Systematic Review and Meta-Analysis

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Risk factors for age-related macular degeneration

Updated systematic review and meta-analysis

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Abstract

Background: Age-related macular degeneration (AMD) is a leading cause of irreversible visual loss in the elderly population, affecting millions of the people worldwide. AMD has a substantial effect on quality of life in older individuals. Understanding and identifying risk factors are crucial for developing preventive strategies.

Methods: Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, we conducted a comprehensive literature search across databases including PubMed, Scopus, and Web of Science up to January 28, 2024. Studies were selected using standardized inclusion and exclusion criteria, and the quality of the studies was assessed via the Newcastle Ottawa Scale. Meta-analysis was conducted using Review Manager software to pool the odds ratio (OR) of each included risk factors at the 95% confidence interval (CI).

Results: Eighteen of the 2640 identified studies met the inclusion criteria for the meta-analysis. Older age compared to younger age, male gender compared to female gender, smoking, hypertension, cardiovascular diseases, and diabetes were statistically significant predictors for AMD occurrence, with ORs of 1.11 (95% CI = 1.06–1.15, $P < .00001$), 1.63 (95% CI = 1.13–2.35, $P = .009$), 1.86 (95% CI = 1.33–2.6, $P = .0003$), 1.24 (95% CI = 1.09–1.4, $P = .0007$), 1.44 (95% CI = 1.11–1.87, $P = .006$), and 1.44 (95% CI = 1.3–1.6, $P < .00001$), respectively. Other factors, such as body mass index, cerebrovascular diseases, cholesterol, and triglycerides, were not significantly associated with AMD.

Conclusion: This updated meta-analysis highlights the significance of modifiable risk factors for AMD, including smoking, hypertension, cardiovascular diseases, and diabetes. Early identification of AMD accompanied by strategic management of these modifiable risk factors may preserve patients' visual acuity without advancing to advanced stages.

Abbreviations: AMD = age-related macular degeneration, BMI = body mass index, CI = confidence interval, CRP = C-reactive Protein, CVD = cardiovascular disease, DM = diabetes mellitus, HDL = high-density lipoprotein, HTN = hypertension, HTs = hormonal treatments, MeSH = medical subject headings terms, NR = not reportedOR = odds ratio, PRISMA = preferred reporting items for systematic reviews and meta-analyses, PROSPERO = the International prospective register of systematic reviews, RPE = retinal pigment epithelium, SDstandard deviation WHO = World Health Organization.

Keywords: age-related macular degeneration, AMD, meta-analysis, risk factors, systematic review

1. Background

Age-related macular degeneration (AMD) is the most prevalent cause of blindness in the elderly population, and it is considered a chronic foveal condition that affects a significant portion of the global population.[1] The worldwide incidence of AMD cases is estimated to be between 30 and 50 million, and as people age, these numbers are expected to rise significantly.[1] This condition is divided into 2 categories: Dry and Wet AMD. The presence of lipid and protein deposits known as drusen, which are found between the retinal pigment epithelium (RPE) and the Bruch membrane and may be linked to alterations in retinal pigmentation, are indicative of dry or early AMD, which is asymptomatic. While late AMD, also known as wet AMD, is a vision-threatening condition that causes choroidal neovascularization to occur in the retina.[2]

According to the World Health Organization, in the absence of effective intervention and medical treatment for AMD, the global population affected by this condition is expected to increase to approximately 288 million individuals by the year

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The datasets generated during and/or analyzed during the current study are publicly available.

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2040.[3] In developed nations, AMD is the primary cause of irreversible vision impairment and blindness in people 60 years of age and older. Therefore, it significantly decreases the quality of life of patients and is a leading cause of depression and impairment in the elderly population.[3] It is projected that the health and socioeconomic burden associated with AMD will rise significantly in the near future because of the limited treatment options available for the wet type of the disease and the continually increasing geriatric population.[4,5]

Although the exact cause of AMD is still unclear, a number of studies have suggested that it results from a complicated interplay of hereditary, environmental, and personal variables.[6] As people age, waste products containing lipofuscin accumulate in the cells of the RPE. This accumulation is further exacerbated by malfunction of the Bruch membrane, which increases the membrane's permeability and leads to the deposition of proteins and lipids between the Bruch membrane and the retinal pigment layer. After several years, the death of RPE cells eventually results in the death of photoreceptor cells, which causes vision loss. Certain studies have shown that molecular factors may be the cause of AMD, as evidenced by the accumulation of C-reactive protein (CRP) in complement factor H.[7]

Due to the absence of definitive treatment for AMD and its complications, preventive strategies are needed. A critical aspect in the prevention of AMD is to remain informed about the associated risk factors and to acquire the necessary comprehension to identify and manage any preventable comorbidities that could contribute to its development. Therefore, we performed this systematic review and meta-analysis to provide an updated review on the last published study that was more than 2 years ago.[8]

2. Methods

This systematic review and meta-analysis followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines[9] and utilized the methodological framework provided by the Cochrane Handbook of Systematic Reviews of Interventions.[10] The review protocol was prospectively registered with the International prospective register of systematic reviews (PROSPERO) database (registration ID: CRD42023479050).[11]

In this study, 3 reviewers conducted study selection independently, while other reviewers independently extracted data and assessed study quality. Eventually, all coauthors reviewed the final data and discussed all the points of disagreements, with additional input as needed.

2.1. Literature search strategy

A comprehensive search strategy was implemented to identify relevant studies published within the preceding 2 decades, up to January 28, 2024. The databases searched included PubMed, Scopus, and Web of Science. The search approach was developed in cooperation with senior authors and included the use of Medical Subject Headings (MeSH) terms, free text terms, and the application of Boolean operators. The search string was formulated as follows: "(AMD OR ARMD) AND (risk factor OR risk factors OR determinant) AND (age OR smoking OR cigarette smoking OR cataract surgery OR family history OR BMI OR cardiovascular disease OR hypertension OR blood pressure OR HTN OR fibrinogen OR gender OR ethnicity OR diabetes OR DM OR iris color OR cerebrovascular disease OR stroke OR cholesterol OR HDL OR triglycerides OR serum lipids OR edema OR edema OR complications OR satisfaction) AND (prospective cohort OR case control OR cross-sectional studies)." The reference lists of the included studies were thoroughly reviewed to identify any additional relevant publications.

2.2. Study selection

Studies were first screened by the titles and abstracts using Rayyan QCRI software.[12] The full texts of the included articles were subsequently screened. Inclusion criteria were as follows: studies published without time frame limitations; English-language publications; observational (cohort, case-control, cross-sectional) studies; studies involving adult participants; and studies reporting data on predefined outcomes of interest. Exclusion criteria included non-English publications, studies not addressing the outcomes of interest, pediatric studies, narrative reviews, case reports, case series, and studies with a high risk of bias or low methodological quality. Duplicate studies were identified and excluded.

2.3. Outcome measures

The primary outcome measure in this study was late AMD, defined as neovascular AMD and geographic atrophy. For each study, we included data across all available time points, including baseline, 3 months, 6 months, and follow-up, and all available measures.

2.4. Data extraction

A structured data extraction sheet was prepared in Microsoft Excel for the data extraction. The baseline data of the included studies were extracted, encompassing variables such as sample size, study design, country, age, and gender. Additionally, outcome data presented as the prediction effect size were extracted, including the odds ratio (OR) for different risk factors, such as age, gender, body mass index (BMI), smoking, hypertension, cardiovascular diseases, diabetes, cerebrovascular diseases, triglycerides levels, and total cholesterol.

2.5. Quality assessment

The quality of the included observational cohort studies was appraised using the Cochrane-provided Newcastle-Ottawa scale tool.[13] With the exception of the comparison question, which is eligible for 2 stars, each of the 8 questions can receive a maximum of 1 star. As a result, zero is the lowest score, and 9 is the highest. Research with a score of 0 to 3 was deemed to be of low quality, 4 to 6 was regarded as of moderate quality, and 7 to 9 was deemed to be of high quality.

2.6. Meta-analysis

The Meta-analysis was conducted using Review Manager version 5.4 software[14] We used the generic inverse variance for the pooled analysis of ORs by applying the random-effect model to account for heterogeneity among the studies. We implemented a confidence interval (CI) of 95%, and a *P*-value was considered statistically significant if it was ≤ .05. Heterogeneity was assessed using the I^2 statistic and a *P*-value of .05.

2.7. Sensitivity analysis

Sensitivity analysis was conducted using the leave-one-out method on OpenMetaAnalyst to investigate which studies caused heterogeneity present in the heterogeneous outcomes.

2.8. Publication bias

Publication bias was evaluated for the variables of age and smoking via funnel plot asymmetry analyses conducted in Review Manager (RevMan) version 5.4 software.[15]

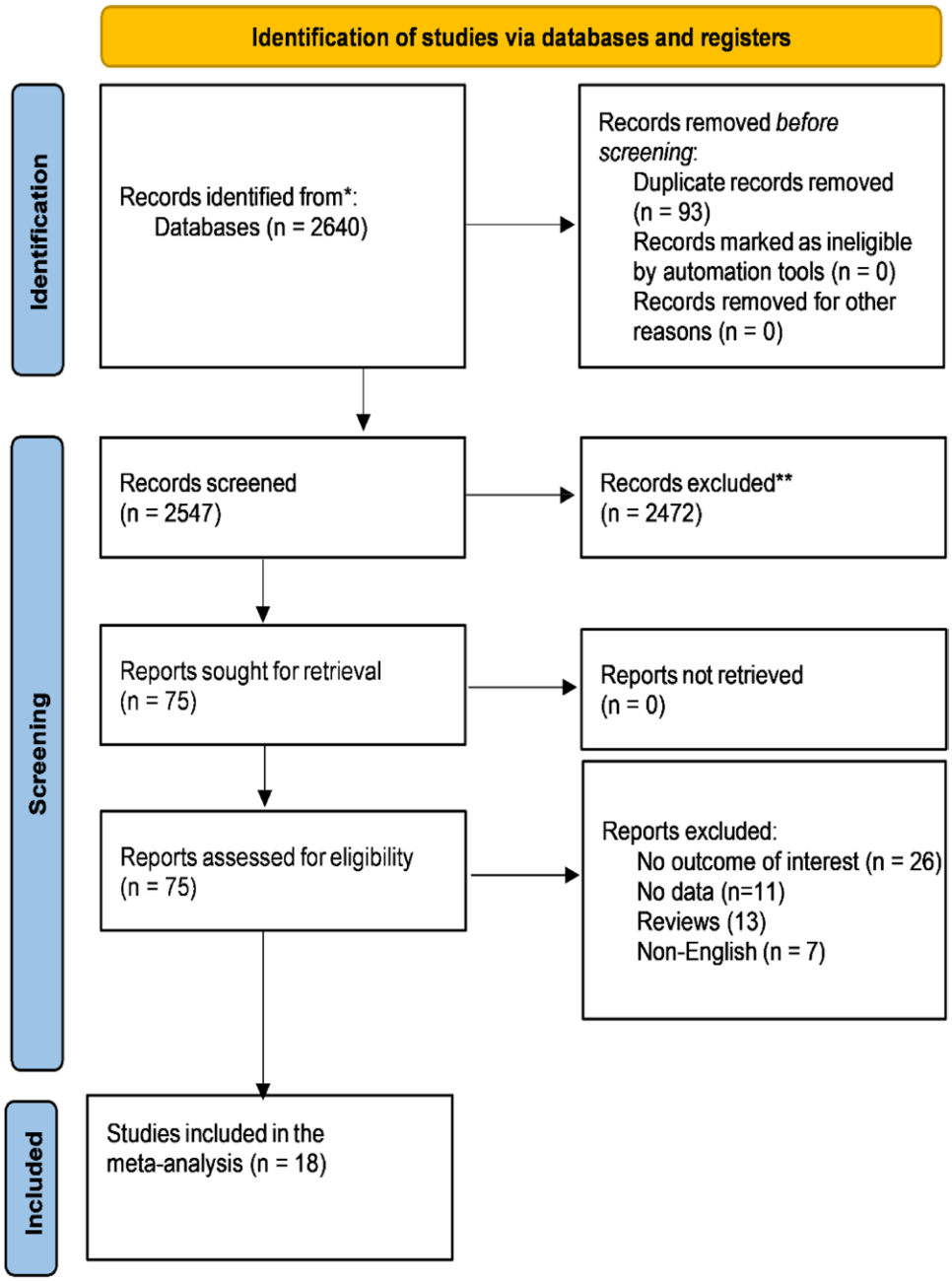

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for the searching and screening.

3. Results

3.1. Search results and screening

Following a comprehensive search across relevant databases, a total of 2640 articles were initially identified, with 93 duplicates. Subsequently, 2547 articles underwent title and abstract screening, leading to the exclusion of 2472 articles. This process left 75 articles for full-text screening. A more thorough revision was done to the remaining 75 studies. Thirteen of these were review articles that did not meet the inclusion criteria, 7 were non-English articles, 26 were eliminated because of irrelevant results, and 11 because there was not enough data for a meta-analysis. A final number of 18 studies were included in the meta-analysis (Fig. 1).[16–33]

3.2. Quality assessment

The quality assessment revealed that among the cross-sectional studies, 3 were categorized as high quality, while 4 were rated as moderate quality. Among the case-control studies, 2 were deemed high quality, and 1 was classified as moderate quality. Concerning cohort studies, 3 were identified as high quality, with 5 were categorized as moderate quality (Table 1).

3.3. Baseline characteristics

This systematic review and meta-analysis encompassed a total of 44,440 patients who were diagnosed with AMD and whose ages ranged from 40 to over 85 years old. Among the 18 included studies, the predominant study design was cohort

Table 1

Quality assessment of included studies using the Newcastle Ottawa scale for case-control studies.

Study name	Representativeness of the samples (★)	Sample size (★)	Nonresponse rate (★)	Ascertainment of screening/ surveillance tool (max★★)	The potential confounders were investigated by subgroup analysis or multivariable analysis (★)	Assessment of the outcome (max★★)	Statistical test (★)	Quality level
Cachulo 2015	★	★	–	★	★	★★	★	High (7)
Cackett 2008	★	–	★	★★	★	★★	★	High (8)
Fraser-Bell 2005	★	–	–	–	★	★★	★	Moderate (5)
Fraser-Bell 2008	★	–	–	★	★	★	★	Moderate (5)
Kawasaki 2008a	–	–	–	★	★	★	★	Moderate (4)
Kawasaki 2008b	★	★	★	★	★	★★	★	High (8)
Park 2023	★	★	★	★	★	★	★	Moderate (7)

Study name	Is the case definition adequate? (★)	Representativeness of the cases (★)	Selection of Controls (★)	Definition of Controls (★)	Comparability of cases and controls on the basis of the design or analysis (max★★)	Ascertainment of exposure (★)	Same method of ascertainment for cases and controls (★)	Nonresponse rate (★)	Quality level
Hogg 2008	★	★	★	★	★	★	–	–	Moderate (6)
Hu 2016	★	★	★	★	★★	★	★	–	High (8)
Mehta and Daigavane 2022	★	★	★	★	★	★	★	–	High (7)

Study name	Representativeness of the exposed cohort (★)	Selection of the non exposed cohort (★)	Ascertainment of exposure (★)	Demonstration that outcome of interest was not present at start of study (★)	Comparability of cohorts on the basis of the design or analysis (max★★)	Assessment of outcome (★)	Was follow-up long enough for outcomes to occur? (★)	Adequacy of follow-up of cohorts (★)	Quality level
Buch 2005	★	★	★	–	★	★	★	–	Moderate (6)
Anastasopoulos 2018	★	★	★	–	★	★	★	★	High (7)
Leske 2006	★	★	★	–	★★	★	★	–	High (7)
Miyazaki 2005	★	★	★	–	★	★	–	–	Moderate (5)
Tan 2007	–	★	★	–	★	★	★	–	Moderate (5)
Tomany 2004	★	★	★	–	★	★	★	–	Moderate (6)
Hogg 2023	★	★	★	–	★★	★	★	★	High (8)
Cho 2014	–	★	★	–	★	★	★	★	Moderate (6)

(8 studies), followed by 7 cross-sectional studies and 3 case-control studies. These studies were conducted across various countries, including USA, UK, Japan, Korea, Denmark, and others, as summarized in Table 2.

3.4. Meta-analysis

3.4.1. Findings by risk factor.

1. **Age:** With an OR of 1.11 (95% CI = 1.06–1.15; $P < .00001$), advanced age was found to be a significant risk factor for AMD. Figure 2 demonstrates significant heterogeneity ($I^2 = 84\%$, $P < .00001$).
2. **Gender:** With an OR of 1.63 (95% CI = 1.13–2.35; $P = .009$), showed that male gender was associated with increased risk of AMD compared to female gender, with OR of 1.63 (95% CI = 1.13–2.35, $P = .009$) and there was no heterogeneity among the results ($I^2 = 36\%$, $P = .15$; Fig. 3).
3. **Smoking:** Exhibited a significant association with increased risk of AMD with OR of 1.86 (95% CI = 1.33–2.6, $P = .0003$), and there was significant heterogeneity among the results ($I^2 = 81\%$, $P < .00001$; Fig. 4).
4. **Hypertension:** With an OR of 1.24 (95% CI = 1.09–1.4; $P = .0007$), seems to be a significant determinant of AMD. There was no evidence of heterogeneity ($I^2 = 0\%$, $P = .85$; (Fig. 5).
5. **Cardiovascular Disease:** An OR of 1.44 (95% CI = 1.11–1.87; $P = .006$) indicated a significant correlation between AMD and CVD. Figure 6 shows moderate heterogeneity ($I^2 = 67\%$, $P = .003$).
6. **Diabetes:** Due to its OR of 1.44 (95% CI = 1.3–1.6; $P < .00001$), diabetes was considered a significant risk factor for AMD. There was no evidence of heterogeneity ($I^2 = 0\%$, $P = .46$; Fig. 7).
7. **Other Risk factors:** There was no statistically significant association between AMD and other risk factors, such as BMI, cerebrovascular disorders, cholesterol, or triglyceride levels (Figs. 8–11).

3.5. Sensitivity analysis

Sensitivity analysis was conducted using the leave-one-out method for the association between age and risk of AMD, and the results showed that the removal of each study was not associated with resolving heterogeneity. However, the heterogeneity in the smoking outcome was resolved by the removal of studies by Park et al[30] and Hogg et al[23] (Fig. 12).

3.6. Publication bias

The assessment of publication bias using funnel plots for age and smoking outcomes showed no evidence of publication bias (Figs. 13 and 14).

Table 2

Baseline characteristics of the included studies.

Study ID	Country	Design	Age (yr)	Gender, male n (%)	Sample size
Buch 2005	Denmark	Cohort	60 to 80	53 (32.5%)	163
Cachulo 2015	Portugal	Cross-sectional	55 to >85	1291 (43.4%)	2975
Cackett 2008	Singapore	Cross-sectional	40 to 80	1566 (48%)	3280
Anastasopoulos 2018	USA	Cohort	70.8 (5.8)	502 (55.5%)	904
Fraser-Bell 2005	USA	Cross-sectional	40 to 89	310 (72.4%)	428
Fraser-Bell 2008	USA	Cross-sectional	54.6	623 (1484)	1484
Hogg 2008	UK	Case-control	74.97 (6.76)	188 (45.1%)	417
Hu 2016	Taiwan	Case-control	67.4 (12.1)	1174 (59.6%)	1970
Kawasaki 2008a	Singapore	Cross-sectional	59.4 (11.3	1570 (48%)	3265
Kawasaki 2008b	Japan	Cross-sectional	67.5 (9.1)	31 (48.4%)	64
Leske 2006	USA	Cohort	55 (10.3)	942 (2356)	2356
Miyazaki 2005	Japan	Cohort	64 (8)	384 (40%)	961
Tan 2007	Australia	Cohort	64.4	1040 (42.4%)	2454
Tomany 2004	Australia	Cohort	63.3	4098 (43%)	9523
Mehta and Daigavane 2022	India	Case-control	65.8 (6.72)	54 (41.54%)	130
Hogg 2023	UK	Cohort	63.5 (8.9)	NR	3386
Cho 2014	Korea	Cohort	55.2 (0.2)	3419 (43.2%)	7899
Park 2023	Korea	Cross-sectional	>50	NR	2781

Age is presented as mean (SD) or range.
NR = not reported, SD = standard deviation.

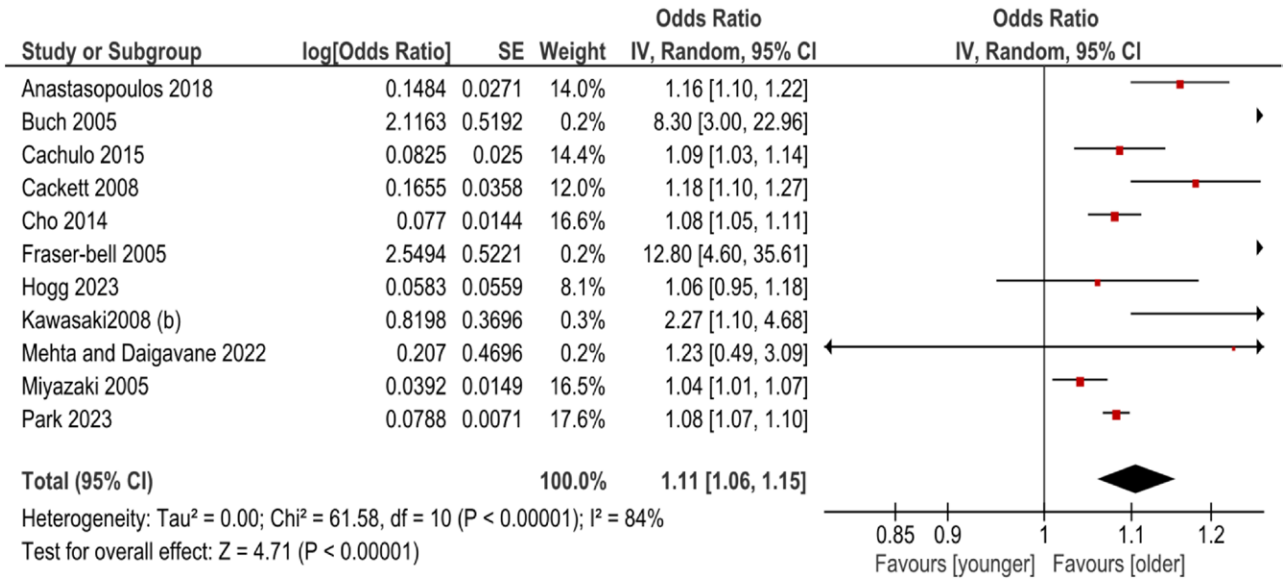

Figure 2. The association of older age with increased risk of AMD. AMD = age-related macular degeneration, CI = confidence interval, IV = independent variable, SE = standard error.

4. Discussion

The present study demonstrated the presence of several risk factors for the occurrence of AMD. This includes older age, male gender, smoking, hypertension, cardiovascular diseases, and diabetes. On the other hand, other factors showed no statistical significance regarding the occurrence of AMD, such as cerebrovascular diseases, BMI, cholesterol, and triglyceride levels.

In contrast to the last published review,[8] our comprehensive search was conducted through 3 different databases (PubMed, Scopus, and Web of Science), whereas they used 2 databases (Medline and Cochrane). In addition, we reported a significant association with male gender, whereas the previous review found inconsistent associations with gender.

The current study found that advanced age is a significant risk factor for AMD. This finding is consistent with that of Evans[16] who reported that age is the greatest risk factor for AMD. Furthermore, although age-related alterations can contribute to AMD pathogenesis, a disease phenotype can only be created when these changes are paired with additional genetic, environmental, and lifestyle risk factors, contributing to the complex interplay underlying AMD pathogenesis.[17] We also noted that a higher risk of AMD is linked to cardiovascular disorders.

In accordance with our results, a study by Feng et al[18] showed that AMD increases the risk of CVDs, and late-stage AMD has a greater influence on CVD risk than early-stage AMD. Evidence also indicates that the progression of subclinical cardiovascular disease is higher in AMD patients than in controls,[19] but not vice versa.[20] This corroborates the causal direction shown in our investigation. In addition, previous studies by Duan et al[21] and Vassilev et al[22] revealed that AMD is strongly related to an elevated risk of myocardial infarction. Furthermore, consistent with the literature, multiple other studies[23–25] showed a correlation between both AMD and hypertension. However, in contrast to earlier findings, other studies have shown no significant relationships between AMD and blood pressure.[26,27]

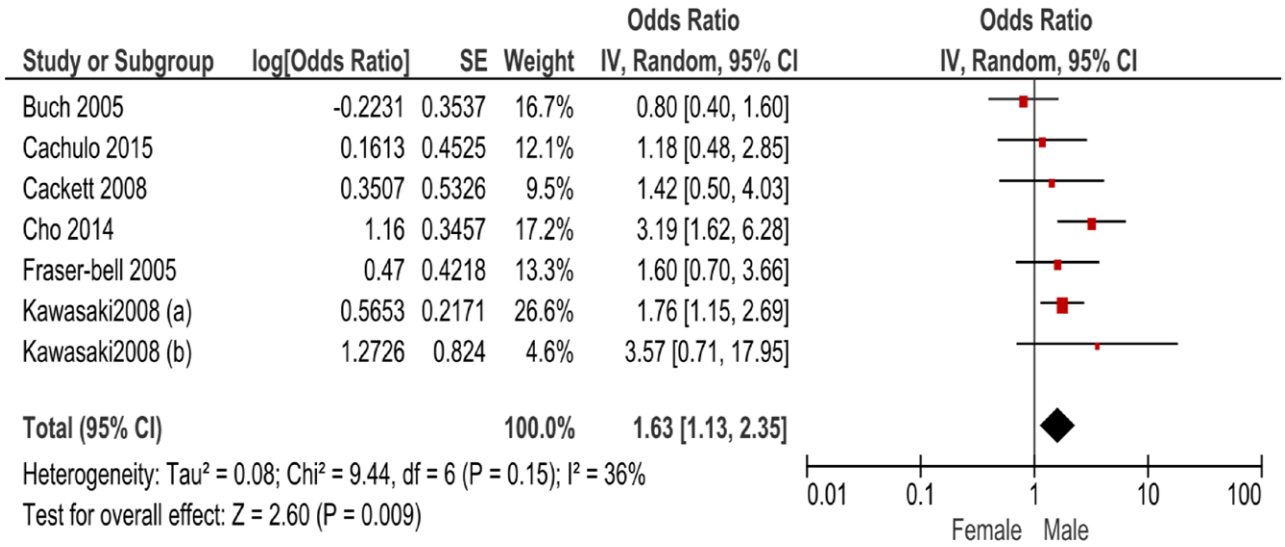

Figure 3. Comparison between males and females regarding the risk of AMD. AMD = age-related macular degeneration, CI = confidence interval, IV = independent variable, SE = standard error.

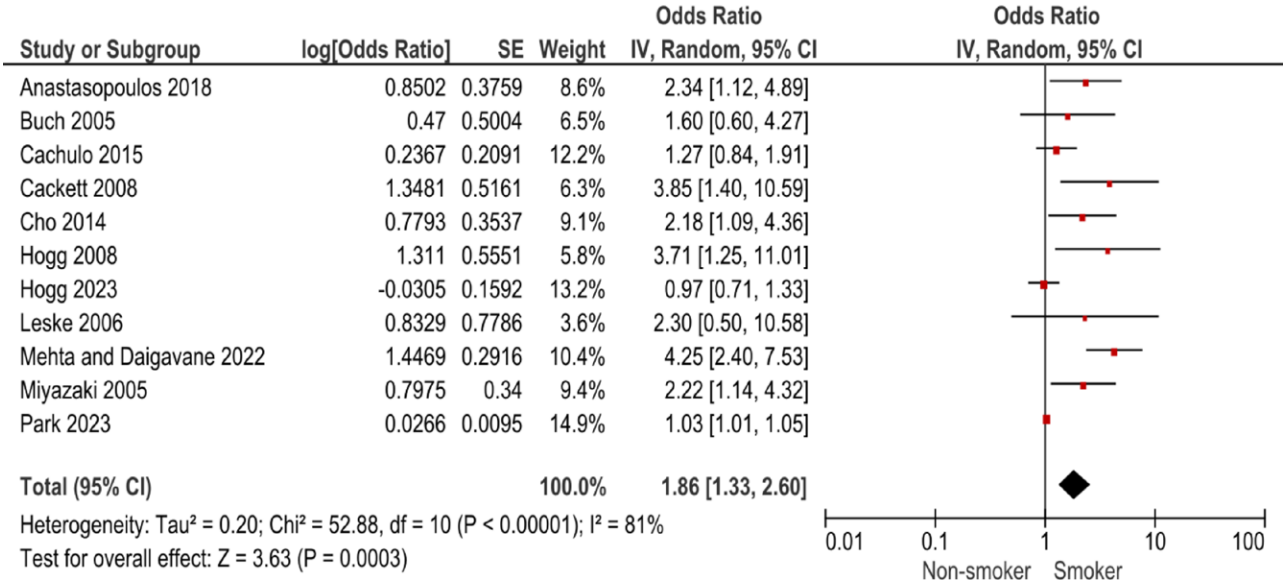

Figure 4. The association between smoking and increased risk of AMD. AMD = age-related macular degeneration, CI = confidence interval, IV = independent variable, SE = standard error.

Based on the National Eye Institute, female patients accounted for 65% of prevalent AMD cases in 2010.[28] However, mixed results regarding gender were reported in previous literature.[29] This study reported higher susceptibility among males compared to females. A possible explanation for this might be the preventive impact of hormonal treatments on the development of AMD in women.[30]

Another important finding is the strong association between AMD and smoking status. While Thornton et al[31] confirmed the strong association, other studies found no association between smoking and AMD.[32,33] Diabetes mellitus was also shown to be significantly associated with AMD in the present study, which corresponds to prior literature.[34]

Additionally, our findings regarding the nonsignificant association of cholesterol and triglycerides with AMD add to the ongoing debate about the role of lipids in AMD pathogenesis. While some studies have identified elevated lipids as a risk factor,[35,36] our analysis suggests that the impact may be less direct than previously thought. This highlights the necessity for further research to dissect the lipid-AMD relationship, potentially examining lipid subtypes and their interactions with other metabolic conditions. Divergent viewpoints exist concerning the correlation between AMD and stroke. Numerous studies revealed no significant associations between AMD and stroke, in line with the results of the current study.[37,38] Moreover, mixed reports were published regarding the association of BMI and AMD. Ulaş et al[39] demonstrated that high BMI is associated with an increased risk of late AMD. Alternatively, Tomany et al[40] found no significant association between AMD and BMI, which is compatible with our results. The existing meta-analysis provides a comprehensive overview of risk factors that lead to AMD. However, there are several limitations. These include the different study designs of the included

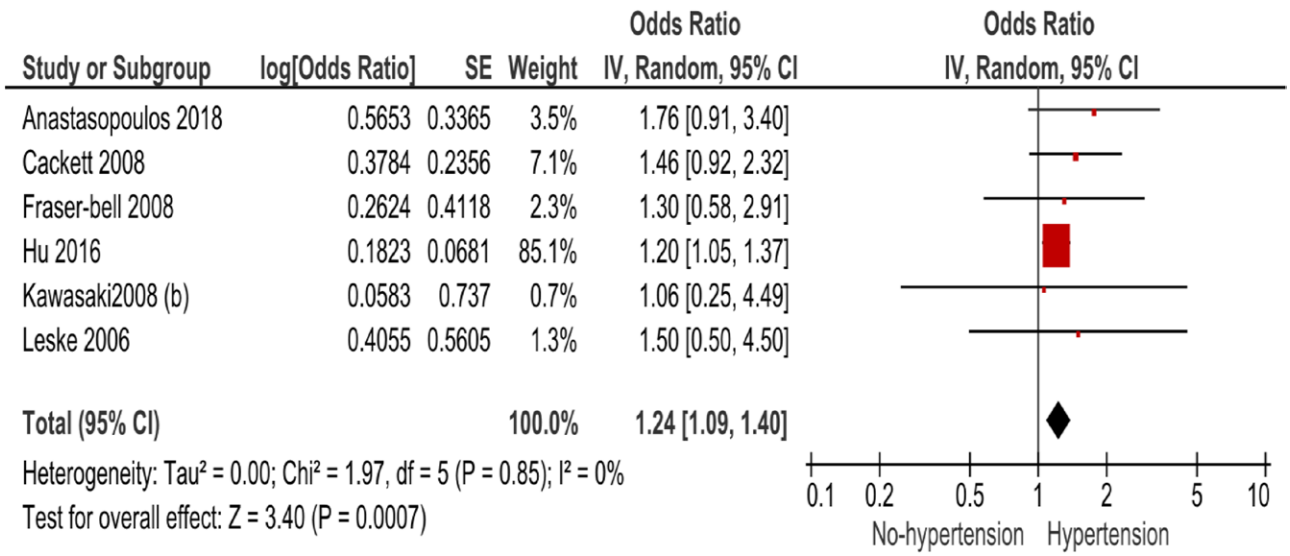

Figure 5. The association between hypertension and risk of AMD. AMD = age-related macular degeneration, CI = confidence interval, IV = independent variable, SE = standard error.

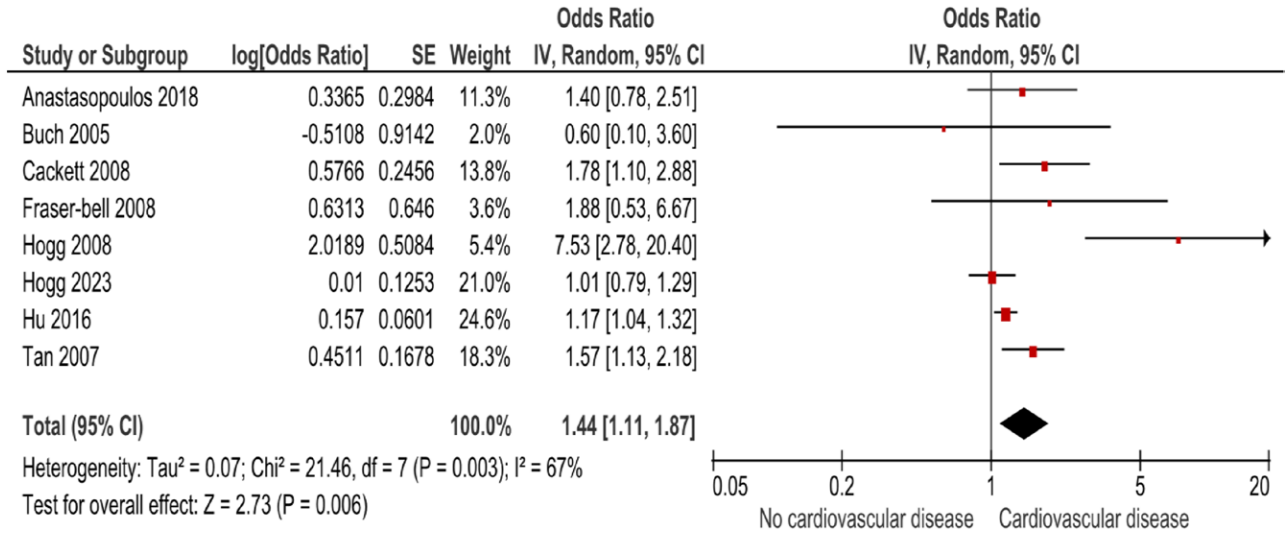

Figure 6. The association between cardiovascular diseases and risk of AMD. AMD = age-related macular degeneration, CI = confidence interval, IV = independent variable, SE = standard error.

articles, such as cross-sectional, case-control, and cohort studies. The observational nature of these study designs marks a major limitation. The differences in adjustments of the calculated OR in the included studies may account for heterogeneity in some outcomes. Therefore, we recommend further longitudinal studies with adjustments for all possible confounders to provide more accurate insights into the main risk factors of AMD.

5. Conclusion

There are few therapeutic options available for advanced-stage AMD. AMD is a complex illness that results in irreversible sight loss and is linked to a number of modifiable and non-modifiable risk factors. When sight loss has already occurred and there is no viable treatment, the condition is typically diagnosed in its latter stages. Therefore, early diagnosis is the key to prevent the progression of this disease.

Author contributions

Conceptualization: Raghad Babaker, Lama Alzimami, Abdullah Al Ameer, Majed Almutairi, Rahaf Alam Aldeen, Hamad Alshatti, Najwan Al-Johani.

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Project administration: Raghad Babaker, Lama Alzimami, Abdullah Al Ameer, Majed Almutairi, Rahaf Alam Aldeen, Hamad Alshatti, Najwan Al-Johani.

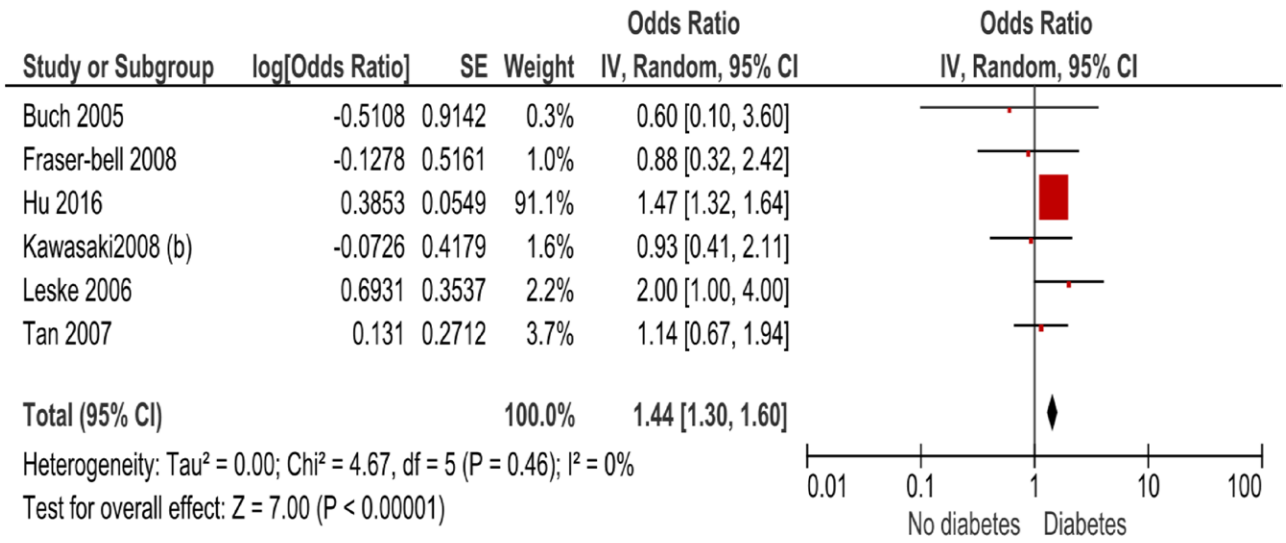

Figure 7. The association between diabetes and risk of AMD. AMD = age-related macular degeneration, CI = confidence interval, IV = independent variable, SE = standard error.

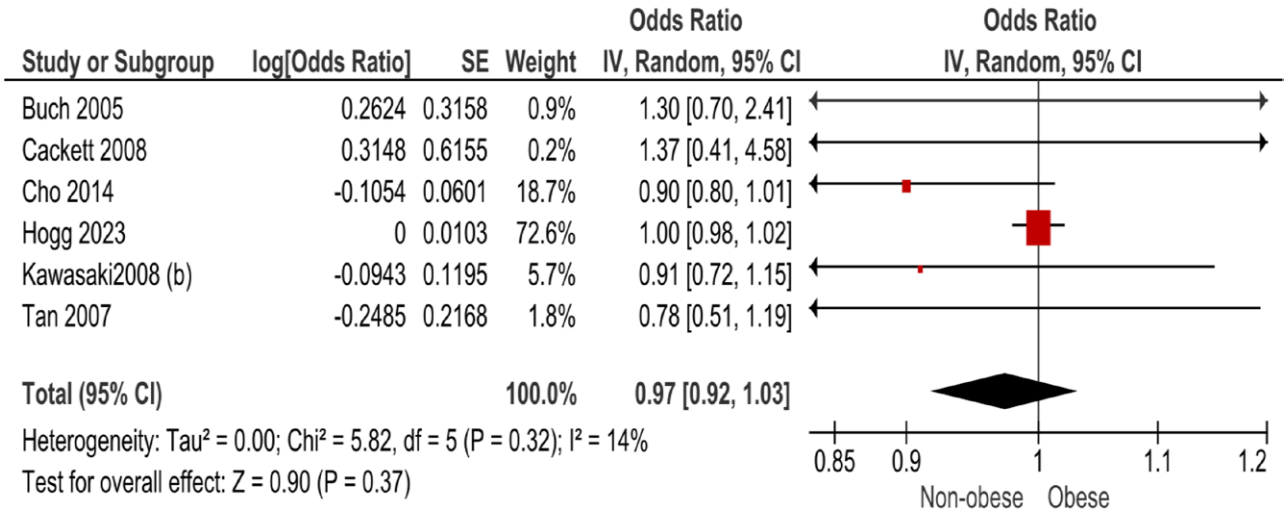

Figure 8. The relationship between BMI and risk of AMD. AMD = age-related macular degeneration, BMI = body mass index, CI = confidence interval, IV = independent variable, SE = standard error.

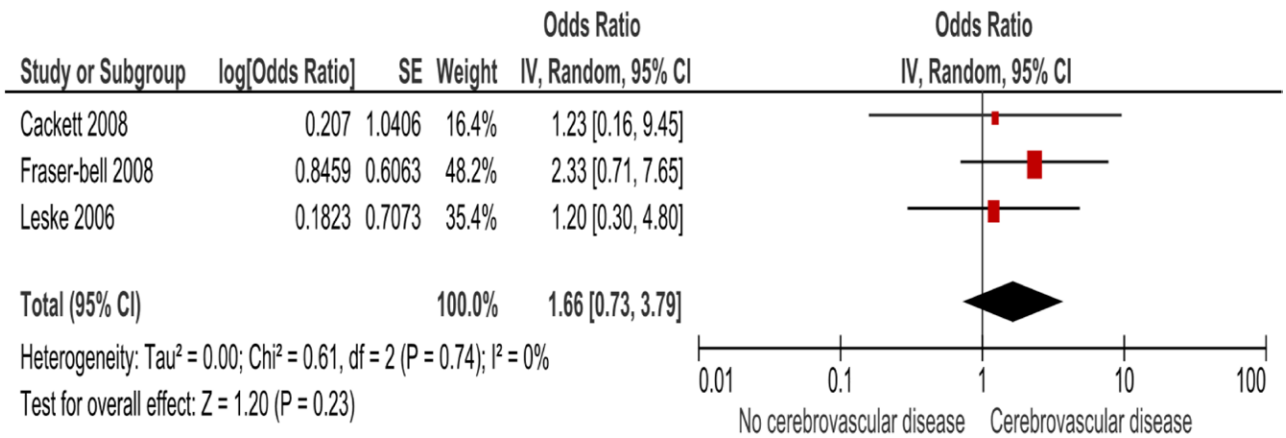

Figure 9. The relationship between cerebrovascular diseases and risk of AMD. AMD = age-related macular degeneration, CI = confidence interval, IV = independent variable, SE = standard error.

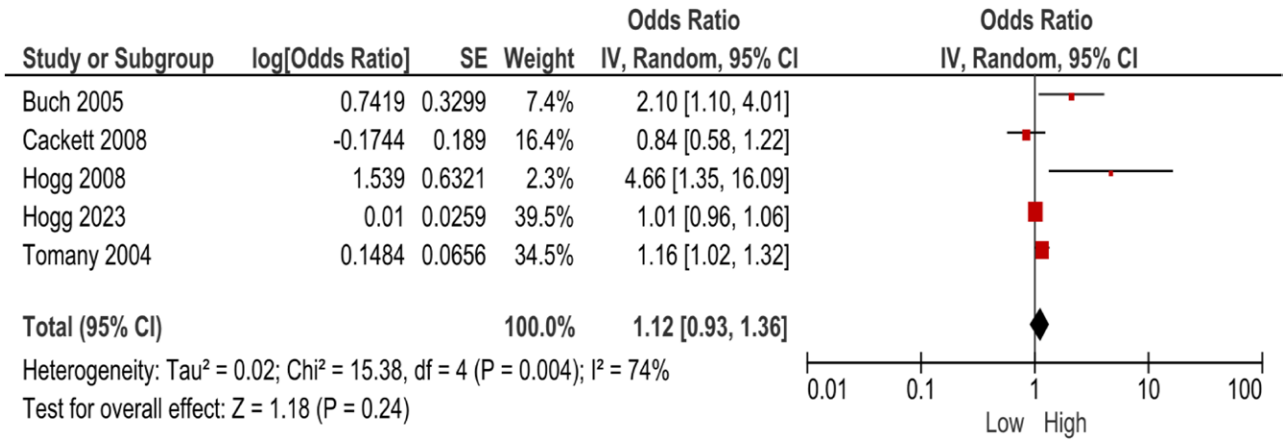

Figure 10. The relationship between cholesterol levels and risk of AMD. AMD = age-related macular degeneration, CI = confidence interval, IV = independent variable, SE = standard error.

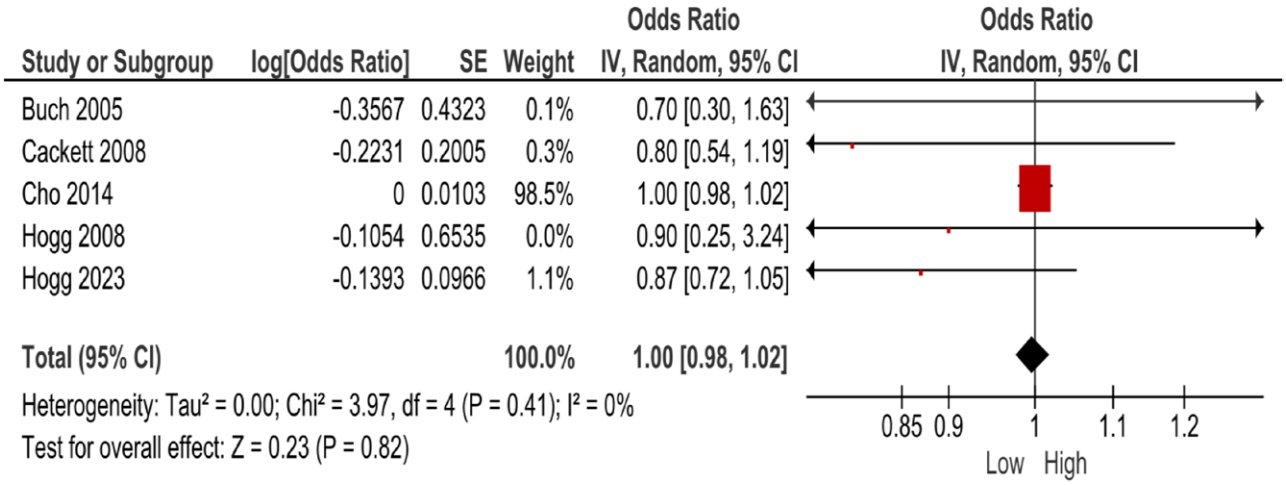

Figure 11. The relationship between triglycerides levels and risk of AMD. AMD = age-related macular degeneration, CI = confidence interval, IV = independent variable, SE: standard error.

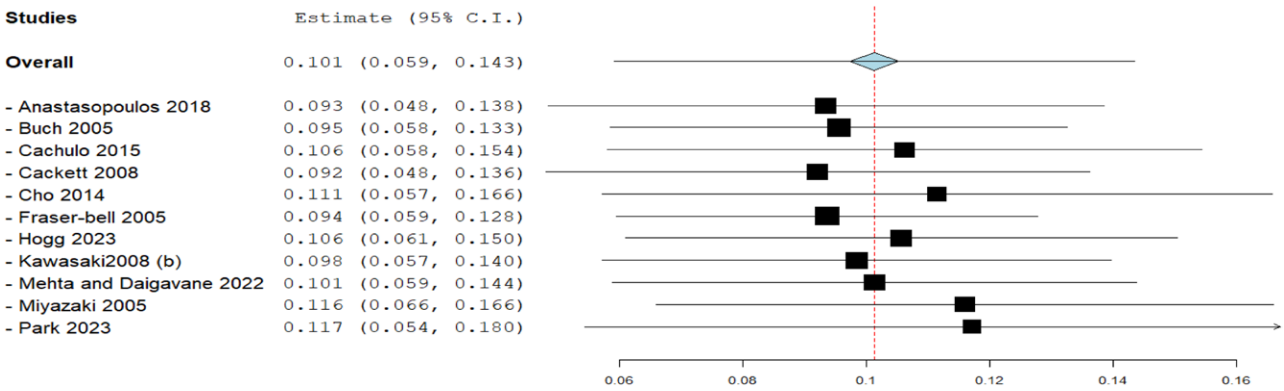

Figure 12. Leave-one-out analysis of the association of age and smoking with the risk of age-related macular degeneration.

Resources: Raghad Babaker, Lama Alzimami, Abdullah Al Ameer, Majed Almutairi, Rahaf Alam Aldeen, Hamad Alshatti, Najwan Al-Johani.
Software: Raghad Babaker, Lama Alzimami, Abdullah Al Ameer, Majed Almutairi, Rahaf Alam Aldeen, Hamad Alshatti, Najwan Al-Johani.
Supervision: Raghad Babaker, Abdulaziz Al Taisan.
Validation: Raghad Babaker.
Visualization: Raghad Babaker.
Writing – original draft: Raghad Babaker, Lama Alzimami, Abdullah Al Ameer, Majed Almutairi, Rahaf Alam Aldeen, Hamad Alshatti, Najwan Al-Johani.
Writing – review & editing: Raghad Babaker.

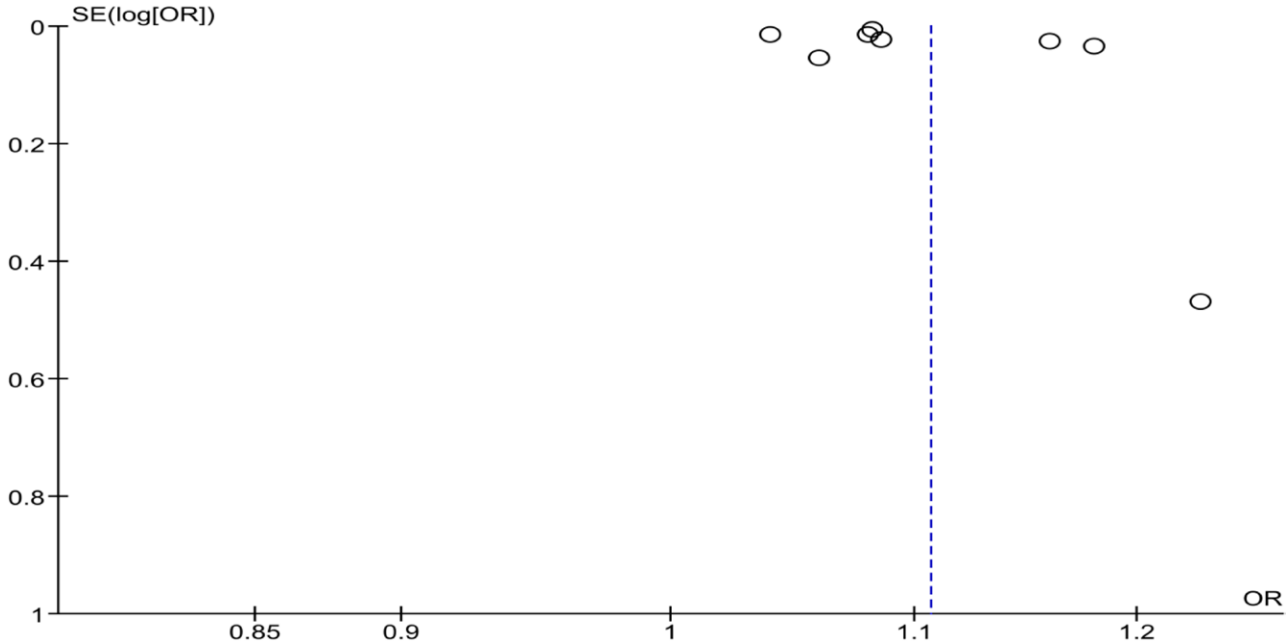

Figure 13. Publication bias of the association between age and risk of AMD. AMD = age-related macular degeneration, OR = odds ratio, SE = standard error.

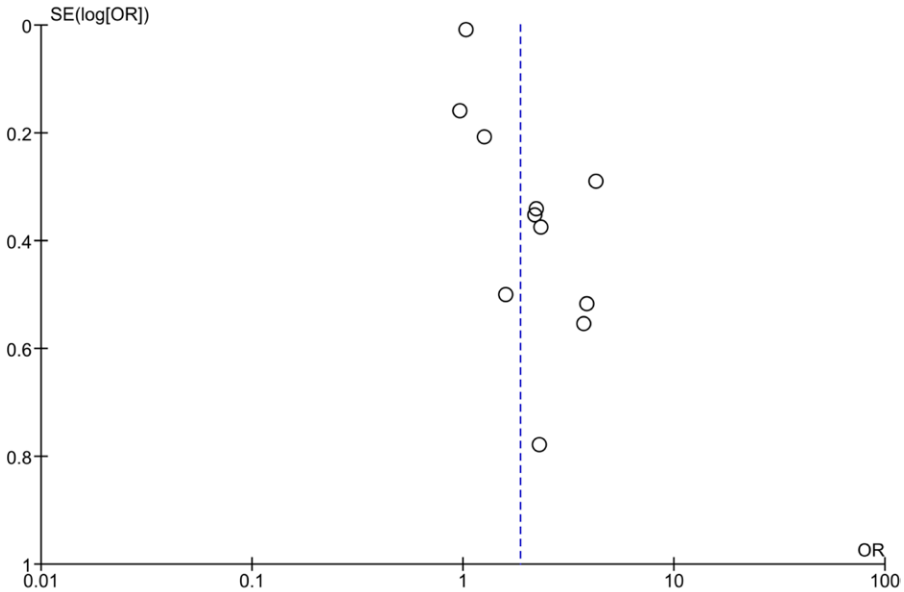

Figure 14. Publication bias of the association between smoking and risk of AMD. AMD = age-related macular degeneration, OR = odds ratio, SE = standard error.

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