Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis

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Summary

Background Numerous population-based studies of age-related macular degeneration have been reported around the world, with the results of some studies suggesting racial or ethnic differences in disease prevalence. Integrating these resources to provide summarised data to establish worldwide prevalence and to project the number of people with age-related macular degeneration from 2020 to 2040 would be a useful guide for global strategies.

Methods We did a systematic literature review to identify all population-based studies of age-related macular degeneration published before May, 2013. Only studies using retinal photographs and standardised grading classifications (the Wisconsin age-related maculopathy grading system, the international classification for age-related macular degeneration, or the Rotterdam staging system) were included. Hierarchical Bayesian approaches were used to estimate the pooled prevalence, the 95% credible intervals (CrI), and to examine the difference in prevalence by ethnicity (European, African, Hispanic, Asian) and region (Africa, Asia, Europe, Latin America and the Caribbean, North America, and Oceania). UN World Population Prospects were used to project the number of people affected in 2014 and 2040. Bayes factor was calculated as a measure of statistical evidence, with a score above three indicating substantial evidence.

Findings Analysis of 129 664 individuals (aged 30–97 years), with 12 727 cases from 39 studies, showed the pooled prevalence (mapped to an age range of 45–85 years) of early, late, and any age-related macular degeneration to be 8·01% (95% CrI 3·98–15·49), 0·37% (0·18–0·77), and 8·69% (4·26–17·40), respectively. We found a higher prevalence of early and any age-related macular degeneration in Europeans than in Asians (early: 11·2% *vs* 6·8%, Bayes factor 3·9; any: 12·3% *vs* 7·4%, Bayes factor 4·3), and early, late, and any age-related macular degeneration to be more prevalent in Europeans than in Africans (early: 11·2% *vs* 7·1%, Bayes factor 12·2; late: 0·5% *vs* 0·3%, 3·7; any: 12·3% *vs* 7·5%, 31·3). There was no difference in prevalence between Asians and Africans (all Bayes factors <1). Europeans had a higher prevalence of geographic atrophy subtype (1·11%, 95% CrI 0·53–2·08) than Africans (0·14%, 0·04–0·45), Asians (0·21%, 0·04–0·87), and Hispanics (0·16%, 0·05–0·46). Between geographical regions, cases of early and any age-related macular degeneration were less prevalent in Asia than in Europe and North America (early: 6·3% *vs* 14.3% and 12·8% [Bayes factor 2·3 and 7·6]; any: 6·9% *vs* 18·3% and 14·3% [3·0 and 3·8]). No significant gender effect was noted in prevalence (Bayes factor <1·0). The projected number of people with age-related macular degeneration in 2020 is 196 million (95% CrI 140–261), increasing to 288 million in 2040 (205–399).

Interpretation These estimates indicate the substantial global burden of age-related macular degeneration. Summarised data provide information for understanding the effect of the condition and provide data towards designing eye-care strategies and health services around the world.

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Introduction

Age-related macular degeneration accounts for 8·7% of all blindness worldwide and is the most common cause of blindness in developed countries,[1–5] particularly in people older than 60 years. Its prevalence is likely to increase as a consequence of exponential population ageing. There have been significant advances in the management of exudative or so-called wet age-related macular degeneration with the introduction of anti-angiogenesis therapy, and patients now have effective treatment options that can prevent blindness and, in many cases, restore vision.[6–10] However, these treatments are expensive and not available to all patients in many countries.[11–14] Thus, understanding the prevalence, burden, and population impact is essential for adequate health care planning and provision, which require both precise and contemporary estimates of disease prevalence.

Although there have been many population-based studies of age-related macular degeneration around the world, there are no summarised data to guide global strategies. Furthermore, studies have suggested substantial racial or ethnic differences in disease prevalence. In the Baltimore Eye Study, people of European (white) ancestry were more likely to have early and late-stage disease than were those of African

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See Online for appendix

ancestry.[15,16] Two meta-analyses done in populations of European[17] and Asian ancestry[4] suggest that, in people aged 40–79 years, the age-specific prevalence of late age-related macular degeneration in Asians (0·56%) was similar to that in Europeans (0·59%), but early signs were less common in Asians (6·8%) than in Europeans (8·8%). No studies had systematically compared the prevalence of the condition across geographical regions.

To address this gap, we did a systematic review of the literature to estimate the prevalence of age-related macular degeneration, and assess differences by ethnicity, region, and sex, and to project the number of individuals affected worldwide by the condition in 2020 and 2040.

Methods

Search strategy

We systematically reviewed publications that reported prevalence of age-related macular degeneration by searching the electronic databases of PubMed, Web of Science, and Embase for relevant papers published up to May, 2013, with the following search terms (formatted for PubMed search): ("Macular Degeneration"[Mesh] AND ("Prevalence"[Mesh] OR "Epidemiology"[Mesh] OR "Cross-Sectional Studies" [Mesh] OR "Cohort Studies"[Mesh])); (("age-related maculopathy"[All Fields] OR "age-related maculopathy"[All Fields] OR "age-related macular degeneration"[All Fields] OR "age related macular degeneration"[All Fields] OR "macular degeneration"[All Fields]) AND ("prevalence"[All Fields] OR "incidence"[All Fields] OR "epidemiology"[All Fields] OR "risk factors"[All Fields])).

The strategy identified all articles used in previous reviews.[4,17] Reference lists of identified reports were also scanned to identify other relevant studies. The initial search was scrutinised in detail by clinician scientist XS and reviewed by senior clinician scientist C-YC. Data were checked by statisticians (WLW, XL). Disagreements were resolved by discussion.

Inclusion and exclusion criteria

Our meta-analysis was done according to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines.[18] The full texts of potentially relevant articles were reviewed to identify studies that met the inclusion and exclusion criteria. The two criteria for inclusion were: a population-based study from a defined geographic area; and a standardised photographic assessment of age-related macular degeneration.

Population-based studies were included if they quantified the prevalence (including early, late, and exudative or neovascular age-related macular degeneration, and geographic atrophy) in population-based samples, with clearly defined methods of sampling. A response rate of 50% or higher was considered adequate for inclusion,[19] with the exception of the European Eye Study (EUREYE) study[20] since it was a large population study (45%); sensitivity analysis showed almost no effect on our robust model estimates (appendix p 9). Surveys or audits of hospital eye departments or clinics were excluded. Studies inviting non-specific volunteers or particular professions were excluded, as were studies that relied on self-reported diagnoses or did fundus examinations only in those with reduced vision.

For the standardised photographic assessment, we included studies that had used retinal photography and standardised grading methods to diagnose and classify lesions (ie, grading of retinal photographs following either the Wisconsin age-related maculopathy grading system,[21] the international classification for age-related macular degeneration,[22] or the Rotterdam staging system[23]) with reproducible grading results.

Studies fulfilling any one of the following were excluded: use of only clinical examination by ophthalmoscopy or slit-lamp biomicroscopy for diagnosis (ie, lack of any grading reproducibility assessment); reports of number of eyes with age-related macular degeneration as opposed to the number of individuals; studies in which determination of prevalence was not one of the primary study objectives (eg, studies determining risk factors); and studies not population-based, but were interview-based or audits of hospital eye departments. Although we did not specifically exclude non-English literature, the studies included in the final analysis were all in English.

The classification systems used to define those with early, late, and any age-related macular degeneration (geographic atrophy and neovascular age-related macular degeneration) in each study were recorded with the Wisconsin age-related maculopathy grading system[21] or the international classification.[22] Early disease was defined as either any soft drusen (distinct or indistinct) and pigmentary abnormalities or large soft drusen 125 μm or more in diameter with a large drusen area (>500 μm diameter circle) or large soft indistinct drusen in the absence of signs of late-stage disease. Late age-related macular degeneration was defined as the presence of any of the following: geographic atrophy or pigment epithelial detachment, subretinal haemorrhage or visible subretinal new vessel, or subretinal fibrous scar or laser treatment scar.

Statistical analysis

Because intrinsic difficulties exist when undertaking a meta-analysis of data from varied studies with differing characteristics such as disease definition, age distribution of the sample, and prevalence estimates stratified by age and sex versus single prevalence estimates, we constructed statistical models to best describe and fit our extracted data. Heterogeneity issues were addressed in our pooled meta-analysis using a hierarchical Bayesian approach to establish the worldwide prevalence of age-related macular degeneration. This approach models the hierarchical

structure of data extracted, taking into account the difference in age distribution across the studies and the effects of ethnicity, sex, and region, to ensure greater precision in prevalence estimates.

Meta-analyses can be described in a hierarchical Bayesian model. The number of people with age-related macular degeneration (y_{ij}) can be specified as binomially distributed: $y_{ij} \sim Binomial(n_{ij}, p_{ij})$, where n_{ij} is the total number of participants and p_{ij} is the prevalence of age-related macular degeneration in i^{th} the study of the j^{th} category of the varying covariate (eg, each study might consist of more than one ethnicity).

In the Bayesian approach, prevalence p_{ij} is considered as a random variable (that has a probability density distribution) by contrast with a fixed unknown parameter (an unknown value) in the classical approach. Hence, the logit transformation of p_{ij} follows a normal distribution: $logit(p_{ij}) = u_{ij}$ and $u_{ij} \sim Normal(u_{ij}, \sigma^2)$, where $\sigma^2 = 1/\tau$.

To investigate and account for the heterogeneity within and between studies, we modelled u_{ij} as a linear combination of covariates that varies across studies (ie, age, sex, ethnicity, and regions). Hence, our base model to pool the overall prevalence of age-related macular degeneration was: $u_{ij} = \beta_0 + \beta_1 * agel_{ij} + \beta_2 * ageu_{ij} + \beta_3 * ageu_{ij}$, where $agel_{ij}$ and $ageu_{ij}$ are the centred and standardised lower and upper bounds of the age group range for participants of each study and $ageui_{ij}$ is a right censoring indicator for studies with right-censored age range data for the upper bound (eg, 80 or more years). The lower bound of age range was centred to 45 years and the upper bound was 85 years, and then standardised by dividing by their respective standard deviations to ensure that pooled estimates were comparable since they were being mapped onto the same age range (45–85 years). Sex, ethnicity, and region covariates were then individually added to the base model to establish their effect and for covariate-specific pooled prevalence. The percentage of variability in prevalence estimates due to various sources of heterogeneity compared with chance alone were examined (appendix pp 1–3).

Finally, non-informative prior (to represent ignorance) was specified for residual variability τ using the conjugate gamma distribution: $Gamma(0{\cdot}01,\ 0{\cdot}01)$. Gamma distribution is applicable to unknown quantities that take values between 0 and infinity. All age coefficients and intercept in the model were specified with non-informative normal priors—ie, $\beta \sim Normal(0,\ 0{\cdot}0001)$.

The Gibbs sampler algorithm, an iterative Markov-chain Monte Carlo technique, was used to estimate the posterior distributions of our random variables using the R and JAGS program.[24,25] We used the JAGS software (version 3.3.0), running from R version 3.0.2 (R Development Core Team, 2013) to implement the Gibbs sampler, using specific marginal posterior densities.[24,25] Convergence estimation was assessed by calculating the Gelman–Rubin convergence statistics.[24,25]

Ethnicity, region, and gender effects

Bayesian hypothesis testing was done to examine the effect of ethnicity, geographic regions, and sex on the prevalence of any, early, and late age-related macular degeneration. Bayes factors were used to compare hypotheses of differences between groups, implementing the Gibbs variable selection as proposed by Dellaportas and colleagues[26] using the JAGS software. The comparison of the posterior probabilities of hypothesis is given by:

$$\underbrace{\frac{P(H_1|data)}{P(H_0|data)}}_{\text{(posterior odds)}} = \underbrace{\frac{P(data|H_1)}{P(data|H_0)}}_{\text{(Bayes factor)}} \times \underbrace{\frac{P(H_1)}{P(H_0)}}_{\text{(prior odds)}}$$

where H_0 is the null hypothesis and H_1 is the alternative hypothesis. Jeffreys[27] proposed an interpretation scheme for the magnitude of Bayes factors in terms of weak (1–3), substantial (3–10), strong (10–30), very strong (30–100), and decisive (>100) for H_1, whereas Bayes factors of less than 1 suggest support for the null hypothesis.

We assessed four major ethnic groups (European ancestry populations [Europeans], African ancestry populations [Africans], Asians, and Hispanics) and six geographic regions (Africa, Asia, Europe, Latin America and the Caribbean, northern America, and Oceania). Publication year was also tested to assess the trend of prevalence over the years for consideration in projection estimates.

Because the random effect model is the most frequently used meta-analytical method to account for the heterogeneity between the studies by incorporating a random effect estimate of between-study variation in the weighting, we did a simulation study to assess and compare the hierarchical Bayesian approach and the random effect methods (appendix pp 1–3, 9).

Projection estimates

Model $\mu_{ijk} = \beta_{0k} + \beta_{1k} * age_{ij} + \beta_2 * ageui_{ij} + \beta_3 * study_i$ was used to estimate the prevalence for each year increase in age for the k^{th} region. Global and region effects were incorporated as fixed and random effects in β_{0k} and β_{1k}. Age-specific prevalence was often reported as an interval (eg, 40–49 years) or censored (eg, 80 years or more) age range in the published papers, and hence the median of interval was used to represent the age interval, and censored age range was taken as the age with a censoring indicator in the analysis model. The estimated prevalence was used to calculate the global and region-specific total number of individuals with age-related macular degeneration in 2020 and 2040 by multiplying the age-specific and region-specific estimated prevalence rates to the UN World Population Prospects data.[28] Age-group-specific prevalence rates were assumed to remain constant for our global projection to 2040, since Bayesian

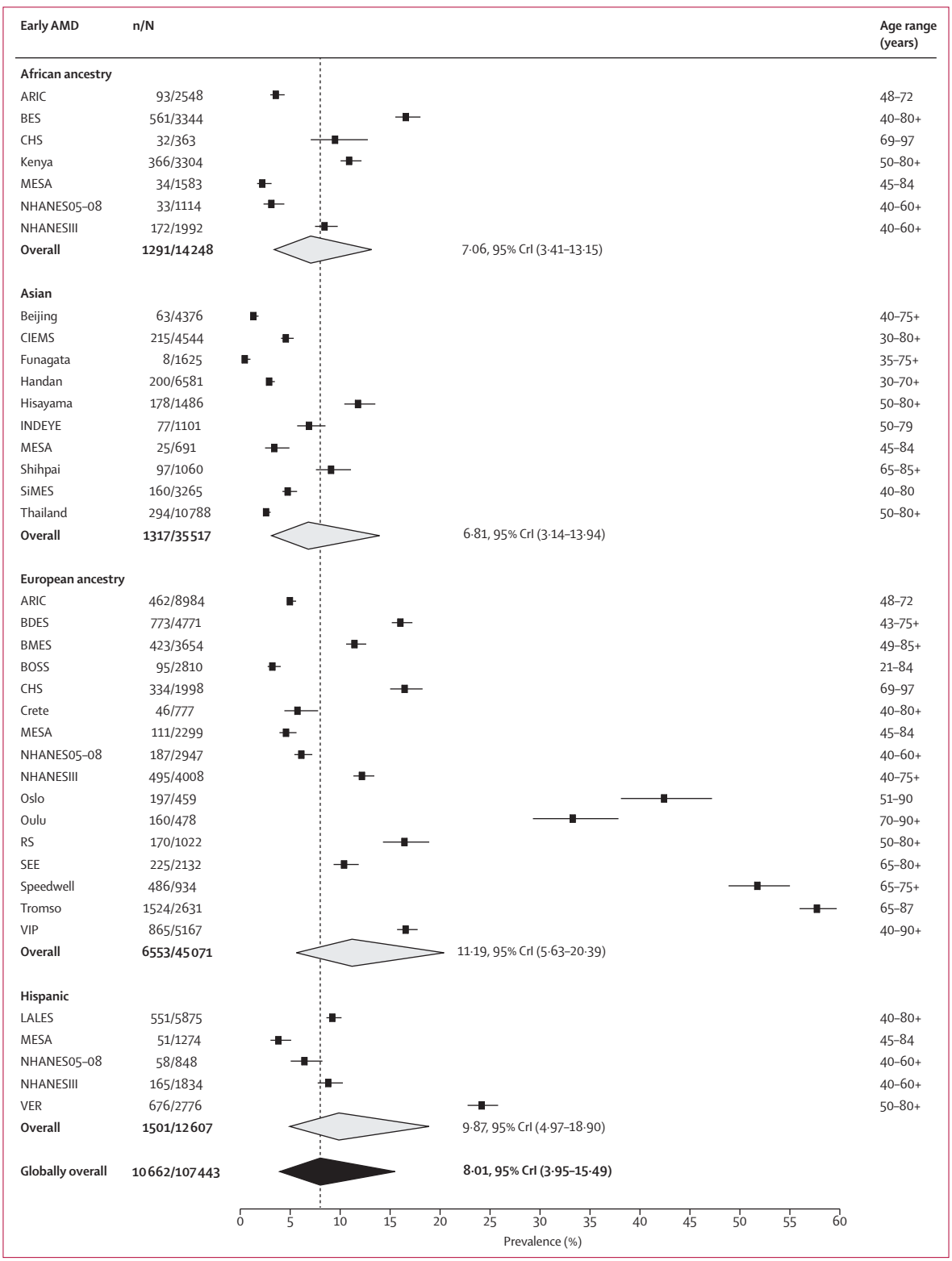

Figure 1: **Overall and race-specified pooled prevalence of early age-related macular degeneration (AMD)**
Dashed line refers to the overall pooled prevalence estimate presented in bold. See appendix (p 7, 8) for study references.

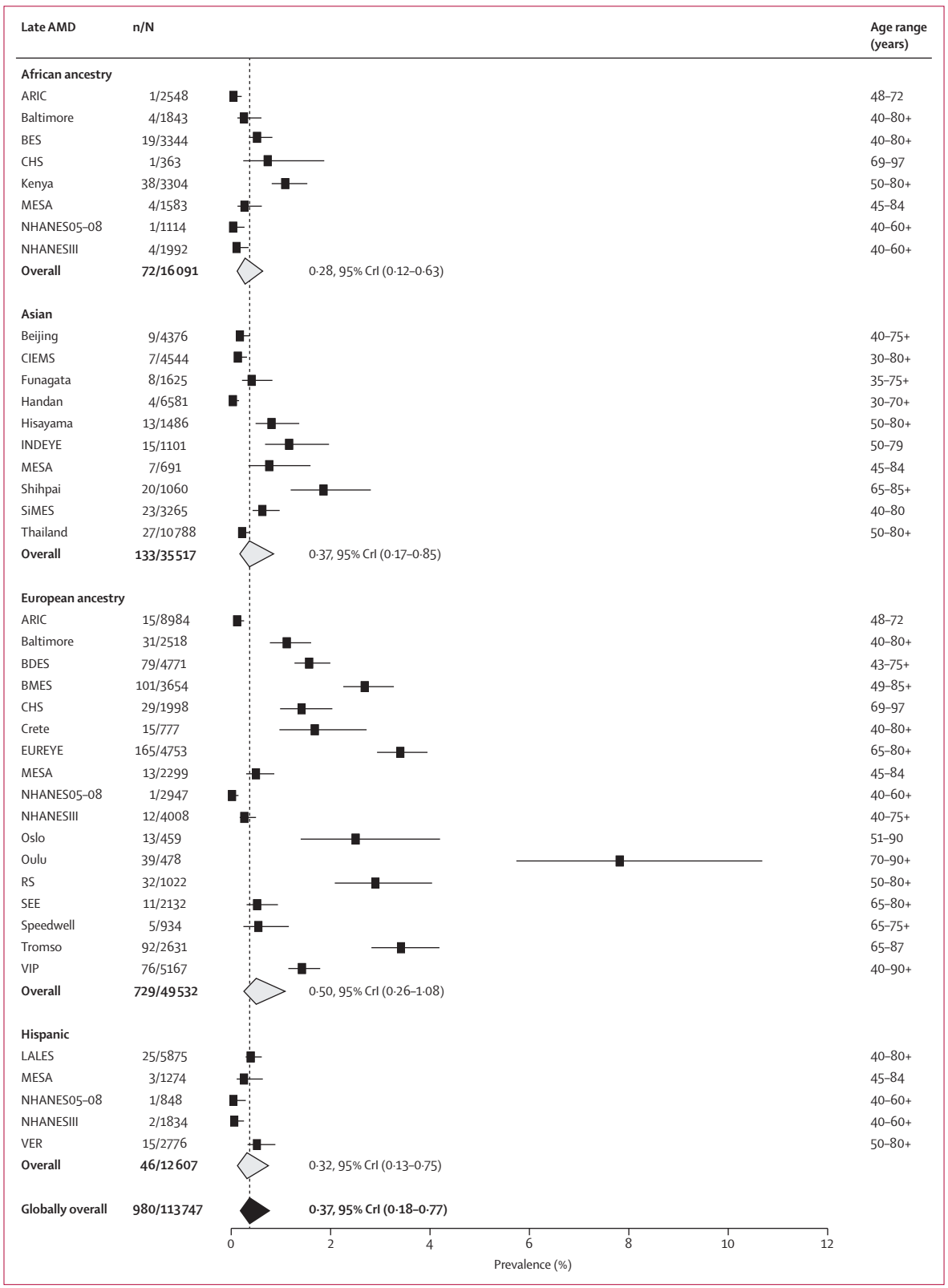

Figure 2: **Overall and race-specified pooled prevalence of late age-related macular degeneration**
Dashed line refers to the overall pooled prevalence estimate presented in bold.

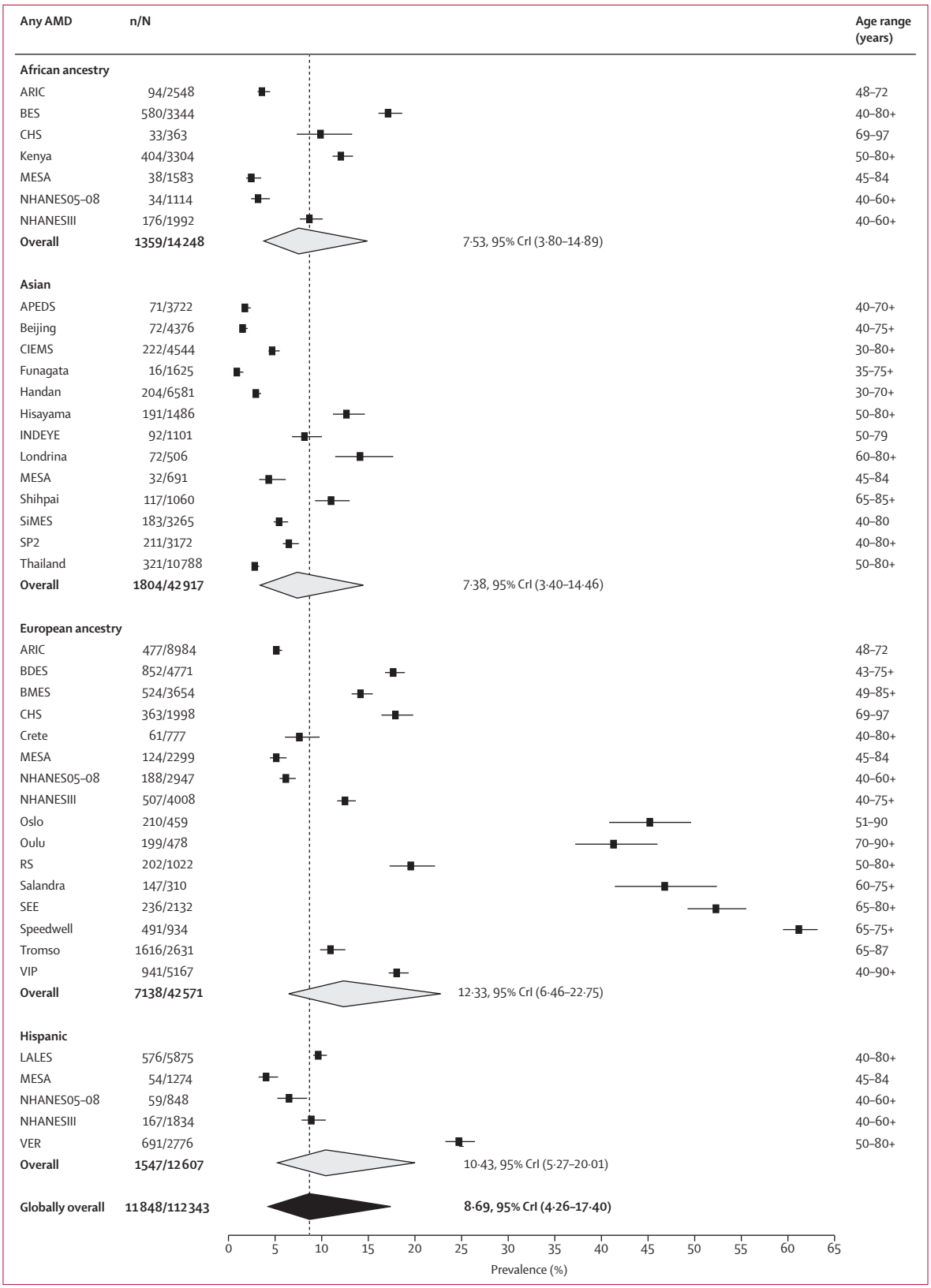

Figure 3: **Overall and race-specified pooled prevalence of any age-related macular degeneration**
Dashed line refers to the overall pooled prevalence estimate presented in bold.

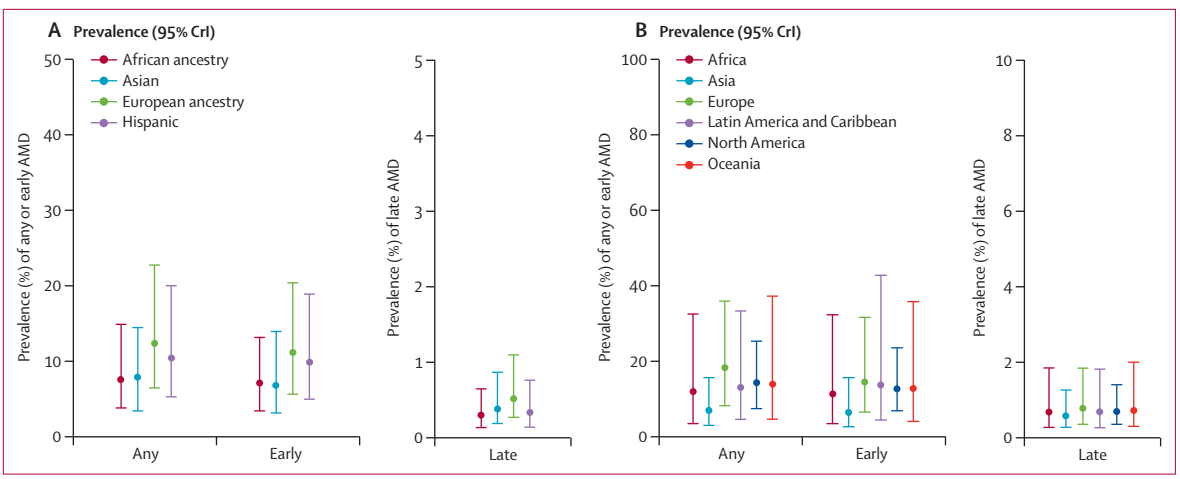

Figure 4: **Prevalence of age-related macular degeneration (AMD) by ethnic group (A) and (B) geographical region**
Error bars=95% CrI.

hypothesis testing of the publication year covariate in our review showed no trend for prevalence from 1989 to 2013.

Role of the funding source

The sponsors of this study had no role in study design, data collection, data analysis, data interpretation, or writing of the report, or in the decision to submit for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

2751 published original research articles, letters, abstracts, and review articles based on abstracts and titles were identified as of May, 2013, from our literature search (appendix pp 4–8). After initial abstract review, 54 potentially eligible articles were retrieved for assessment. Of these, we applied the inclusion and exclusion criteria and identified 39 eligible articles reporting on 39 population-based studies (12727 cases in 129664 participants and five ethnic ancestry groups; appendix pp 4–8). Data from patients with early, late, and any age-related macular degeneration were pooled separately. Of the study participants, 43·5% were of European ancestry, 12·4% were of African ancestry, 33·1% were Asian, 9·7% Hispanic, and 1·3% other.

Figure 1–3 shows the overall and ethnic-specific pooled prevalence of age-related macular degeneration. The lack of overlap in credible intervals from graphical inspection of forest plots suggests the presence of heterogeneity. Further analysis showed that heterogeneity in ethnicity and geographic regions for any stage were 99·5% (95% CrI 99·2–99·8) and 99·7% (99·5–99·9), respectively (appendix p 11). The pooled global prevalences (accounting for various sources of heterogeneity) of early and late-stage disease in adult populations were 8·01% (95% CrI 3·95–15·49) and 0·37% (0·18–0·77), respectively. The overall prevalence of any age-related macular degeneration was 8·69% (95% CrI 4·26–17·40). Detailed estimated prevalence by subtypes, ethnicity, and age groups from meta-analysis using the hierarchical Bayesian approach are provided in the appendix (pp 12,13).

Early age-related macular degeneration was more prevalent in populations of European ancestry (11·2%) than in Asians (6·8%), with a Bayes factor of 3·9, suggesting substantial evidence for the difference between groups (appendix p 10). Likewise, any age-related macular degeneration was more prevalent in populations of European ancestry than Asian (12·3% *vs* 7·4%; Bayes factor 4·3). Compared with African ancestry populations, people of European ancestry had higher prevalence of early, late, or any age-related macular degeneration (late: 12·3% *vs* 7·5%; Bayes factor 31·3, suggesting very strong evidence). Geographically, early and any disease were less prevalent in Asia than in Europe and northern America (all Bayes factors >2; figure 4 and appendix p 10). There was no evidence of difference in the prevalence of early, late, or any age-related macular degeneration between sexes (all Bayes factors <0·05, appendix p 10). Eight (21%) of the 39 studies provided information on geographic atrophy and neovascular subtypes. Subgroup analysis showed similar overall prevalence of geographic atrophy (0·44%, 95% CrI 0·15–1·36) and neovascular age-related macular degeneration (0·46%, 0·18–1·08). Europeans had a higher prevalence of geographic atrophy (1·11%, 95% CrI 0·53–2·08) than Africans (0·14%, 0·04–0·45), Asians (0·21%, 0·04–0·87), and Hispanics (0·16%, 0·05–0·46). There was no difference in prevalence of neovascular age-related macular degeneration between ethnicities.

The prevalence of early and late disease increased with age in each of the ethnic groups and regions (figure 5). Prevalence of late disease in populations with European ancestry increased most rapidly after age 75 years, with a similar trend seen in Europe and Oceania regions.

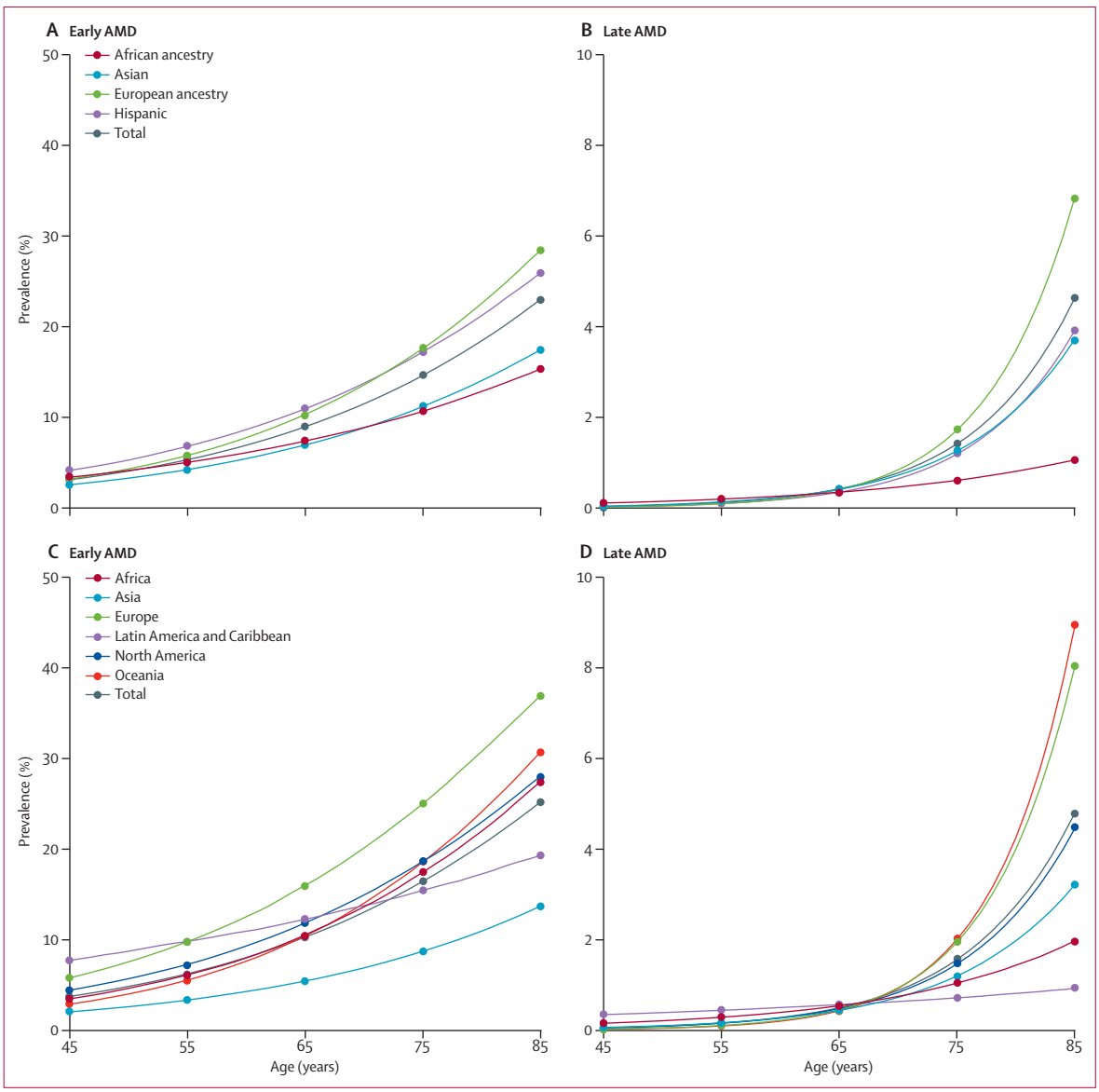

Figure 5: **Age trends of prevalence of age-related macular degeneration (AMD) by ethnicity (A and B) and region (C and D)**

The projected number of people with age-related macular degeneration by region in the years 2014, 2020, and 2040 are shown in figure 6 and the appendix (pp 14–16). In the year 2020, global projected cases of any age-related macular degeneration are 196 million (95% CrI 140–261), rising to 288 million (205–399) in 2040, with the largest number of cases in Asia (113 million [60–203] in 2040). Europe is expected to be second to Asia in the number of projected cases (69 million [40–109] in 2040), followed by Africa (39 million [12–93]), Latin America and the Caribbean (39 million [15–82]), North America (25 million [15–38]), and Oceania (2 million [1–5]). Pairwise comparison between geographical regions showed statistical evidence for the larger projected number of people with any age-related macular degeneration in 2040 in Asia compared with Latin America and the Caribbean, northern America, and Oceania, and up to 2038 for Africa (appendix pp 17,18).

Discussion

This systematic review and meta-analysis has shown that 8·7% of the worldwide population has age-related macular degeneration, and the projected number of people with the disease is around 196 million in 2020, increasing to 288 million in 2040. We found substantial evidence that early age-related macular degeneration was more prevalent in Europe than in Asia, but that rates of late onset were similar. These results confirm those of previous meta-analyses[4] and multiethnic population-based studies.[15] Asian (Chinese) people might be more

likely to develop exudative or neovascular age-related macular degeneration than white people,[15,29] but our subgroup analysis suggests no evidence for ethnicity difference. Also, most population-based studies were unable to reliably diagnose polypoidal choroidal vasculopathy, which often manifests like exudative age-related macular degeneration. Taking into consideration that polypoidal choroidal vasculopathy is markedly more common in Asians than in Europeans, we could be overestimating the true prevalence of late disease in Asians.[30–32] Our study also provides strong evidence that early, late, and any age-related macular degeneration is more prevalent in people of European ancestry than those of African ancestry, which validates observations derived from previous individual studies, such as the Baltimore Eye Study.[15,16] These patterns are in line with a previous multiethnic population-based study in the USA, whereby the prevalence of early disease was highest in people of European ancestry, compared with Hispanics, Asians (Chinese), and African Americans.[15]

Our meta-analysis updates two earlier reviews focused on single ethnicities, one in Europeans by Rudnicka and colleagues[17] and one in Asians by Kawasaki and colleagues.[4] In our study, compared with the Asian meta-analysis, we included four additional Asian studies published after 2010, including the Handan Eye Study,[33] the Central India Eye and Medical Study,[34] one multiethnic Asian cohort study in Singapore,[35] and one study in Thailand.[36] Unlike Rudnicka and colleagues, six studies published between 1970 and 1990 were excluded since they relied only on eye examinations, without taking fundus photos, and used study-specific definitions.[29,37–41] We included only participants with internationally recognised definitions of age-related macular degeneration[21,22] confirmed using retinal photographs.

Analysis of pooled prevalence by geographical regions showed greater variability, indicated by the larger 95% credible intervals compared with prevalence pooled by ethnic ancestry groups. This finding could be due to heterogeneity contributed by various ethnic groups within each region, and lends further support to the hypothesis that inherited genetic factors determined by ethnic ancestry play a substantial part in age-related macular degeneration,[42–44] in addition to established environmental risk factors such as smoking. Northern America and Europe had a higher pooled prevalence of early and any age-related macular degeneration than in Asia, in accordance with the higher prevalence in people of European ancestry than in Asians, as reported both in the literature and substantiated in our meta-analysis.

Female gender was considered a weak risk factor, with inconsistent association for late age-related macular degeneration.[45,46] In our meta-analysis, there was no evidence of gender difference in both early and late prevalence. This finding is consistent with previous reviews in people of European ancestry, where no significant gender difference was found in the prevalence of neovascular age-related macular degeneration or geographic atrophy.[47] Similarly in Asians, men do not have a higher prevalence of late disease than women after adjusting for risk factors such as smoking.[48–50]

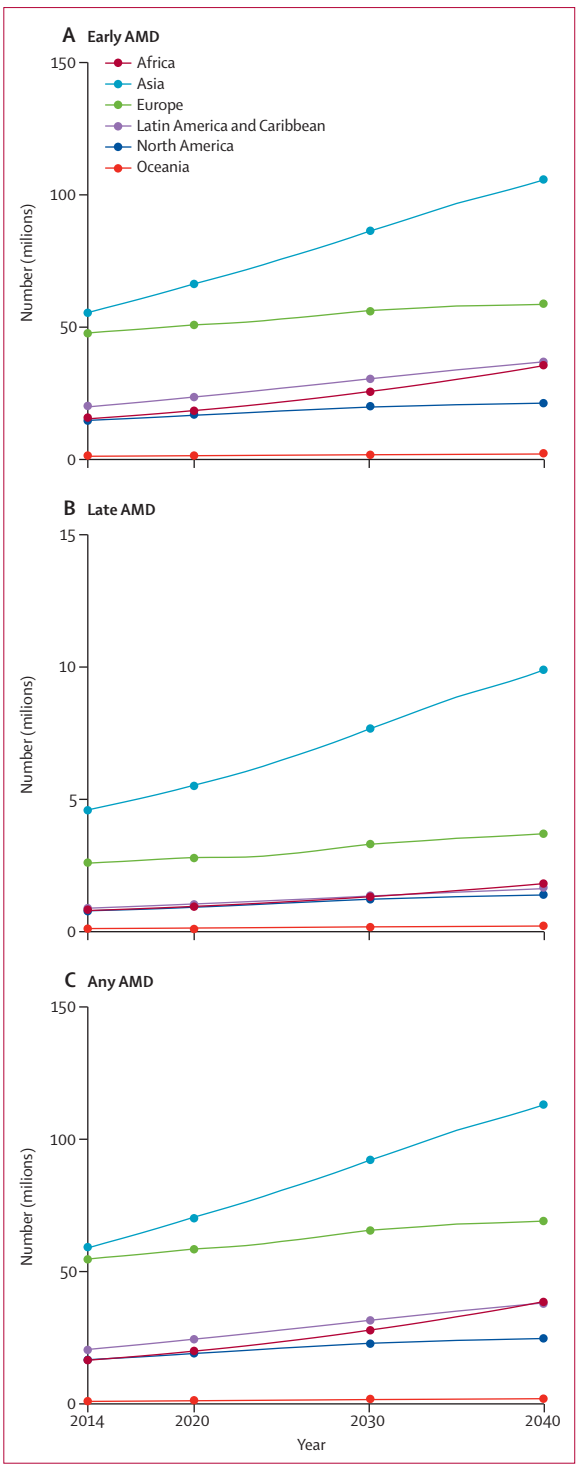

Figure 6: **Projection of number of people with early and late age-related macular degeneration (AMD) by regions in 2014, 2020, and 2040**

Asia accounts for more than 60% of the world population and hence will see the largest projected number of cases of age-related macular degeneration (a third of the cases globally), and is expected to increase more rapidly than other regions over the years, despite having the lowest estimated prevalence currently. Europe, being the third most populous region (11%) with the highest prevalence of age-related macular degeneration, follows after Asia in the number of projected cases, with a moderate increase over the years. The trends and differences between regions are mainly affected by the demographic progression in population structure (ie, an ageing population) of the regions based on UN population projection data.[28] These findings are important, since more than two-thirds of affected patients in Asia, Africa, and Latin America might not have access to expensive anti-angiogenesis therapies now widely used in North America and Europe.

The strength of our study is that we pooled data that used fundus photography and standardised protocols to assess age-related macular degeneration. Our study was limited by the fact that, despite the large number of studies included in this meta-analysis, our subgroup analysis on the prevalence of late disease subtypes (ie, neovascular age-related macular degeneration *vs* geographic atrophy) by ethnicity used data from only eight studies. Moreover, there is evidence that without harmonisation of classification systems and definitions of lesions, estimates of early age-related macular degeneration might substantially vary due to several factors. These include varying definitions used for grading the disease and inconsistencies in quality of images.[51] Although there are inherent disadvantages in undertaking a meta-analysis based on datasets pooled together from disparate population studies, we have attempted to circumvent this issue by only including studies in which standard protocols are used to grade fundus photos.

There is substantial evidence for higher prevalence of early disease in people of European ancestry than in Asians, and early and late disease in people of European ancestry than in those of African ancestry. We noted that late prevalence increases rapidly after age 75 years, especially in people of European ethnicity and in Europe and Oceania regions, but Asia will see the largest number of people with the condition despite currently having the lowest prevalence. These data provide important information for the design and implementation of eye care programmes for both specific ethnic groups and geographical regions, as well as worldwide.

Contributors

XS and C-YC reviewed the literature. WLW and XL checked and analysed the data. XS and WLW drafted the manuscript. C-YC, RK, CMGC, and TYW did the critical revision.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

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