prevalence of early and intermediate AMD was found to be much higher using the Beckman Classification compared with the 3CACSS (45%, 95% CI 41.8% to 48.7%; compared with 17%, 95% CI 14.5% to 19.7%), while no difference was seen regarding late AMD. This highlights the large impact of the underlying classification system and the need for an international consensus on a standardised AMD classification system.

Our estimates for prevalence of late AMD compare well to international estimates. The pooled estimate of any late AMD in Europe published by Wong *et al* was 0.75%, increasing from 0.03% in the 45–49 age group to 5.33% in those aged 80 to 84 years. In a meta-analysis by Rudnicka *et al*, the prevalence of any late AMD in individuals of European ancestry increased from 0.08% in the age group 50–55 years to 20.1% in the age group 90 years and older.[19] This underlines the importance of age-specific pooled prevalence estimates.

In the analysis of time-trends, we found no change of reported AMD prevalence in studies initiated from 1982 until 2013. The E3 Consortium reported a decreasing prevalence for late AMD in the last decade, especially in older age groups.[3] Rudnicka *et al* described that estimates were stable over time when only more recent and rigorously designed studies were included.[19] Similar to any AMD, we found prevalence of any late AMD to be stable in studies published since 1996 implying that ageing is the major factor in our projection estimate. Other than early AMD stages, late AMD classification is very comparable across different classification systems.

Comparing our results to similar studies, for example, populations of white European ancestry including North America and Australia, incidence was slightly higher for late AMD in the study by Rudnicka *et al*. (3.5 per 1000/year; 50+).[27] Comparing our 5 year incidence estimate (0.7%) to international data, we found a slightly lower estimate in the Melbourne Visual Impairment Project (0.49%) and higher estimates in the Beaver Dam Eye Study (0.9%), Blue Mountains Eye Study (3.7%) and Singapore Malay Eye Study (1.0%). Again, this underscores the heterogeneity of data from various studies and the complexity of accurate incidence estimations.

Just as we found higher prevalence rates, our projection of increase of AMD prevalence is higher than previously published data. Wong *et al* projected the number of Europeans with any AMD to increase from 55 million in 2014 to 69 million in 2040. The E3 Consortium found an increase of any AMD in the EU from 17.7 million in 2013 to 26.3 million in 2040, using Eurostat data and assuming a stable prevalence over time. Some of these discrepancies may be due to different classification systems used.[26]

Strengths of the study include the thorough study design and analyses including meta-regression for all factors previously reported to affect heterogeneity and prevalence or incidence estimates in meta-analyses of AMD. In accordance to current recommendations,[28] we performed our analyses based on the MOOSE and STROBE statements. Included studies were evenly distributed between northern and southern Europe.

However, our study has several limitations, which need to be considered when interpreting the results. We found high heterogeneity between the included prevalence studies, which could only be partially addressed by our meta-regression analyses as we did not have access to raw data. As mentioned above, prevalence and incidence estimates may differ widely depending on the underlying classification system. The diagnostic procedures were comparable in all studies except two. Fluorescein angiography (FA) was not performed in any of the population-based studies. The absence of OCT or FA may cause an underestimation of the prevalence of early (small drusen may be overlooked in not-optimal quality fundus photographs, but detectable on SD-OCT) and late AMD (especially small areas of atrophy or choroidal neovascularisations). Most included studies were carried out in France, Italy and Germany and only two studies from Eastern Europe were identified. Thus, the study results need to be applied with caution to individual countries, in particular in Eastern Europe. Furthermore, we used reported data for both our prevalence and incidence estimate, which is likely to have affected the accuracy of our estimates. Last, the reference periods for incidence rates varied between studies, which may have reduced precision of our incidence estimates. However, as these differences were small, they are unlikely to affect our estimates to a large extent.

In conclusion, we found steadily increasing numbers of prevalent and incident cases of all stages of AMD in Europe until 2050. This will require considerable additional healthcare service and resource allocation, which should be considered already today in all European healthcare systems.

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