Is sunlight exposure a risk factor for age-related macular degeneration? A systematic review and meta-analysis

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ABSTRACT

Background Epidemiologists have recently investigated sunlight exposure as a risk factor for age-related macular degeneration (AMD), but there remains an ongoing dispute over this association due to insufficient evidence and unreliable data.

Objectives To analyse comprehensively the epidemiological literature concerning the association between AMD and sunlight exposure.

Methods We systematically reviewed the epidemiological literature concerning the association between AMD and sunlight exposure. An electronic search was performed of PubMed, Web of Science and CNKI, which was supplemented by hand searching. The selection of studies, data abstraction and quality assessment were performed independently by three reviewers. After these steps, we performed a random-effects meta-analysis, followed by subgroup analysis and sensitivity analysis, including a random-effects meta-regression for study-specific covariates.

Results Fourteen studies were identified. Twelve studies identified an increasing risk of AMD with greater sunlight exposure, six of which reported significant risks. The pooled OR was 1.379 (95% CI 1.091 to 1.745). The subgroup of non-population-based studies revealed a significant risk (OR 2.018, 1.248 to 3.265, p=0.004). We identified the gross domestic product (GDP) per capita (p=0.048), but not the latitude (p=0.21), as a factor that led to heterogeneity according to the meta-regression.

Conclusions The epidemiological literature published to date indicates that individuals with more sunlight exposure are at a significantly increased risk of AMD. The OR significantly decreased with increasing GDP per capita.

INTRODUCTION

Age-related macular degeneration (AMD) is a common disease accounting for most cases of blindness in older individuals in many western countries.[1] AMD is caused by the accumulation of drusen in the macula, which is the most important part of the retina, and this process ends in serious irreversible visual impairment.[2] Past studies have demonstrated that up to half of the ageing population, both men and women, has drusen and/or pigmentary irregularities.[3–5] As the leading cause of older people's blindness in most developed countries,[6] AMD accounts for 14% of individuals' blindness over 55 years and for 37% of cases in people over 75 years of age.[7] Based on clinical and pathological features, AMD is divided into two periods: the early stage is the geographic form, also known as 'dry AMD', which accounts for 90% of the disease; the later stage is the exudative form, referred to as 'wet AMD', which makes up the other 10%. Unfortunately, no curative treatment for AMD is available, and therefore, AMD results in irreversible vision loss. The best treatment option is thus to prevent further deterioration. Consequently, much work has been performed to identify risk factors for AMD. The risk factors identified to date that might affect the development of AMD include age, gender, genetic factors, smoking, cardiovascular disease, iris colour and sunlight exposure.[4] However, the unreliable data regarding sunlight exposure make this risk factor more controversial.

To end the debate, a systematic review and meta-analysis was performed to assess the association between sunlight exposure and AMD. We hypothesise that sunlight exposure is indeed a risk factor for AMD and that heterogeneity between studies is due to study-specific covariates, including latitude and gross domestic product (GDP) per capita. A significant negative correlation between the strength of OR and latitude was observed.

METHODS AND MATERIALS

Study design

In accordance with the meta-analysis of observational studies in epidemiology (MOOSE),[8] we performed a meta-analysis of current epidemiological studies. The study type was not limited. We retrieved articles from PubMed, Web of Science and CNKI (up to 25 March 2012) and also searched by hand. Related articles and potentially relevant articles were also screened.

Inclusion and exclusion criteria

Epidemiological studies that met both of the following items were selected: the study concerned the association between AMD and sunlight exposure, and OR for the sunlight exposed/unexposed groups and their 95% CI were presented or the frequency of AMD in the exposed/unexposed group was available in the paper. 'UV exposure', 'visible light exposure' and 'blue light exposure' were regarded as sunlight exposure.

Case reports, comments and experimental study designs in laboratory settings were excluded. Studies that reported only OR and its p value but failed to present the corresponding 95% CI were excluded. We also eliminated studies that reported only the χ^2 value with no raw data/table listing the

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frequencies of AMD in sunlight the exposed/unexposed groups. Ultimately, we excluded two publications based on the same set of data.

Search strategy

There was no restriction about language. We searched PubMed, Web of Science and CNKI using the terms 'AMD', 'risk OR incidence OR epidemiologic' and 'sunlight OR UV OR ultraviolet OR blue light OR visible light'. To complement the electronic search, a hand search of the relevant reviews and references of the included articles was performed.

Data abstraction

Two authors extracted information from the eligible articles. The information below was extracted: name of first author, year of publication, study type, study location and latitude, source of the study populations, OR of the sunlight exposed/unexposed and their 95%CI. When articles did not present OR but included sufficient crude data, we calculated the OR ourselves. Whenever possible, the highest dose group was always extracted as the exposed group, and the lowest dose group was extracted as the unexposed group. The maximally adjusted OR was always preferred. For publications that did not indicate their study locations, we contacted the authors for it. Google Earth was used to identify the latitude of each study location. We obtained the GDP per capita from the International Monetary Fund report (2010–11). For large countries, namely the USA and China in this meta-analysis, the GDP per capita varied substantially from one place to another. Therefore, Wikipedia was used to determine the accurate GDP per capita of eligible studies' locations in China and the USA. We calculated GDP per capita from crude data when no records were available. Whenever disagreements occurred, they were settled through discussion among all authors until a consensus was reached.

Statistical analysis

OR with 95% CI were applied to evaluate the strength of the association between AMD and sunlight exposure. The statistical significance of the pooled OR was assessed using the Z-test. The χ^2 goodness of fit was used to test Hardy–Weinberg equilibrium. We investigated the degree of heterogeneity between eligible studies using Q-statistics, for which $p<0.05$ indicated evidence of significant heterogeneity. In addition, we also performed a random-effects meta-regression to determine the extent of heterogeneity due to study-specific covariates, namely GDP per capita and latitude in our model. We considered a p value less than 0.1, rather than 0.05, to indicate that the corresponding covariate was a source of heterogeneity so as not to leave out any potential sources.

Publication bias was explored by constructing a funnel plot for the included studies; which asymmetric plots indicate the possible existence of publication bias. Egger's test was performed to assess the degree of asymmetry, and we considered a p value less than 0.05 to be evidence of publication bias. To explore the robustness of our result, sensitivity analysis, omitting one study at a time, was performed to identify potential outliers. All statistical tests were two-sided. Meta-analysis and meta-regression were both performed using Stata V.10.0.

Quality assessment

We assessed the methodological quality of eligible studies using two checklists that were previously designed separately for cohort/case–control studies and cross-sectional studies.[9] Both checklists contain nine items pertaining to population selection, comparability and ascertainment of outcomes. For both checklists, the item 'Are confounding factors identified and strategies to deal with them stated' would be given a 'yes' answer if sex and age or more other confounding factors were adjusted. The details and results are presented in table 1 and table 2.

Table 1 Joanna Briggs Institute critical appraisal for cohort/case–control study

Author	1	2	3	4	5	6	7	8	9
The Eye Disease Case–Control Study Group[10]	Y	Y	Y	Y	Y	N	Y	Y	Y
Delcourt *et al*[1]	Y	Y	Y	Y	Y	N	Y	Y	Y
Tomany *et al*[11]	Y	NC	Y	Y	Y	Y	Y	Y	Y
Khan *et al*[20]	N	Y	NC	N	Y	N	NC	Y	Y
Chu[14]	N	NC	Y	Y	Y	N	NC	Y	Y
Hirakawa *et al*[16]	N	Y	Y	Y	Y	N	NC	Y	Y
Xu[15]	N	NC	Y	N	Y	N	NC	Y	Y
Xu[12]	N	NC	NC	Y	Y	N	NC	Y	Y

1, Is sample representative of patients in the population as a whole? 2, Are the patients at a similar point in the course of their condition/illness? 3, Has bias been minimised in relation to selection of cases and of controls? 4, Are confounding factors identified and strategies to deal with them stated? 5, Are outcomes assessed using objective criteria? 6, Was follow-up carried out over a sufficient time period? 7, Were the outcomes of people who withdrew described and included in the analysis? 8, Were outcomes measured in a reliable way? 9, Was appropriate statistical analysis used?
N, no; NC, not clear; Y, yes.

RESULTS

Characteristics of eligible studies

A total of 465 articles was identified in the electronic search, of which 76 studies were from Pub Med; the other 389 studies were from Web of Scienceand CNKI. Four hundred and forty-five studies were excluded after we reviewed their titles and abstracts. Eight studies were eliminated after review of the full text because they did not meet our inclusion criteria. In addition, we added two articles identified in the hand search. Therefore, 14 eligible studies, including seven case–control studies and seven non-case–control studies were identified. Among the 14 eligible articles, 11 were published in English and three in Chinese. Five studies were conducted in China, four in Europe and the other four in the USA. Five of the seven non-case–control studies were recruited from the general population. Among the case–control studies, two selected their cases

Table 2 Joanna Briggs Institute critical appraisal for cross-sectional study

Author	1	2	3	4	5	6	7	8	9
Taylor *et al*[27]	N	Y	N	Y	Y	N	N	Y	Y
Cruickshanks *et al*[17]	Y	Y	N	Y	Y	N	Y	Y	Y
Bai *et al*[19]	Y	Y	Y	Y	Y	N	Y	Y	Y
Vojnikovic *et al*[21]	N	N	N	Y	Y	N	N	NC	Y
Borjan and Lasic[18]	Y	N	N	Y	Y	N	N	Y	Y
Fletcher *et al*[13]	Y	Y	Y	Y	Y	N	N	Y	Y

1, Was study based on a random or pseudo-random sample? 2, Were the criteria for inclusion in sample clearly defined? 3, Were confounding factors identified and strategies to deal with them stated? 4, Were outcomes assessed using objective criteria? 5, If comparisons are being made, was there sufficient description of the groups? 6, Was follow-up carried out over a sufficient time period? 7, Were the outcomes of people who withdrew described and included in the analysis? 8, Were outcomes measured in a reliable way? 9, Was appropriate statistical analysis used?
N, no; NC, not clear; Y, yes.

Table 3 Information abstracted from 14 eligible studies

First author name	Study location	Latitude	Published year	Type	Base*	Adjusted	GDP per capita (in US$)	OR	LL	UL
Taylor	Chesapeake	36.77°N	1990	No	2	NO	29642	1.06	1.012	1.11
Group	USA	42°N	1992	Case–control	1	YES	48387	1.1	0.6	2.1
Cruickshanks	BeaverDam_Wis	43.45°N	1993	No	1	YES	40623	1.1	0.6	2
Delcourt	Sete	43.4°N	2001	Case–control	1	YES	35156	0.7	0.52	0.94
Tomany	BeaverDam_Wis	43.45°N	2004	No	1	YES	43661	1.18	0.85	1.64
Bai	Fuping, Jingbian and Yang County	35°N	2005	No	1	NO	14457	0.52	0.23	1.17
Khan	Britain	53°N	2006	Case–control	2	NO	36090	1.42	0.92	2.18
Vojnikovic	Island Rab	44.77°N	2007	No	2	NO	13720	7.79	1.89	31.99
Chu	Beijing	39.9°N	2007	Case–control	2	YES	11307	4.68	1.32	16.58
Borjan	The island of Solta and Zagreb	45.8°N	2007	No	1	NO	17578	4.63545	2.14888	9.99937
Hirakawa	Kagoshima	31.58°N	2008	Case–control	2	YES	34740	2.3	1.19	4.46
Fletcher	Europe	50°N	2008	No	1	YES	43008	1.09	0.84	1.41
Xu Z	Changchun	43.82°N	2009	Case–control	2	NO	About 6000	3.953	2.096	7.463
Xu W	Wuhan	30.58°N	2009	Case–control	2	YES	About 10000	1.06	0.56	2.02

For the item Base, 1 represented population-based and 2 represented non-population-based. LL and UL represented the lower and upper limit of OR 95% CI, respectively.
GDP, gross domestic product.

randomly from the general population or population-based medical centre. A summary of the 14 eligible studies is presented in table 3.

We found OR adjusted for age and sex or more other confounders in seven[1 10–15] of the 14 articles. The subjects of one Japanese study [16] were restricted to lifelong male dwellers over 50 years old. Another study[17] presented an OR adjusted only for age. OR presented for the other studies were not adjusted for any confounders.

The methods for assessing sunlight exposure and grouping criteria varied among the included studies. Three studies[1 11 13] grouped participants by estimating individual average doses of ultraviolet (UV) or blue light exposure. Four studies[12 15 18 19] used the estimated hours spent outdoors per day. Six studies [10 11 14 17 20 21] assessed individuals' exposure based on their jobs, and people with outdoor jobs were divided into the exposed group. The other study,[16] which was conducted in Japan, used a special method based on the total length of facial wrinkles in the region of the upper cheek and temporal areas next to the eyes; individuals with lengths greater than 0.1314 were considered the more exposed group.

Results of the meta-analysis

The results of the random-effects meta-analysis indicated a significantly increased risk of AMD in the more exposed group, with a pooled OR of 1.379 (95% CI 1.091 to 1.745, p=0.007; moment-based estimate of between-studies variance 0.116, p=0.000 for heterogeneity). A forest plot with details is presented in figure 1.

Subgroup analysis

Neither the results of non-case–control studies nor those of case–control studies (OR 1.266, 0.948 to 1.692 and OR 1.598, 0.955 to 2.672, respectively) varied substantially from the pooled OR for all studies, although neither risk of the two groups was significant. Similar circumstances were also identified for studies grouped by continent. However, the pooled OR of the American subgroup, which consisted of four studies,

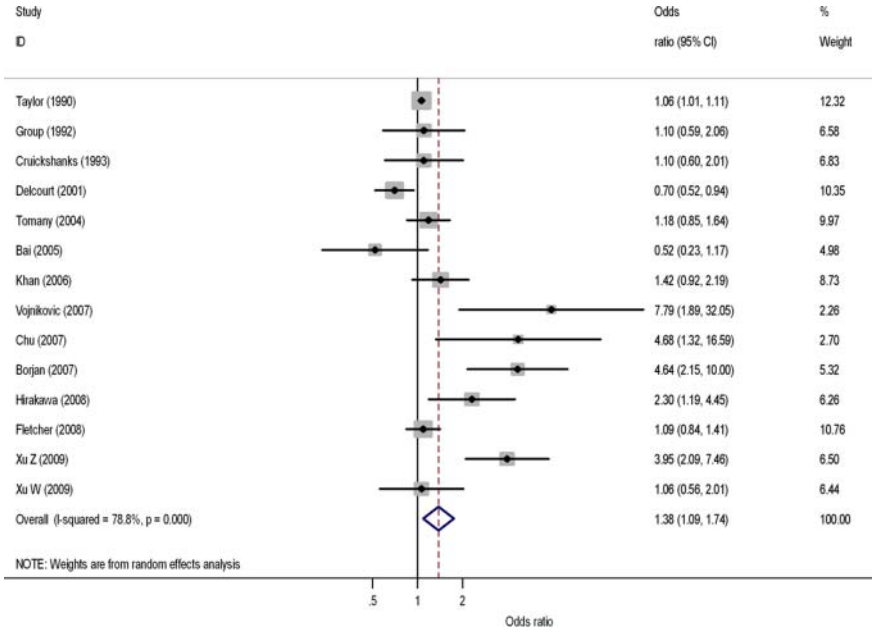

Figure 1 Forest plot of the 14 eligible studies with details. It shows a pooled OR of 1.379 (95% CI 1.091 to 1.745, p=0.007), indicating that sunlight exposure was a significant risk factor for age-related macular degeneration.

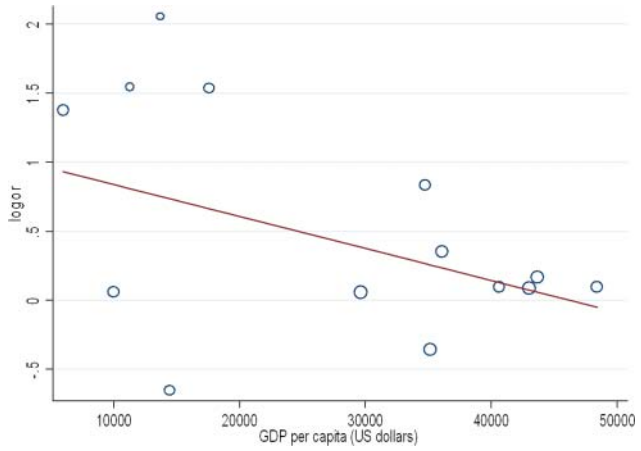

Figure 2 Result of the meta-regression indicated that the OR varied significantly with gross domestic product (GDP) per capita (p=0.048), and a negative correlation was found.

indicated a significant association between sunlight exposure and AMD (OR 1.063, 1.015 to 1.112). In subgroups classified by study population (population-based or not), a significant outcome was found for the non-population-based group (OR 2.018, 1.248 to 3.265, p=0.004).

The pooled adjusted OR for lower latitude (<40°, three studies), 1.977 (95% CI 0.926 to 4.218), was greater than that for higher latitude (OR 0.991, 0.792 to 1.240), suggesting that latitude did affect the strength of the association between sunlight exposure and AMD. However, unexpected results of the meta-regression did not offer sufficient evidence to convince us that latitude was a covariate that led to heterogeneity (p=0.21), as per our hypothesis that there was a decreasing gradient of OR with increasing latitude. The same test for the GDP per capita indicated that pooled OR significantly varied with this covariate, and a negative correlation between the two was detected (figure 2, p=0.048). Sensitivity analysis confirmed that the pooled OR was stable whenever one study was excluded at a time, indicating that our result is reliable. .Result of Egger's test showed no significance (p=0.079), whereas the funnel plot (figure 3) is asymmetric.

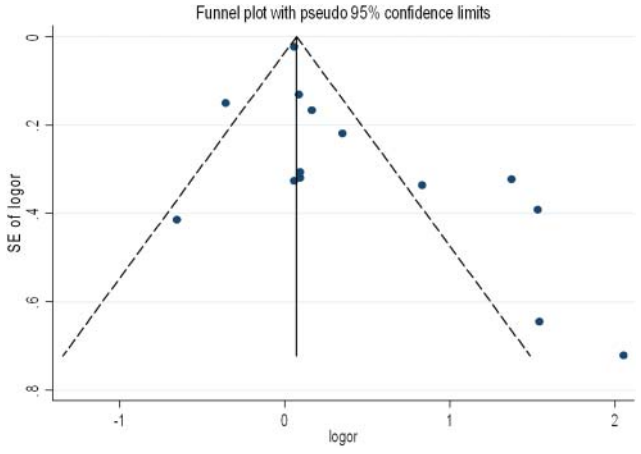

Figure 3 The funnel plot for the 14 eligible studies. Its asymmetry indicates a possible existence of publication bias, whereas the result of Egger's test did not (p=0.079).

DISCUSSION

Although the aetiology of AMD still remains unclear, there is already a consensus that damage to retina pigment epithelium (RPE) cells is a critical process in the development of AMD.[22] A study reported that the geographic atrophy of RPE accounted for serious irreversible vision loss in nearly 20% of all AMD patients.[23] The vital role of RPE lies in its participation in metabolic and supportive functions that supply oxygen and remove waste from the retina.[7] Therefore, damage to RPE cells will result in the apoptosis of photoreceptor cells and accumulation lipofuscin in the macula.

Accordingly, numerous in-vitro and in-vivo studies focusing on damage to RPE cells induced by UV and visible light, especially blue light, have been performed in the past few decades. A loss of viability was observed in RPE cells after irradiation by either UVA or UVB.[24 25] Blue light was also found to decrease the viability of RPE cells by nearly 40%.[26]

Although the experimental evidence seemed sufficient, epidemiological evidence was unstable. This study is the first meta-analysis to review the epidemiological studies published to date to explore the relationship between sunlight exposure and AMD. The results of our meta-analysis yielded a significant pooled OR of 1.379 (95% CI 1.091 to 1.745), supporting our hypothesis that sunlight exposure is indeed a risk factor for AMD.

Great heterogeneity was found among the 14 eligible studies (p<0.001). With the help of subgroup analysis and meta-regression, the GDP per capita, the source of study population, the latitude of study location and the methodological quality of the studies were determined to be potential sources of variability. Funnel plots indicated that the sample size was a potential factor leading to heterogeneity, but Egger's test (p=0.079) ruled out this factor.

Among the subgroups divided by continent, the American subgroup reported a significant pooled OR. However, given that the pooled OR of this subgroup is dominated by one extremely large study,[27] this finding is unreliable.

The risk for the non-population-based subgroup was significant, whereas the risk for population-based studies was not. This implies that study quality and methodological limitations have an impact on our results. These factors could introduce selection bias and thus resulted in the overestimation of the strength of the relationship between sunlight exposure and AMD.

Although the meta-regression provided insufficient evidence to support our hypothesis regarding latitude, we still believe the hypothesis is tenable. Generally, the lower the latitude of the study region, the more sunlight to which the general population is exposed. Conversely, a higher latitude means there is less sunlight exposure in general, which should result in a smaller OR. As shown in table 2, the latitudes of the included studies ranged from 30.58°N (Wuhan) to 53°N (Britain); thus, none of the included studies were performed in the southern hemisphere or in the tropical region of the northern hemisphere. This lack of data suggests that the relationship between the strength of OR and the corresponding latitude is relatively imprecise. In addition, two more reasons should be noted. First, the lower-latitude group reported a much greater risk than the higher-latitude group, and second, only 14 studies focusing on the association between sunlight exposure and AMD were identified. Therefore, one outlier caused by deficiency may lead to an obvious variation in our results. This limitation may have resulted in imprecise OR and an unclear association between the strength of OR and latitude. Besides, two studies conducted

in the same area (Cruickshanks *et al*[17] and Tomany *et al*[11] in the Beaver dam) reported distinctly different OR, contradicting this hypothesis.

There was an interesting and unexpected discovery that the GDP per capita, instead of latitude, played an important role in the heterogeneity among studies. As shown in figure 2, a negative correlation between GDP per capita and the pooled OR was found. This correlation might be easy to explain. Generally, countries with higher GDP per capita often have better healthcare systems and higher standards of medical care. Regular physical examinations help identify individuals with soft drusen, and these patients can be urged to take measures to prevent further deterioration. In addition, people in developed countries are better educated and more aware of the benefits of outdoor ocular protection, such as wearing a hat or sunglasses. This may have resulted in the underestimation of the association between sunlight exposure and AMD because eligible studies with higher latitudes were often conducted in developed countries.

For several reasons, we believe that the risk of AMD due to sunlight exposure is underestimated. First, various criteria were used to classify the exposed and unexposed groups. For example, the Eye Disease Case–Control Study Group[15] used the criterion 'mainly works outdoors' to define the exposed group, whereas Cruickshanks *et al*[17] used 'time outside at work >1/2 and ≤1/4' to identify the exposed and unexposed groups, respectively. These differences in grouping criteria could lead to an underestimation of the risk because individuals who were exposed to substantial amount of sunlight but did not meet the grouping criteria would be classified as unexposed. The fact that leisure time outdoors was ignored also reduced pooled OR for similar reasons. Other researchers, such as Xu[15] and Khan *et al*[20] used 'ever worked outdoors' and 'worked/lived in sunny climate ≥5 years', respectively. These factors could group people who were not exposed to much sunlight in the exposed group, consequently resulting in an underestimation of the risks. Protective measures taken by the exposed group could also lessen sunlight radiation and lower the true risk. Second, among the 14 studies, only five[12 14 15 18 21] were conducted in developing countries. As we mentioned above, a greater level of economic development implies a better healthcare system and more awareness of the benefits of protection from the sun. As a result, the OR in developed countries are most likely to be relatively lower. The results of meta-regression provided strong evidence for this association. Therefore, it is reasonable for us to consider that an iceberg phenomenon exists, which would introduce bias and would make the result less significant. Third, according to the subgroup analysis, in general, lower latitude seemed to be correlated with higher OR. However, the 14 eligible studies were all conducted in temperate zones, and the lowest latitude was 30.58°.[12] No study aimed at determining the risk of AMD due to sunlight exposure among people who live in tropical environments met our inclusion criteria, which also resulted in an underestimation of the risk.

Factors leading to the overestimation of the true association cannot be ignored. One such factor is that the unadjusted OR revealed a significant risk but the OR of the adjusted group did not. A similar result was found for the non-population-based and population-based subgroups, indicating that the pooled OR might be raised due to methodological deficiencies.

The limitations of this meta-analysis should be noted. First, due to various grouping criteria and methodological limitations, the pooled OR might be underestimated. Second, the eligible studies only covered those that were written in English and Chinese, thus there may have been a language bias. In addition, although the funnel plot looked asymmetrical, the result of Egger's test was not significant (p=0.079). Therefore, there was insufficient evidence to conclude that publication bias existed in our study. Another issue is that our meta-analysis did not include studies performed in tropical areas or the southern hemisphere. Despite these limitations, this analysis makes an important contribution to the field because this study was the first meta-analysis to explore the relationship between sunlight exposure and AMD.

CONCLUSION

In summary, the epidemiological literature published to date indicates that individuals with higher levels of sunlight exposure are at significantly increased risk of AMD. Subgroup analysis suggested latitude might be a covariate that is negatively correlated with the strength of association, although the meta-regression offered insufficient evidence to support it. In contrast, the meta-regression demonstrated that the OR significantly decreased with increasing GDP per capita. The source of the study population and the methodological quality of the studies were also determined to be potential sources of heterogeneity. In the future, more studies using larger scales and better methodologies will help confirm our findings, will identify other potential risk factors for AMD, and will clarify the uncertain relationship between OR strength and latitude.

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Contributors GCL provided the idea for this meta-analysis. The article was mainly written by GYS, and was revised mainly by GCL. They also participated in extracting data from eligible papers. LW supervised the data analysis. All co-authors participated in the discussion that aimed at forming a consensus. All authors have read and approved the final manuscript. G-CL and GYS contributed equally, and are the co-first authors for this paper.

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