Geo-Epidemiology of Age-Related Macular Degeneration: New Clues Into the Pathogenesis

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• PURPOSE: To evaluate the demographic, geographic, and race-related variables that account for geographic variability in prevalence rates of age-related macular degeneration (AMD).

• DESIGN: Systematic review, meta-regression, and decision-tree analysis.

• METHODS: A systematic literature review of PubMed, Medline, Web of Science, and Embase databases identified population-based studies on the prevalence of AMD published before May 2014. Only population-based studies that took place in a spatially explicit geographic area that could be geolocalized, and used retinal photographs and standardized grading classifications, were included. Latitude and longitude data (geolocalization) and the mean annual insolation for the area where survey took place were obtained. Age-standardized prevalence rates across studies were estimated using the direct standardization method. Correlations between the prevalence of AMD and longitude and latitude were obtained by regression analysis. A hierarchical Bayesian meta-regression approach was used to assess the association between the prevalence of AMD and other relevant factors. We further investigated the interplay between location and these factors on the prevalence of AMD using regression based on conditional-inference decision trees.

• RESULTS: We observed significant inverse correlations between latitude or longitude, and crude or age-standardized prevalence rates, of early and late AMD ($P < .001$). Metaregression analysis showed that insolation, latitude, longitude, age, and race have a significant effect on the prevalence rates of early and late AMD ($P < .001$). Decision-tree analysis identified that the most important predictive variable was race for early AMD ($P = .002$) and insolation for late AMD ($P = .001$).

• CONCLUSIONS: Geographic position and insolation are key factors in the prevalence of AMD. (Am J Ophthalmol 2016;161:78–93. © 2016 by Elsevier Inc. All rights reserved.)

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AGE-RELATED MACULAR DEGENERATION (AMD), A progressive chronic disease of the central retina, is a major cause of blindness worldwide.[1] The prevalence of AMD is likely to increase as a consequence of exponential population aging; the projected number of people with the disease in 2040 is around 288 million.[2] The progressive deterioration of vision associated with AMD significantly reduces quality of life.[3] Therefore, AMD will be a major medical and socioeconomic challenge, worldwide, in the coming years.

It is generally accepted that AMD is the result of a complex interaction between genetic and environmental factors.[4] Smoking is the most consistently identified modifiable risk factor, but abdominal obesity and dietary factors may also affect AMD incidence and progression.[5] A significantly higher concordance rate in monozygotic than dizygotic twins and in families suggests a genetic predisposition to AMD[6]; recently, family linkage analysis and genome-wide association studies have revealed important genetic contributions to the development of AMD.[7] The precise pathogenesis is still poorly understood. Investigations to identify probable risk factors and their interplay, in order to develop prevention and intervention strategies, have been recommended.

Geo-epidemiology is a new approach, which compares epidemiologic data across different geographic regions and populations, in the process identifying causative genetic, environmental, and socioeconomic factors.[8] We evaluated the geo-epidemiology of AMD. We carried out a systematic review of population-based studies on the prevalence of AMD with the aim of: (1) evaluating the correlation between geographic location and the prevalence of AMD; (2) determining the demographic, geographic, and race-related variables that may account for the variability in prevalence rates; and (3) evaluating the interplay between geographic location and these variables on the prevalence of AMD.

METHODS

THE REVIEW AND ANALYSIS WERE CONDUCTED USING THE Preferred Reporting Items for Systematic Reviews and

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Meta-analyses (PRISMA) statement and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines.[9,10]

• **PROTOCOL:** Before the review, we developed a protocol, including eligibility criteria, search strategies, criteria for study selection, methods for extracting related data, methods for assessing study quality, and statistical methodology.

• **INFORMATION SOURCES, ELIGIBILITY CRITERIA, SEARCH, AND STUDY SELECTION:** The worldwide prevalence of AMD was the focus of our search. Studies on the prevalence of AMD were systematically reviewed by searching the electronic databases and scanning reference lists of articles, and by consultation with experts in the field. Where necessary, study authors were contacted for additional information or for clarification of their methods and results. The search was applied to the PubMed, Medline, Web of Science, and Embase databases by combining search terms for prevalence (prevalence, epidemiology, incidence) with keywords for AMD (macular degeneration, age-related maculopathy, age related maculopathy, age-related macular degeneration, age related macular degeneration, macular degeneration). Observational studies published up to May 2014 were considered for inclusion in this review. No publication date or publication status restrictions were imposed.

Eligibility of studies was assessed independently in an unmasked standardized manner by 2 senior investigators (A.L., C.M.). Disagreements between reviewers were resolved by consensus.

We considered all population-based studies representative of the resident population that: (1) quantified the prevalence rates of early and late AMD; (2) took place in a spatially explicit geographic area (ie, province, state, city, and region) that could be geolocalized; and (3) used a standardized photographic assessment of AMD.

We excluded surveys or audits of hospital eye departments or clinics, studies inviting nonspecific volunteers or particular professions, studies that relied on self-reported diagnoses or carried out fundus examinations only in those with reduced vision, studies that used only a clinical examination by ophthalmoscopy or slit-lamp biomicroscopy, studies on specific ethnic groups (ie, not representative of the overall population at the sampling site) or immigrants, studies on populations aged <40 years or >80 years, and reports not written in English or reporting the number of eyes with AMD as opposed to the number of individuals. Studies that reported a prevalence of an area greater than 10 degrees of latitude and longitude, without a specific location of the place where the study had been carried out, were also excluded.

Standardized photographic assessment of AMD included retinal photography and standardized grading methods to diagnose and classify lesions (ie, grading of retinal photographs following either the International Classification [IC][11] or the Wisconsin Age Related Maculopathy [WARM] grading system,[12] or a modification thereof) with reproducible grading results. 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 AMD was defined as the presence of any of the following: geographic atrophy or pigment epithelial detachment, subretinal haemorrhage or visible subretinal new vessels, subretinal fibrous scar, or laser treatment scar.

Latitude and longitude data for the survey area (geolocalization), as reported in each study, were obtained using Google Earth 6.0.2. (http://earth.google.com/intl/it/). For each area, we also calculated the mean annual insolation (ie, the amount of solar radiation incident on the surface of the earth) on the horizontal surface, expressed in $kWh/m^2/day$ obtained from the National Aeronautics and Space Administration (NASA) Atmospheric Science Data Center.[13]

• **DATA COLLECTION PROCESS:** We developed a data extraction sheet (based on the Cochrane Consumers and Communication Review Group's data extraction template),[14] pilot tested it on 5 randomly selected included studies, and refined it accordingly. One author (A.L.) extracted the data from included studies, and the second author (M.R.) checked the extracted data.

• **DATA ITEMS:** Regarding the prevalence of AMD, information was extracted from each included study on the following: (1) study design; (2) setting of enrollment; (3) characteristics of participants, including number, age range, mean (or median) age or midpoint of the age range, race; (4) method of diagnosis of AMD and classification system; (5) age-specific prevalence rates of early and late AMD observed in a given age category (5-year or 10-year age groups). Articles reporting prevalence on more than 1 geographic area were recorded separately for each geographic area (eg, a single report giving prevalence from 2 cities was treated as 2 studies). To evaluate the geolocalization of each area studied, the latitude and longitude generally accepted for the city to the nearest minute were used, if the study population was defined by a city. When larger regions had been studied, such as at a province, state, region or country level, and city level, the mean center point of the area was calculated and the latitude and longitude of that center point to the nearest minute was used, using standard geographic coordinates.

• **RISK OF BIAS:** To ascertain the validity of the eligible studies, the study design, the size and representativeness of the study population (ie, the presence of selection bias), the validity of outcomes (risk of confounding or