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**Research Article**

# Alcohol Intake is Associated with Functional and Structural Alterations in Retinal Microcirculation: A Systematic Review & Meta-Analysis

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## Abstract

**Background:** Alcohol consumption is associated with cardiovascular morbidity; however, its impact on microcirculation remains incompletely understood. We aimed to i) consolidate existing knowledge of the effect of this dietary habit on retinal microcirculation, ii) assess the utility of retinal microcirculation indices to monitor changes in alcohol consumption habits and potentially relevant treatment strategies.

**Methods:** Based on a registered protocol (PROSPERO ID: CRD420251023213) we identified eligible studies evaluating the association of alcohol consumption with: Central Retinal Artery Equivalent (CRAE), Central Retinal Vein Equivalent (CRVE), Arterio-Venous Ratio (AVR), Fractal Dimension (FD), Vascular Skeleton Density (VSD), retinal vascular tortuosity, Vessel Diameter Index (VDI), Wall Cross-Sectional Area (WCSA), Wall-Lumen Ratio (WLR), Flickering Light-Induced Dilation (FID), Retinal Blood Flow (RBF) and Retinal Blood Flow Velocity (RBFV).

**Results:** Overall, 13 studies were identified. Alcohol consumption was associated with narrowed CRAE, dilated CRVE, trend for lower AVR and FD, low vascular tortuosity, VSD and FID values and alteration in VDI (acute effect). Meta-analysis was performed in 9 studies; alcohol intake was significantly associated with narrowed CRAE (heavy alcohol intake, $p<0.05$ and alcohol intake as a continuous variable, $p<0.05$) and larger CRAE (low alcohol intake, $p<0.05$). Gender and age meta-regression analysis were statistically non-significant.

**Conclusion:** Alcohol consumption appears to be associated with adverse, dose-dependent alterations in retinal microcirculation, with the most consistent evidence observed for retinal arteriolar narrowing at higher intake levels. Alcohol intake should be considered when evaluating retinal microcirculation. Retinal indices might represent useful tools in monitoring the effects of alcohol intake reduction interventions; however, this hypothesis requires validation in well-designed studies.

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**Keywords:** CRAE; CRVE; AVR; FD; Tortuosity; FID; Alcohol

**Abbreviations:** AVR - Arteriolar-to-Venular Diameter Ratio; CRAE - Central Retinal Artery Equivalent; CRVE - Central Retinal Vein Equivalent; FD - Fractal Dimension; FID - Flicker light-induced dilation in retinal microvascular diameter; RBF - Retinal Blood Flow; RBFV - Retinal Blood Flow Velocity; VSD - Vascular Skeleton Density; VDI - Vessel Diameter Index; WCSA - Wall Cross-sectional Area; WLR - Wall-lumen Ratio

## Introduction

The retinal microcirculation represents a highly specialized and complex vascular network of the human body. Its evaluation is especially useful for clinical and research purposes, as it enables a quick, easy and non-invasive in vivo observation of the human central nervous system microcirculation [1], providing - at the same time - a window to other microcirculations, such as those of the heart [2,3], the brain [4,5] and the kidney [6,7], that share common anatomical and functional features.

Retinal vascular assessment encompasses both qualitative and quantitative approaches. The latter includes all the clinically visible changes of retinopathy via fundoscopy, such as arteriovenous nicking, flame-shaped retinal hemorrhages, cotton-wool spots and optic disc edema [8]. The former methodology enables a more sensitive and reproducible evaluation of microvascular alterations using standardized structural and functional biomarkers. Central Retinal Artery Equivalent (CRAE), Central Retinal Vein Equivalent (CRVE), Arterio-Venous Ratio (AVR), Fractal Dimension (FD), Vascular Skeleton Density (VSD), retinal vascular tortuosity, Wall Cross-Sectional Area (WCSA) and Wall-Lumen Ratio (WLR) are some of the most widely used structural biomarkers; Flickering Light-Induced Dilation (FID) in retinal vessel diameter, Retinal Blood Flow (RBF) and Retinal Blood Flow Velocity (RBFV) are some of the most widely used functional biomarkers included in important well-designed observational studies [9–15].

Lifestyle factors exert both acute and chronic effects on retinal microcirculation [16]. The available methodologies for monitoring the retinal architecture enable the study of the possible role of these lifestyle factors on fundus damage and occurrence of Cardiovascular Disease (CVD) events (cerebral infarctions-brain, myocardial infarctions-heart and renal failure-kidney) [1]. Among these factors, alcohol consumption is highly prevalent and remains a subject of ongoing debate concerning its CVD effects [17]. Epidemiological evidence suggests a complex, potentially non-linear relationship between alcohol intake and cardiovascular risk, often described as J-shaped, mediated through effects on i) risk factors (e.g., lipid profiles, Carotid Intima-Medial Thickness [cIMT], and insulin sensitivity), ii) hemostatic factors (e.g., fibrinogen levels and platelet reactivity), iii) inflammation and iv) the ischemia–reperfusion mechanism [18,19]. Whether similar dose-dependent effects extend to the retinal microvasculature has not been comprehensively evaluated.

Importantly, adverse retinal microvascular phenotypes, such as narrower CRAE, wider CRVE, reduced FD, increased retinal vascular tortuosity, lower VSD and impaired FID (both arteriolar and venular) have been associated with elevated CVD risk [cardiovascular mortality, incident stroke and incident Coronary Heart Disease (CHD)] [20–26]. Understanding how alcohol consumption influences these retinal biomarkers may provide mechanistic insight into alcohol-related cardiovascular risk and inform both ophthalmic and systemic risk assessment. To date, no systematic review and meta-analysis has comprehensively evaluated the association between alcohol consumption and retinal microvascular structural and functional indices. Therefore, aims of the present study were: (i) to systematically synthesize existing evidence on the relationship between alcohol consumption and retinal microvascular biomarkers, and (ii) to explore whether retinal microvascular indices may serve as potential tools for monitoring alcohol-related vascular effects and lifestyle interventions.

## Methods

This systematic review and meta-analysis was based on a predefined protocol registered to PROSPERO (PROSPERO ID: CRD420251023213), compliant with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines **(Table S1)** [27].

The data supporting the findings of this study are deposited in a database at Cardiovascular Prevention and Research Unit and are available from the corresponding author upon reasonable request.

*Table S1: Fusion Table of MOOSE and PRISMA 2020 Checklists*

| Section and Topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review. | Page 1 |
| **ABSTRACT** | | | |
| Abstract | 2 | See the PRISMA 2020 for Abstracts checklist. | Page 2 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of existing knowledge. | Pages 4,5 |
| Objectives | 4 | Provide an explicit statement of the objective(s) or question(s) the review addresses. | Page 5 |
| **METHODS** | | | |
| Eligibility criteria | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | Page 6 |

| | | | |
|---|---|---|---|
| Information sources | 6 | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. | Page 5 |
| Search strategy | 7 | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | Pages 5,6 & Supplement |
| Selection process | 8 | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | Page 6 |
| Data collection process | 9 | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | Pages 5,6 |
| Data items | 10a | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect. | Page 7 |
| | 10b | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. | Page 7 |
| Study risk of bias assessment | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | Page 8 |
| Effect measures | 12 | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results. | Page 8 |
| Synthesis methods | 13a | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)). | Pages 8,9 |
| | 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | Pages 8,9 |
| | 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | - |
| | 13d | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. | Pages 8,9 |
| | 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). | Pages 8,9 |
| | 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | Page 9 |
| Reporting bias assessment | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | Pages 8,9 |
| Certainty assessment | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. | Pages 8,9 |
| **RESULTS** | | | |
| Study selection | 16a | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. | Page 9 |
| | 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | Figure 1 |
| Study characteristics | 17 | Cite each included study and present its characteristics. | Table 1 & Supplement |
| Risk of bias in studies | 18 | Present assessments of risk of bias for each included study. | Page 8 |
| Results of individual studies | 19 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. | Page 9-13 & Table 1 |
| Results of syntheses | 20a | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. | Pages 13-15 |
| | 20b | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | Pages 13-15 |

| | | | |
|---|---|---|---|
| | 20c | Present results of all investigations of possible causes of heterogeneity among study results. | Page 15 |
| | 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. | Page 15 |
| Reporting biases | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. | Page 13, 15 |
| Certainty of evidence | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | - |
| **DISCUSSION** | | | |
| Discussion | 23a | Provide a general interpretation of the results in the context of other evidence. | Page 15,16 |
| | 23b | Discuss any limitations of the evidence included in the review. | Page 18 |
| | 23c | Discuss any limitations of the review processes used. | Page 18 |
| | 23d | Discuss implications of the results for practice, policy, and future research. | Pages 18,19 |
| **OTHER INFORMATION** | | | |
| Registration and protocol | 24a | Provide registration information for the review, including register name and registration number, or state that the review was not registered. | Page 5 |
| | 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | Page 5,6 |
| | 24c | Describe and explain any amendments to information provided at registration or in the protocol. | - |
| Support | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. | Page 19 |
| Competing interests | 26 | Declare any competing interests of review authors. | Page 19 |
| Availability of data, code and other materials | 27 | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | Page 5 |

*From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71*

*For more information about PRISMA Checklist, visit: http://prisma-statement.org/prismastatement/checklist.aspx***Table S1a.** *Management of the quality scoring criteria (cohort subscale of the Newcastle-Ottawa assessment scale) for all the observational studies included in the current systematic review.*

**This criterion will be assessed only in studies calculating AVR (the cut of point of AVR is 0,82). In these studies, this criterion will be omitted, and the total star of selection could be maximum 4 instead of 5.*

**Literature search**

Two independent reviewers (L.Y. and E.A.) systematically screened PubMed and Scopus (https://pubmed.ncbi.nlm.nih.gov/ and https://www.scopus.com/home.uri) from inception until 1st of November 2025 to identify eligible studies investigating the association between alcohol consumption with the structure (retinal vessel diameter, wall thickness etc.) and blood flow of retinal vasculature. The final database search was updated on 1 February 2026. The search strategy combined terms related to alcohol exposure (described in detail below as exposure biomarkers) with terms describing retinal microvascular biomarkers, including structural and functional indices (described in detail below as outcome biomarkers). The detailed search terms are provided in the supplement ("supplementary methods" section). All reference lists of the derived eligible articles were hand-searched for potential eligible studies not identified through the database search ("snowball" procedure). Only articles in English and studies published after 2000 were considered. Eligible studies were evaluated for possible population overlap in case of same study name, authors, laboratory/university, participant number, chronological period, sample size, outcome under study and type of statistical analysis. In case of overlap, we opted for the most recent study or higher sample size per biomarker. Moreover, duplicates between the two databases were removed. Discrepancies between the two reviewers were solved through team consensus.

**Eligibility criteria**

We considered as eligible published cohort, cross-sectional, case-control studies, case-reports and case-series, as well as primary or secondary analyses of randomized/non-randomized controlled trials and cross-over studies exploring the association between alcohol consumption - on the one hand - and structural / functional retinal vessel biomarkers on the other hand. We included studies of general population or studies focused on specific high-risk populations, such as patients with stroke, hypertension, cardiovascular disease, diabetes mellitus, chronic kidney disease and specific ocular diseases (for example glaucoma). Only studies assessing the retinal microcirculation (branches of the central retinal artery and vein) were included; studies focusing exclusively on the choroidal circulation were excluded.

**Exclusion criteria**

Observational studies with less than 100 participants and interventional studies with less than 20 participants were excluded. Additionally, studies involving children and adolescents, rare genetic disorders, in vitro and animal models were excluded. Moreover, studies in languages other than English, published before 2000, reviews, systematic reviews, narrative reviews and meta-analyses were also excluded.

**Exposure factors:**

The exposure of interest was alcohol consumption, assessed using self-reported questionnaires or interviews in observational studies and standardized alcohol administration protocols in interventional studies. Due to heterogeneity in reporting, alcohol intake was categorized according to study-specific

definitions and, where possible, harmonized into approximate intake categories (low, moderate, high) based on grams of alcohol per day. For the purposes of the meta-analysis, low alcohol consumption was approximated as <10 g/day and high alcohol consumption as >20 g/day, based on prior literature and international guidelines [9,12].

**Outcome measures:**

The primary outcome measures of our study were retinal microvascular biomarkers classified as follows:

i) structural biomarkers: (a) Central Retinal Artery Equivalent (CRAE), (b) Central Retinal Vein Equivalent (CRVE), (c) Arteriolar-to-Venular Diameter Ratio (AVR), (d) Fractal Dimension (arteriolar and venular) (FD), (e) Vascular Skeleton Density (VSD), (f) retinal vascular tortuosity, (g) Vessel Diameter Index (VDI), (h) Wall Cross-Sectional Area (WCSA), (i) Wall-Lumen Ratio (WLR).

ii) functional biomarkers: (a) Flicker Light-Induced Dilation (FID) in retinal microvascular diameters, (b) Flow Density (FDen), (c) Retinal Blood Flow (RBF), (d) Retinal Blood Flow Velocity (RBFV).

Definitions and methodological details for each biomarker are provided in the Supplementary Material.

**Data extraction**

A predefined spreadsheet was used to extract the following data: publication details (authors, year), study information (geographical region, design, population under study, sample size), study sample characteristics (age, sex, body mass index, history of hypertension, diabetes mellitus or dyslipidemia), alcohol consumption, retinal vessel biomarkers ascertainment (assessment method, definition, method/scale of quantification) and mean values and standard deviation of these biomarkers. The corresponding author was contacted in case of missing data.

**Risk of bias assessment**

We evaluated studies for risk of bias using the Newcastle-Ottawa scale [28] and Jadad Assessment Scale [29] for all the observational and interventional studies included, respectively. For the Newcastle-Ottawa scale, the following criteria were assessed: representativeness of the exposed population; selection of the non-exposed group; exposure (alcohol consumption) ascertainment; outcome absence at study onset; comparability of the exposed and non-exposed group for age, hypertension, diabetes and sex; assessment of outcome quality measurement. Cross-sectional studies, by definition, did not receive any points for longitudinal assessment items (outcome absence at study onset, follow-up period length and completion). For the Jadad scale, the following criteria were assessed: randomization, blinding and withdrawals/ dropouts. The detailed pre-defined handling of each criterion for the purposes of this systematic review is outlined in the supplementary tables S2a, S2b, S3a and S3b.

**Statistical analysis**

Meta-analyses were conducted where sufficient and comparable data were available. Due to data availability, quantitative synthesis was feasible only for the structural biomarkers CRAE, CRVE and AVR. For each eligible study, we extracted estimates and 95% CIs of associations between retinal vessel diameter biomarkers and alcohol consumption. We extracted data for associations of CRAE (10 studies), CRVE (8 studies), AVR (5 studies) and FD (2 studies) with alcohol consumption, however only 8 studies for CRAE, 6 studies for CRVE and 4 studies for AVR provided all necessary data to conduct a meta-analysis. Random-effects meta-analysis of the beta coefficients was performed using the method described by Der Simonian and Laird [30]. All analyses were performed separately for the association between CRAE, CRVE and AVR with alcohol consumption. To assess between-study heterogeneity we calculated the I2 and assessed significance with the Cochran Q statistic. To explore potential sources of heterogeneity, we performed subgroup analyses stratified by alcohol intake level (low and high) and level of statistical adjustment (studies adjusted for age, sex, blood pressure/hypertension and heart rate, among other factors). Despite the heterogeneity of measuring alcohol consumption across the studies included, in the present meta-analysis, low and high alcohol consumption were defined as: low alcohol consumption ~ <10g/day and high alcohol consumption ~ >20g/day [9,12] (standard serving unit 14gr of pure alcohol according to Dietary Guidelines for Americans, 2020-2025 (USDA) [31]). Meta-regression analyses were performed to explore the modifying effects of mean age and sex distribution on pooled associations. Statistical significance was defined as a two-sided $p<0.05$. All analyses were conducted with the STATA Software version 13.0 (Stata Corporation, College Station, TX, USA).

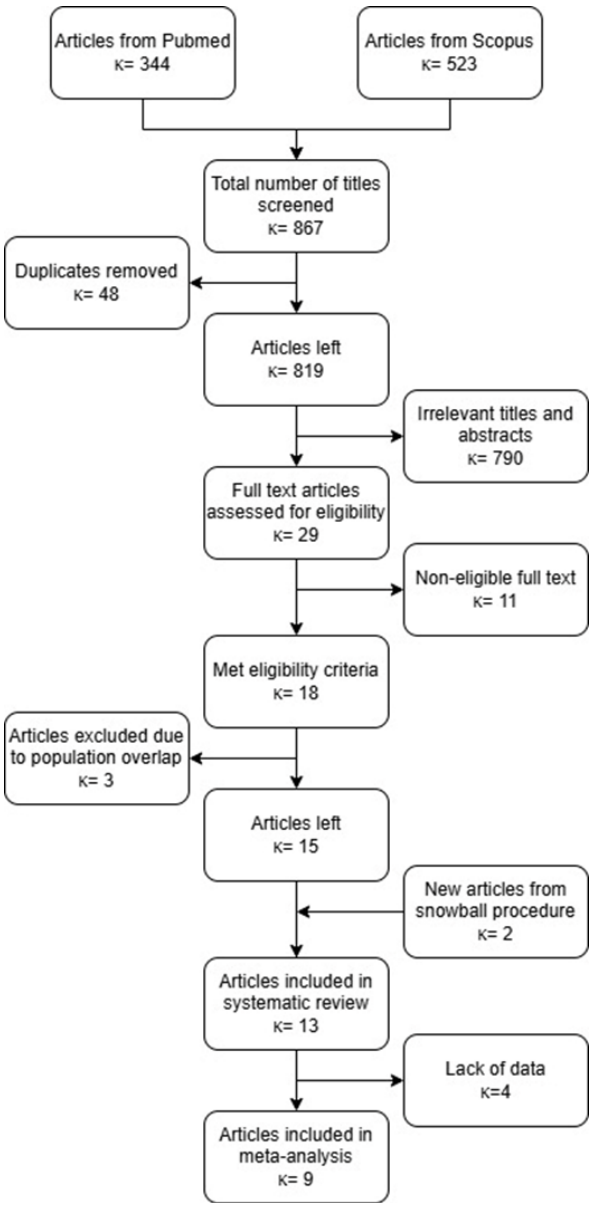



*Figure 1: Study selection process flowchart.*

## Results

### Literature review

The final literature search was performed on 1st of February 2026 and yielded 867 articles. Thus, 344 articles derived through PubMed and 523 articles derived through Scopus were cumulatively screened for eligibility. After excluding 854 articles, the present systematic review finally included 13 articles and the meta-analysis 9 articles (for further details see exclusion criteria and Figure 1). The study selection process is summarized in the PRISMA flow diagram **(Figure 1)**.

### Study Characteristics

Our search retrieved a total number of 13 articles investigating the association between alcohol consumption and retinal vessel diameter (12 articles including structural biomarkers and 1 article including functional biomarker) **(Tables 1a-1c and supplementary Tables S4a-S4c)**. The included studies were published between 2004 and 2025 and comprised 7 cross-sectional studies, 5 cohort studies and 1 interventional study, with a total of >60,000 participants (sample sizes ranged from 181 to 32226 participants for the observational studies). Alcohol

*Table 1a: Characteristics and results of cross-sectional studies included.*

| Author / Year | N | Population /Age yrs | Ascertainment of exposure | Assessment of outcome | Alcohol type / frequency | Retinal biomarkers | Coef. | Adjustment | Results |
|---|---|---|---|---|---|---|---|---|---|
| **Maugana V.F. et al. (2021)** | 566 | Young adults / | Self-reported questionnaire | Fundus Photography (Zeiss Fundus FF-450plus), Dynamic Retinal Vessel Analyzer / Visualis 2.81, | Alcohol consumption (YES/NO) | CRAE | β (95%CI) | Age, gender, income interaction, ethnicity, BMI, SBP, triglycerides, C-reactive protein, active energy expenditure, cotinine, CRVE | -0.09 (-0.16 to -0.01) p= 0.027 |
| | | 20-30 | | VesselMap 2, Imedos Systems GmbH, Jena, Germany | (all alcoholic drinks) | CRVE | r | Age, gender, income interaction, ethnicity | 0.08 p= 0.041 |
| | | | | | | AVR | β (95%CI) | Age, gender, income interaction, ethnicity, BMI, SBP, triglycerides, C-reactive protein, active energy expenditure, cotinine | -0.09 (-0.17 to -0.01) p= 0.033 |
| **Dervenis N. et al. (2019)** | 1614 | General population / >60 | Interview | Fundus Photography (Carl Zeiss Meditec, Dublin, CA, USA) / IVAN software | Occasional | CRAE | SE | Age, gender, weight, height, SBP, DBP, IOP, smoking, vegetable consumption, afternoon sleep, HTN, CVD history, ophthalmic medication, lens | -2.109 p= 0.017 |
| | | | | | (<1 unit/ month) Regular (≥1 unit/ month) (all alcoholic drinks) | CRVE | SE | Age, gender, weight, height, SBP, DBP, IOP, smoking, vegetable consumption, afternoon sleep, HTN, CVD history, ophthalmic medication, lens | -1.17 p= 0.379 |
| | | | | | | AVR | SE | Age, gender, weight, height, SBP, DBP, IOP, smoking, vegetable consumption, afternoon sleep, HTN, CVD history, ophthalmic medication, lens | -0.0056 |
| | | | | | | | | | p= 0.1077 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Karatzi K. et al. (2016)** | 181 | Increased CVD risk adults / 51.32±12.42 | Interview | Fundus Photography (Topcon TRC-NW8) / (SVA-T and Vesselmap 2, software, Visualis, Imedos Systems UG, Jena, Germany | Serving sizes: 30ml High alcoholic drinks (i.e. vodka, whiskey), 125ml Wine (all types), 250ml Beer (g/day) | CRAE | β | Age, gender, HTN, smoking, hyperlipidemia, family history of CAD, existence of autoimmune disease, drugs for hyperlipidemia and hypertension, calories, CRVE | Alcohol: (Left) -0.071 p=0.262 |
| | | | | | - | | | | (Right) -0.034 p=0.600 |
| | | | | | Total daily alcohol intake (all alcoholic drinks) | | | | High Alcohol: (Left) -0.053 p=0.429 |
| | | | | | | | | | (Right) -0.023 p=0.742 |
| | | | | | | | | | Wine: (Left) -0.006 p=0.927 |
| | | | | | | | | | (Right) 0.009 p=0.891 |
| | | | | | | | | | Beer: (Left) -0.126 p=0.057 |
| | | | | | | | | | (Right) -0.101 p=0.136 |
| | | | | | | CRVE | β | Age, gender, HTN, smoking, hyperlipidemia, family history of CAD, existence of autoimmune disease, drugs for hyperlipidemia and hypertension, calories, CRAE | Alcohol: (Left) 0.085 p=0.203 |
| | | | | | | | | | (Right) 0.036 p=0.607 |
| | | | | | | | | | High Alcohol: (Left) 0.073 p=0.291 |
| | | | | | | | | | (Right) -0.010 p=0.888 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Wine: (Left) -0.027 p=0.699 |
| | | | | | | | | | (Right) 0.000 p=0.997 |
| | | | | | | | | | Beer: (Left) 0.053 p=0.447 |
| | | | | | | | | | (Right) -0.005 p=0.944 |
| | | | | | | AVR | β | Age, gender, HTN, smoking, hyperlipidemia, family history of CAD, existence of autoimmune disease, drugs for hyperlipidemia and hypertension, calories, | Alcohol: (Left) -0.120 p=0.137 |
| | | | | | | | | | (Right) -0.064 p=0.438 |
| | | | | | | | | | High Alcohol: (Left) -0.086 p=0.304 |
| | | | | | | | | | (Right) -0.019 p=0.825 |
| | | | | | | | | | Wine: (Left) (Left) 0.001 p=0.988 |
| | | | | | | | | | (Right) 0.007 p=0.931 |
| | | | | | | | | | Beer: (Left) -0.150 p=0.068 |
| | | | | | | | | | (Right) -0.102 p=0.227 |
| **Cheung C.Y. et al. (2011)** | 2915 | Population based / 40-80 | Self-reported questionnaire | Fundus Photography (Canon CR-DGi with a 10D SLR digital camera | Alcohol consumption (YES/NO) | Retinal Arteriolar Tortuosity | β | Age, gender, BMI, high-sensitivity C-reactive protein level, HbA1c, CRAE | -0.091 p=0.099 |
| | | | | backing; Canon, Toyko, Japan) / SIVA software | (all alcoholic drinks) | | | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Liew G. et al. (2008)** | 8794 | Population based / 45-64 | Self-reported questionnaire | Fundus Photography / - | Alcohol consumption (YES/NO) | CRAE | Mean Dif. (95%CI) | MABP, BMI, smoking, CRVE, glucose level, triglyceride, HDL, LDL, WBC, fibrinogen level, albumin level, von Willebrand factor, factor VIII, carotid intima thickness | −1.2 (−1.7 to −0.6) p<0.05 |
| | | | | | (all alcoholic drinks) | CRVE | Mean Dif. (95%CI) | MABP, BMI, smoking, CRAE, glucose level, triglyceride, HDL, LDL, WBC, fibrinogen level, albumin level, von Willebrand factor, factor VIII, carotid intima thickness | 0.9 (0.3 to 1.4) p<0.05 |
| **Wong T.Y. et al. (2006)** | 3457 | CVD free adults / 45-84 | Self-reported questionnaire | Fundus photography (Canon, Lake Success, New York, USA) / IVAN software | Alcohol consumption (YES/NO) | CRAE | β | Age, gender, race-ethnicity, examination center | -2.31 p<0.001 |
| | | | | | (all alcoholic drinks) | CRVE | β | Age, gender, race-ethnicity, examination center | -2.14 p<0.001 |
| **Ikram K. et al. (2004)** | 3825 | Population based / >55 | Interview | Fundus photography (Topcon Optical, LS-4000) / Retinal Analysis | ≤10 g/d (n=2158) | CRAE | Mean Dif. (95%CI) | Age, gender | <=10 g/d: 0.6 (-0.5 to 1.7) p>0.05 |
| | | | | Optimate & Visual | >10 to ≤20 g/d (n=737) | | | | >10 to <=20 g/d: -1.0 (-2.4 to 0.4) p>0.05 |
| | | | | Science, University of Wisconsin-Madison | >20 g/d | | | | >20 g/d: -1.1 (-2.4 to 0.3) p>0.05 |
| | | | | | (n=930) | CRVE | Mean Dif. (95%CI) | Age, gender | <=10 g/d: 0.6 (-0.9 to 2.2) p>0.05 |
| | | | | | | | | | >10 to <=20 g/d: -0.9 (-2.9 to 1.1) p>0.05 |
| | | | | | | | | | >20 g/d: 1.5 (-0.4 to 3.4) p>0.05 |
| | | | | | | AVR | Mean Dif. (95%CI) | Age, gender | <=10 g/d: 0.001 (-0.004 to 0.005) p>0.05 |
| | | | | | | | | | >10 to <=20 g/d: -0.002 (-0.008 to 0.003) p>0.05 |
| | | | | | | | | | >20 g/d: -0.010 (-0.015 to -0.004) p<0.05 |

*Abbreviations: N, number; BMI, body mass index; SBP, systolic blood pressure; CRAE, central retinal artery equivalent; CRVE, central retinal vein equivalent, AVR, arteriovenous ratio; SE, slope estimate; DBP, diastolic blood pressure; IOP, intraocular pressure; CVD, cardiovascular disease; CAD, coronary artery disease; MABP, mean arterial pressure; dif, difference; HDL, high density lipoprotein; LDL, low density lipoprotein; WBC, white blood cells.*

*Table 1b: Characteristics and results of cohort studies included.*

| Author / Year | N | Population /Age yrs | Ascertainment of exposure | Assessment of outcome | Alcohol type / frequency | Retinal biomarker | Coef. | Adjustment | Results |
|---|---|---|---|---|---|---|---|---|---|
| **Zeng X. et al. (2025)** | 32226 | Population based / 40-73 | - | Fundus photography / Deep Learning System - RMHAS algorithm | Moderate: ≤2 units/day for men and ≤1 unit/day for women | CRAE | β (95%CI) | Age, gender, ethnicity, TDI, educational attainment, SER, IOP | 0.23 (0.19 to 0.28) p<0.001 |
| | | | | | | | | Age, gender | 0.25 (0.21 to 0.30) p<0.001 |
| | | | | | | CRVE | β (95%CI) | Age, gender, ethnicity, TDI, educational attainment, SER, IOP | 0.07 (-0.002 to 0.13) p=0.058 |
| | | | | | | | | Age, gender | 0.09 (0.03 to 0.16) p=0.058 |
| | | | | | | AVR | β (95%CI) | Age, gender, ethnicity, TDI, educational attainment, SER, IOP | 0.01 (0.005 to 0.01) p<0.001 |
| | | | | | | | | Age, gender | 0.01 (0.005 to 0.01) p<0.001 |
| | | | | | | FD | β (95%CI) | Age, gender, ethnicity, TDI, educational attainment, SER, IOP | 0.002 (0.001 to 0.003) p<0.001 |
| | | | | | | | | Age, gender | 0.003 (0.002 to 0.004) p<0.001 |
| **Chen Q. et al. (2024)** | 538 | Population based / 40-69 | Questionary | Fundus photography / Deep Learning System - RMHAS algorithm | Low: never or only special occasions | Arteriolar FD | HR (95%CI) | - | Before glaucoma-control matching: 0.03 (0.01 to 0.15) p<0.001 |
| | | | | | | | | | After glaucoma-control matching: |
| | | | | | | | | | 0.35 (0.06 to 2.19) p=0.26 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 1261 | | | | Moderate: once per month to ≤4 times per week | | HR (95%CI) | - | Before glaucoma-control matching: 0.03 (0.01 to 0.11) p<0.001<br>After glaucoma-control matching:<br>0.25 (0.07 to 0.9) p=0.03 |
| | 584 | | | | High: daily or almost daily | | HR (95%CI) | - | Before glaucoma-control matching: 0.02 (0 to 0.1) p<0.001<br>After glaucoma-control matching:<br>0.14 (0.02 to 0.89) p=0.04 |
| | 538 | | | | Low: never or only special occasions | Venular FD | HR (95%CI) | - | Before glaucoma-control matching: 0.15 (0.02 to 1.04) p=0.05<br>After glaucoma-control matching:<br>1.35 (0.18 to 10.13) p=0.77 |
| | 1261 | | | | Moderate: once per month to ≤4 times per week | | HR (95%CI) | - | Before glaucoma-control matching: 0.03 (0.01 to 0.12) p<0.001<br>After glaucoma-control matching:<br>0.2 (0.05 to 0.82) p=0.02 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 584 | | | | High: daily or almost daily | | HR (95%CI) | - | Before glaucoma-control matching: 0.03 (0 to 0.19) p<0.001 |
| | | | | | | | | | After glaucoma-control matching: |
| | | | | | | | | | 0.16 (0.02 to 1.17) p=0.07 |
| | 538 | | | | Low: never or only special occasions | Arteriolar VSD | HR (95%CI) | - | Before glaucoma-control matching: 0.03 (0.01 to 0.12) p<0.001 |
| | | | | | | | | | After glaucoma-control matching: |
| | | | | | | | | | 0.26 (0.06 to 1.22) p=0.09 |
| | 1261 | | | | Moderate: once per month to ≤4 times per week | | HR (95%CI) | - | Before glaucoma-control matching: 0.03 (0.01 to 0.09) p<0.001 |
| | | | | | | | | | After glaucoma-control matching: |
| | | | | | | | | | 0.23 (0.08 to 0.68) p=0.01 |
| | 584 | | | | High: daily or almost daily | | HR (95%CI) | - | Before glaucoma-control matching: 0.03 (0.01 to 0.13) p<0.001 |
| | | | | | | | | | After glaucoma-control matching: |
| | | | | | | | | | 0.22 (0.04 to 1.17) p=0.08 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 538 | | | | Low: never or only special occasions | Venular VSD | HR (95%CI) | - | Before glaucoma-control matching: 0.1 (0.02 to 0.48) p<0.001 |
| | | | | | | | | | After glaucoma-control matching: |
| | | | | | | | | | 0.61 (0.13 to 2.95) p=0.54 |
| | 1261 | | | | Moderate: once per month to ≤4 times per week | | HR (95%CI) | - | Before glaucoma-control matching: 0.04 (0.01 to 0.11) p<0.001 |
| | | | | | | | | | After glaucoma-control matching: |
| | | | | | | | | | 0.26 (0.08 to 0.78) p=0.02 |
| | 584 | | | | High: daily or almost daily | | HR (95%CI) | - | Before glaucoma-control matching: 0.06 (0.01 to 0.28) p<0.001 |
| | | | | | | | | | After glaucoma-control matching: |
| | | | | | | | | | 0.3 (0.06 to 1.55) p=0.15 |
| **Van der Heide F. et al. (2023)** | 3107 | Population based / 40-75) | Questionary | Fundus photography / Dynamic Vessel Analyzer, RHINO software | None: < 1 unit/week | CRAE | β (95%CI) | Age, gender, smoking, diet score, SBP, antihypertensives, total cholesterol/ HDL ratio, lipid-modifying medication, prior CVD, glucose metabolism status, educational level, waist circumference | Continuous Variable (n=3120): -0.01 (-0.04 to 0.02) p=0.20 |
| | | | | | Light: 1 unit/ week to 1 unit/day for men, 1 unit/ week to 0.5 unit/day for women | | | | None vs light (n=964): 0.03 (-0.09 to 0.14) p=0.20 |

| | | | | | | | | | |
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| | | | | | Moderate: > 1 to 2 units/ day for men, > 0.5 to 1 unit/day for women | | | - | Moderate vs light: -0.05 (-0.15 to 0.06) p=0.20 |
| | | | | | High: > 2 units/day for men, > 1 units/day | | | | High vs light: -0.04 (-0.14 to 0.05) p=0.20 |
| | | | | | for women | | | | Continuous Variable (n=3120): -0.06 (-0.09 to -0.03) p<0.001 |
| | | | | | (1 unit was defined as 10 g/day (g/d) of total alcohol, 100g/d of red or white wine, 50g/ day of strong wine, 225g/d of pilsner, 320g/d light alcoholic beer, 160g/d of high alcoholic beer, or 35g/d pf spirits | | | | None vs light (n=964): 0.12 (0.00 to 0.23) p<0.001 |
| | | | | | | | | | Moderate vs light: -0.10 (-0.21 to 0.01) p>0.05 |
| | | | | | | | | | High vs light: -0.10 (-0.19 to 0.00) p<0.001 |
| | | | | | | CRVE | β (95%CI) | Age, gender, smoking, diet score, SBP, antihypertensives, total cholesterol/ HDL ratio, lipid-modifying medication, prior CVD, glucose metabolism status, educational level, waist circumference | Continuous Variable (n=3120): 0.01 (-0.02 to 0.04) p=0.34 |
| | | | | | | | | | None vs light (n=964): 0.01 (-0.11 to 0.12) p=0.34 |
| | | | | | | | | | Moderate vs light: -0.11 (-0.21 to 0.00) p=0.34 |
| | | | | | | | | | High vs light: -0.03 (-0.13 to 0.06) p=0.34 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | - | Continuous Variable (n=3120): -0.02 (-0.05 to 0.01) p=0.01 |
| | | | | | | | | | None vs light (n=964): 0.08 (0.03 to 0.20) p=0.01 |
| | | | | | | | | | Moderate vs light: -0.15 (-0.26 to -0.04) p=0.01 |
| | | | | | | | | | High vs light: -0.05 (-0.15 to 0.04) p>0.05 |
| | | | | | | | Arteriolar FID | β (95%CI) | Age, gender, smoking, diet score, SBP, antihypertensives, total cholesterol/ HDL ratio, lipid-modifying medication, prior CVD, glucose metabolism status, educational level, waist circumference | Continuous Variable (n=3120): -0.00 (-0.04 to 0.03) p=0.38 |
| | | | | | | | | | | None vs light (n=964): -0.01 (-0.15 to 0.12) p=0.38 |
| | | | | | | | | | | Moderate vs light: -0.14 (-0.26 to -0.02) p<0.05 |
| | | | | | | | | | | High vs light: -0.04 (-0.15 to 0.07) p=0.38 |
| | | | | | | | | | - | Continuous Variable (n=3120): 0.01 (-0.02 to 0.04) p=0.26 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | None vs light (n=964): 0.03 (-0.10 to 0.17) p=0.26 |
| | | | | | | | | | Moderate vs light: -0.14 (-0.26 to -0.02) p<0.05 |
| | | | | | | | | | High vs light: -0.02 (-0.13 to 0.08) p=0.26 |
| | | | | | | Venular FID | β (95%CI) | Age, gender, smoking, diet score, SBP, antihypertensives, total cholesterol/ HDL ratio, lipid-modifying medication, prior CVD, glucose metabolism status, educational level, waist circumference | Continuous Variable (n=3120): -0.01 (-0.05 to 0.02) p=0.59 |
| | | | | | | | | | None vs light (n=964): -0.03 (-0.16 to 0.11) p=0.59 |
| | | | | | | | | | Moderate vs light: 0.00 (-0.12 to 0.12) p=0.59 |
| | | | | | | | | | High vs light: -0.05 (-0.16 to 0.06) p=0.59 |
| | | | | | | | | - | Continuous Variable (n=3120): 0.00 (-0.03 to 0.03) p=0.82 |
| | | | | | | | | | None vs light (n=964): -0.04 (-0.17 to 0.10) p=0.82 |
| | | | | | | | | | Moderate vs light: -0.01 (-0.12 to 0.13) p=0.82 |

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| | | | | | | | | | High vs light: -0.04 (-0.14 to 0.07) p=0.82 |
| **Tano T. et al. (2016)** | 1787 | Population-based / 40-74 | Interview | Fundus photography (Nonmyd | Alcohol consumption (YES/NO) | CRAE | β (95%CI) | Age, Genger BMI, BP, HbAc, Cholesterol | Multiple regression analysis: |
| | | | | a-D III; Kowa Inc., Nagoya, | (all alcoholic drinks) | | | | 1.99 (-0.26 to 4.23) p>0.05 |
| | | | | Japan) / Retinal Analysis, Madison USA | | | | - | Single regression analysis: |
| | | | | | | | | | 4.02 (2.13 to 5.9) p<0.001 |
| | | | | | | CRVE | β (95%CI) | - | Single regression analysis: |
| | | | | | | | | | 0.07 (-2.6 to 2.73) p>0.05 |
| **Klein R. et al. (2012)** | 222* | Population based / 43-84 | Questionary | Fundus photography (Slit-lamp camera Topcon) / IVAN software | Heavy (≥4 units/day – all alcoholic drinks) | CRAE | β (95%CI) | Age, HbA, diabetes mellitus status, Creatinine level, hsCRP level, VCAM-1, refraction, cataract, and image focus | Current: |
| | | | | | | | | | −2.54 (−4.79 to −0.28) p=0.03 |
| | | | | | | | | | Past: −2.42 (−4.42 to −0.42) p=0.02 |
| | | | | | | | | Age, refraction, cataract, image focus, and systolic BP | Current: |
| | | | | | | | | | −2.25 (−3.78 to −0.72) p=0.004 |

*Abbreviations: N, number; CRAE, central retinal artery equivalent; TDI, SER; IOP, intraocular pressure; CRVE, central retinal vein equivalent; AVR, arteriovenous ratio; FD, fractal dimension; HR, hazzard ratio; CVD, cardiovascular disease; cCRP,*
**current alcohol consumption*

consumption was predominantly assessed using self-reported questionnaires, with intake expressed as drinks per day, grams per day, or categorical drinking patterns. Retinal imaging modalities included mainly fundus photography but also optical coherence tomography angiography (OCTA), with vessel analysis performed using validated semi-automated or automated software.

**Qualitative synthesis of retinal microvascular biomarkers**
**CRAE:**
***Low alcohol intake:***
Two observational studies, the Maastricht study (cohort study) [9] and the Rotterdam study (cross-sectional study) [12], including 964 and 2158 respectively, examined the possible association between low alcohol intake level and CRAE, however, there was not any association (both p>0.05).

***Moderate alcohol intake:***
Two cohort studies including middle-aged and older participants (32.226 from the UK Biobank [32]) and 1787 from the Aizu Cohort Study [15]) examined the possible association between moderate alcohol intake level and CRAE, however, only the first study showed a statistically significant positive association (p<0.001 for Zeng et al.), while five cross-sectional

*Table 1c: Characteristics and results of interventional studies included.*

| Author / Year | N | Population /Age yrs | Ascertainment of exposure | Assessment of outcome | Alcohol type / frequency | Retinal biomarker | Coef. | Adjustment | Results |
|---|---|---|---|---|---|---|---|---|---|
| **Zeng X. et al. (2025)** | 32226 | Population based / 40-73 | - | Fundus photography / Deep Learning System - RMHAS algorithm | Moderate: ≤2 units/day for men and ≤1 unit/day for women | CRAE | β (95%CI) | Age, gender, ethnicity, TDI, educational attainment, SER, IOP | 0.23 (0.19 to 0.28) p<0.001 |
| | | | | | | | | Age, gender | 0.25 (0.21 to 0.30) p<0.001 |
| | | | | | | CRVE | β (95%CI) | Age, gender, ethnicity, TDI, educational attainment, SER, IOP | 0.07 (-0.002 to 0.13) p=0.058 |
| | | | | | | | | Age, gender | 0.09 (0.03 to 0.16) p=0.058 |
| | | | | | | AVR | β (95%CI) | Age, gender, ethnicity, TDI, educational attainment, SER, IOP | 0.01 (0.005 to 0.01) p<0.001 |
| | | | | | | | | Age, gender | 0.01 (0.005 to 0.01) p<0.001 |
| | | | | | | FD | β (95%CI) | Age, gender, ethnicity, TDI, educational attainment, SER, IOP | 0.002 (0.001 to 0.003) p<0.001 |
| | | | | | | | | Age, gender | 0.003 (0.002 to 0.004) p<0.001 |
| **Chen Q. et al. (2024)** | 538 | Population based / 40-69 | Questionary | Fundus photography / Deep Learning System - RMHAS algorithm | Low: never or only special occasions | Arteriolar FD | HR (95%CI) | - | Before glaucoma-control matching: 0.03 (0.01 to 0.15) p<0.001 |
| | | | | | | | | | After glaucoma-control matching: |
| | | | | | | | | | 0.35 (0.06 to 2.19) p=0.26 |
| | 1261 | | | | Moderate: once per month to ≤4 times per week | | HR (95%CI) | - | Before glaucoma-control matching: 0.03 (0.01 to 0.11) p<0.001 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | After glaucoma-control matching: 0.25 (0.07 to 0.9) p=0.03 |
| | 584 | | | | High: daily or almost daily | | HR (95%CI) | - | Before glaucoma-control matching: 0.02 (0 to 0.1) p<0.001 |
| | | | | | | | | | After glaucoma-control matching: 0.14 (0.02 to 0.89) p=0.04 |
| | 538 | | | | Low: never or only special occasions | Venular FD | HR (95%CI) | - | Before glaucoma-control matching: 0.15 (0.02 to 1.04) p=0.05 |
| | | | | | | | | | After glaucoma-control matching: 1.35 (0.18 to 10.13) p=0.77 |
| | 1261 | | | | Moderate: once per month to ≤4 times per week | | HR (95%CI) | - | Before glaucoma-control matching: 0.03 (0.01 to 0.12) p<0.001 |
| | | | | | | | | | After glaucoma-control matching: 0.2 (0.05 to 0.82) p=0.02 |
| | 584 | | | | High: daily or almost daily | | HR (95%CI) | - | Before glaucoma-control matching: 0.03 (0 to 0.19) p<0.001 |

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|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | After glaucoma-control matching: 0.16 (0.02 to 1.17) p=0.07 |
| | 538 | | | | Low: never or only special occasions | Arteriolar VSD | HR (95%CI) | - | Before glaucoma-control matching: 0.03 (0.01 to 0.12) p<0.001 |
| | | | | | | | | | After glaucoma-control matching: 0.26 (0.06 to 1.22) p=0.09 |
| | 1261 | | | | Moderate: once per month to ≤4 times per week | | HR (95%CI) | - | Before glaucoma-control matching: 0.03 (0.01 to 0.09) p<0.001 |
| | | | | | | | | | After glaucoma-control matching: 0.23 (0.08 to 0.68) p=0.01 |
| | 584 | | | | High: daily or almost daily | | HR (95%CI) | - | Before glaucoma-control matching: 0.03 (0.01 to 0.13) p<0.001 |
| | | | | | | | | | After glaucoma-control matching: 0.22 (0.04 to 1.17) p=0.08 |
| | 538 | | | | Low: never or only special occasions | Venular VSD | HR (95%CI) | - | Before glaucoma-control matching: 0.1 (0.02 to 0.48) p<0.001 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | After glaucoma-control matching: 0.61 (0.13 to 2.95) p=0.54 |
| | 1261 | | | | Moderate: once per month to ≤4 times per week | | HR (95%CI) | - | Before glaucoma-control matching: 0.04 (0.01 to 0.11) p<0.001 |
| | | | | | | | | | After glaucoma-control matching: 0.26 (0.08 to 0.78) p=0.02 |
| | 584 | | | | High: daily or almost daily | | HR (95%CI) | - | Before glaucoma-control matching: 0.06 (0.01 to 0.28) p<0.001 |
| | | | | | | | | | After glaucoma-control matching: 0.3 (0.06 to 1.55) p=0.15 |
| **Van der Heide F. et al. (2023)** | 3107 | Population based / 40-75) | Questionary | Fundus photography / Dynamic Vessel Analyzer, RHINO software | None: < 1 unit/week | CRAE | β (95%CI) | Age, gender, smoking, diet score, SBP, antihypertensives, total cholesterol/ HDL ratio, lipid-modifying medication, prior CVD, glucose metabolism status, educational level, waist circumference | Continuous Variable (n=3120): -0.01 (-0.04 to 0.02) p=0.20 |
| | | | | | Light: 1 unit/ week to 1 unit/day for men, 1 unit/ week to 0.5 unit/day for women | | | | None vs light (n=964): 0.03 (-0.09 to 0.14) p=0.20 |
| | | | | | Moderate: > 1 to 2 units/day for men, > 0.5 to 1 unit/day for women | | | | Moderate vs light: -0.05 (-0.15 to 0.06) p=0.20 |
| | | | | | High: > 2 units/day for men, > 1 units/day | | | | High vs light: -0.04 (-0.14 to 0.05) p=0.20 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | for women | | | - | Continuous Variable (n=3120): -0.06 (-0.09 to -0.03) p<0.001 |
| | | | | | (1 unit was defined as 10 g/day (g/d) of total alcohol, 100g/d of red or white wine, 50g/ day of strong wine, 225g/d of pilsner, 320g/d light alcoholic beer, 160g/d of high alcoholic beer, or 35g/d pf spirits | | | | None vs light (n=964): 0.12 (0.00 to 0.23) p<0.001 |
| | | | | | | | | | Moderate vs light: -0.10 (-0.21 to 0.01) p>0.05 |
| | | | | | | | | | High vs light: -0.10 (-0.19 to 0.00) p<0.001 |
| | | | | | | CRVE | β (95%CI) | Age, gender, smoking, diet score, SBP, antihypertensives, total cholesterol/ HDL ratio, lipid-modifying medication, prior CVD, glucose metabolism status, educational level, waist circumference | Continuous Variable (n=3120): 0.01 (-0.02 to 0.04) p=0.34 |
| | | | | | | | | | None vs light (n=964): 0.01 (-0.11 to 0.12) p=0.34 |
| | | | | | | | | | Moderate vs light: -0.11 (-0.21 to 0.00) p=0.34 |
| | | | | | | | | | High vs light: -0.03 (-0.13 to 0.06) p=0.34 |
| | | | | | | | | - | Continuous Variable (n=3120): -0.02 (-0.05 to 0.01) p=0.01 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | None vs light (n=964): 0.08 (0.03 to 0.20) p=0.01 |
| | | | | | | | | | Moderate vs light: -0.15 (-0.26 to -0.04) p=0.01 |
| | | | | | | | | | High vs light: -0.05 (-0.15 to 0.04) p>0.05 |
| | | | | | | Arteriolar FID | β (95%CI) | Age, gender, smoking, diet score, SBP, antihypertensives, total cholesterol/ HDL ratio, lipid-modifying medication, prior CVD, glucose metabolism status, educational level, waist circumference | Continuous Variable (n=3120): -0.00 (-0.04 to 0.03) p=0.38 |
| | | | | | | | | | None vs light (n=964): -0.01 (-0.15 to 0.12) p=0.38 |
| | | | | | | | | | Moderate vs light: -0.14 (-0.26 to -0.02) p<0.05 |
| | | | | | | | | | High vs light: -0.04 (-0.15 to 0.07) p=0.38 |
| | | | | | | | | - | Continuous Variable (n=3120): 0.01 (-0.02 to 0.04) p=0.26 |
| | | | | | | | | | None vs light (n=964): 0.03 (-0.10 to 0.17) p=0.26 |
| | | | | | | | | | Moderate vs light: -0.14 (-0.26 to -0.02) p<0.05 |
| | | | | | | | | | High vs light: -0.02 (-0.13 to 0.08) p=0.26 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Venular FID | β (95%CI) | Age, gender, smoking, diet score, SBP, antihypertensives, total cholesterol/ HDL ratio, lipid-modifying medication, prior CVD, glucose metabolism status, educational level, waist circumference | Continuous Variable (n=3120): -0.01 (-0.05 to 0.02) p=0.59 |
| | | | | | | | | | None vs light (n=964): -0.03 (-0.16 to 0.11) p=0.59 |
| | | | | | | | | | Moderate vs light: 0.00 (-0.12 to 0.12) p=0.59 |
| | | | | | | | | | High vs light: -0.05 (-0.16 to 0.06) p=0.59 |
| | | | | | | | | - | Continuous Variable (n=3120): 0.00 (-0.03 to 0.03) p=0.82 |
| | | | | | | | | | None vs light (n=964): -0.04 (-0.17 to 0.10) p=0.82 |
| | | | | | | | | | Moderate vs light: -0.01 (-0.12 to 0.13) p=0.82 |
| | | | | | | | | | High vs light: -0.04 (-0.14 to 0.07) p=0.82 |
| **Tano T. et al. (2016)** | 1787 | Population-based / 40-74 | Interview | Fundus photography (Nonmyd | Alcohol consumption (YES/NO) | CRAE | β (95%CI) | Age, Genger BMI, BP, HbAc, Cholesterol | Multiple regression analysis: |
| | | | | a-D III; Kowa Inc., Nagoya, | (all alcoholic drinks) | | | | 1.99 (-0.26 to 4.23) p>0.05 |
| | | | | Japan) / Retinal Analysis, Madison USA | | | | - | Single regression analysis: |
| | | | | | | | | | 4.02 (2.13 to 5.9) p<0.001 |
| | | | | | | CRVE | β (95%CI) | - | Single regression analysis: |
| | | | | | | | | | 0.07 (-2.6 to 2.73) p>0.05 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Klein R. et al. (2012)**<br><br>3.Interobserver-Intraobserver Variability (1 point) | 222* | Population based / 43-84 | Questionary | Fundus photography (Slit-lamp camera Topcon) / IVAN software | Heavy (≥4 units/day – all alcoholic drinks) | CRAE | β (95%CI) | Age, HbA, diabetes mellitus status, Creatinine level, hsCRP level, VCAM-1, refraction, cataract, and image focus | Current: −2.54 (−4.79 to −0.28) p=0.03<br>Past: −2.42 (−4.42 to −0.42) p=0.02 |
| | | | | | | | | Age, refraction, cataract, image focus, and systolic BP | Current: −2.25 (−3.78 to −0.72) p=0.004 |

*Abbreviations: N, number; Coef., coefficient; VDI, vessel diamter index*

*Table S2a: Management of the quality scoring criteria (Newcastle-Ottawa Scale) for all the observational studies included in the current systematic review.*

| | **Selection** | | | | | **Comparability** | **Outcome** |
|---|---|---|---|---|---|---|---|
| **Criterion/ Scoring** | ***Representativeness of the exposed cohort*** | | ***Selection of the non-exposed cohort*** | ***Ascertainment of exposure*** | ***Exclusion of outcome presence at start of study **** | ***Comparability for Age, Sex, Diabetes and Blood Pressure*** | ***Assessment of outcome - Quality of measurement*** |
| **Point awarded if…** | General population-based study | Sample size 1.>100: two points awarded 2.>20 and <100 individuals one point awarded | Drawn from the same community as the exposed cohort | Detailed report about the quality of factors/exposure assessment (alcohol) | Cohort studies in which the outcome addressed is assessed at baseline and either subjects with the outcome are excluded from the study or the increment of the outcome is assessed | 1. Two points awarded if: Adjustment for Age, Sex, BP and Diabetes *<br>2. One point awarded if: adjustment for Age, BP, Diabetes * [*If there are included diabetic individuals in the study] | Detailed report about the quality of Retinal Vessel Analysis:<br>1.Acceptable Machine / Acceptable Software (detailed report) (1 point)<br>2.Experienced observer (1 point)<br>3.Interobserver-Intraobserver Variability |
| Point **not** awarded if… | 1. High-risk population-based study (hypertensive, patients with cardiovascular history, diabetes etc.)<br>2. Random sample<br>3. Sample size smaller than 20 individuals | | 1. Drawn from a different source<br>2. No description of the derivation of the non-exposed cohort | 1. Poor quality<br>2. Method used not reported | 1. Cross-sectional studies,<br>2. Cohort studies which do not fulfil the above criteria | 1. Unadjusted studies for these parameters<br>2. Studies which does not fulfil the above criteria | 1. Method not reported<br>2. Poor quality<br>3. Studies which does not fulfil the above criteria |

studies including 566 adults from the African-Predict study [14], 5034 from the ARIC study [10], 737 from the Rotterdam study [12], 1641 from the Thessaloniki Eye study [33] and 3457 from the MESA study [13], also examined the same association, with only three of them showing a negative association (p=0.027 for Maugana et al., p<0.05 for Liew et al., p<0.001 for Dervenis et al. and p<0.001 for Wong et al.).

***High alcohol intake:***

Two observational studies (one cohort [11] and one cross-sectional study [12]), the Beaver Dam Eye study [11] and The Rotterdam study [12], including 222 and 930 middle-aged and older participants, respectively, examined the possible association between high alcohol intake level and CRAE, however, only the cohort study showed a statistically significant negative association (p=0.03 for Klein et al.).

***Alcohol as a continuous variable:***

In two observational studies (one cohort [9] and one cross-sectional study [34]) including 3120 middle-aged and older participants from the Maastricht study [9] and 181 adults at increased risk but free of CVD [34], the possible association between alcohol consumption (as a continuous variable) and CRAE was examined, however there was no association (both p>0.05).

**CRVE:**

***Low alcohol intake:***

Two observational studies (one cohort [9] and one cross-sectional study [12]) including 964 participants from the Maastricht study [9] and 2158 from the Rotterdam study [12], examined the possible association between low alcohol intake level and CRVE, however, there was not any association (both p>0.05).

*Table S2b. Management of the quality scoring criteria (Jadad Assessment Scale) for all the randomized/non-randomized control trial studies included in the current systematic review.*

| Criterion | | | Scoring |
|---|---|---|---|
| **Randomization** | 1. Was the study described as randomized (this includes the use of words such as randomly, random, and randomization)? = **1 point** | **Additional 1 point if:** For question 1, the method to generate the sequence of randomization was described and it was appropriate (table of random numbers, computer generated, etc.)<br><br>**Deduct 1 point if:** For question 1, the method to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc.) | **Maximum 2 points / Minimum 0 points** |
| **Blinding** | 2. Was the study described as double blind? = **1 point** | **Additional 1 point if:** For question 2 the method of double blinding was described and it was appropriate (identical placebo, active placebo, dummy, etc.)<br><br>**Deduct 1 point if:** For question 2 the study was described as double blind but the method of blinding was inappropriate (e.g., comparison of tablet vs. injection with no double dummy) | **Maximum 2 points / Minimum 0 points** |
| **Withdrawals and dropouts** | 3. Was there a description of withdrawals and dropouts? = **1 point** | | **Maximum 1 point / Minimum 0 points** |
| | | **TOTAL JADAD Score:** | **Maximum 5 points / Minimum 0 points** |

*Table S3a: Results of the quality assessment of all eligible studies (there were only observational studies) according to the cohort subscale of the Newcastle-Ottawa Scale. Articles are sorted in order of decreasing total quality score.*

| Study | Type of Study | Selection | | | | Comparability | Outcome | Total Score |
|---|---|---|---|---|---|---|---|---|
| | | Representativeness of the exposed cohort | Selection of the non-exposed cohort | Ascertainment of exposure | Exclusion of outcome presence at start of study * | | | |
| **Karatzi K. et al. (2016)** | Cross - Sectional | ★★★ | ★ | ★ | ☆ | ★★ | ★★★ | **10** |
| **Klein R. et al. (2012)** | Cohort | ★★★ | ★ | ★ | ☆ | ★★ | ★★★ | **10** |
| **Liew G. et al. (2008)** | Cross – Sectional | ★★★ | ★ | ★ | ☆ | ★★ | ★★☆ | **9** |
| **Van der Heide F. et al. (2023)** | Cohort | ★★★ | ★ | ★ | ☆ | ★★ | ★☆☆ | **8** |
| **Dervenis N. et al. (2019)** | Cross – Sectional | ★★★ | ★ | ★ | ☆ | ☆☆ | ★★★ | **8** |
| **Wong T.Y. et al. (2006)** | Cross – Sectional | ★★★ | ★ | ★ | ☆ | ☆☆ | ★★★ | **8** |
| **Chen Q. et al. (2024)** | Cohort | ★★★ | ★ | ★ | ☆ | ☆☆ | ★☆☆ | **7** |
| **Cheung C.Y. et al. (2011)** | Cross – Sectional | ★★★ | ★ | ★ | ☆ | ☆☆ | ★★☆ | **7** |
| **Ikram K. et al. (2004)** | Cross – Sectional | ★★★ | ☆ | ★ | ☆ | ☆☆ | ★★★ | **7** |
| **Zeng X. et al. (2025)** | Cohort | ★★★ | ★ | ★ | ☆ | ☆☆ | ★☆☆ | **6** |
| **Tano T. et al. (2016)** | Cohort | ★★★ | ☆ | ★ | ☆ | ☆☆ | ★★☆ | **6** |
| **Maugana V.F. et al. (2021)** | Cross – Sectional | ★★★ | ☆ | ★ | ☆ | ☆☆ | ★☆☆ | **5** |

*Table S3b: Results of the quality assessment of all eligible interventional studies according the Jadad Scale. Articles are sorted in order of decreasing total quality score.*

| Study | Randomization | Blinding | Withdrawals & Dropouts | Total Score |
|---|---|---|---|---|
| **Zhu X. et al. (2025) (randomized seld-controlled study)** | ★☆ | ☆☆ | ☆ | **1** |

*Table S4: Supplementary characteristics of studies: (S3a) Cross-sectional studies; (S3b) Cohort studies; (S3c) Interventional studies*

*Table S4a: Cross-sectional studies.*

| Author/Year | Title | Country | Age (years, mean or range) | Male sex (%) | Smoking (%) | BMI (kg/m2) | HTN (%) | DM (%) | DLP (%) | Alcohol (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| **Maugana V.F. et al. (2021)** | Socioeconomic inequalities, modifiable lifestyle risk factors, and retinal vessel calibers: The African-PREDICT Study | South Africa | 20-30 years | Low SES: 48<br>High SES: 47 | Low SES: 29.4<br>High SES: 20.5 | Low SES: 24.8<br>High SES: 25.3 | – | – | – | Low SES: 56.0<br>High SES: 55.9 |
| **Dervenis N. et al. (2019)** | Factors Associated With Retinal Vessel Diameters in an Elderly Population: the Thessaloniki Eye Study | Greece | 68.7±5.7 | 55 | 21.15 | 28.4±4.2 | 51.35 | 11.35 | _ | 77.94 |
| **Karatzi K. et al. (2016)** | Retinal microcirculation in association with caffeinated and alcoholic drinks in subjects at increased cardiovascular risk | Greece | M= 49.5±11.7,<br>F= 53.1±12.9 | 48.6 | M= 68.2,<br>F= 45.4 | M= 27.9±5.5,<br>F= 26.3±4.7 | M= 47.7,<br>F= 32.3 | 0 | M= 29.5,<br>F= 22,6 | M= 14.7±22.5<br>F= 3.90±8.2 |
| **Cheung C.Y. et al. (2011)** | Retinal Vascular Tortuosity, Blood Pressure, and Cardiovascular Risk Factors | Singapore | 40-80 | 47.8 | 20.8 | _ | _ | 22.8 | _ | 1.8 |
| **Liew G. et al. (2008)** | Relative Importance of Systemic Determinants of Retinal Arteriolar and Venular Caliber | Australia | 60 | 45.4 | 16.8 | 27.6 | _ | _ | _ | 57.2 |
| **Wong T.Y. et al. (2006)** | Retinal Vascular Caliber, Cardiovascular Risk Factors, and Inflammation: The Multi-Ethnic Study of Atherosclerosis (MESA) | USA | 61.9±10.4 | 47.7 | 12.6 | 28.3±5.4 | 43.5 | 13.4 | _ | 56.2 |
| **Ikram K. et al. (2004)** | Are Retinal Arteriolar or Venular Diameters Associated with Markers for Cardiovascular Disorders? The Rotterdam Study | Netherlands | 68.0±8.20 | 41 | Current: 23.6<br>EX: 42.9 | 26.3±3.68 | _ | 10 | _ | ≤ 10 g/d= 45.0<br>>10-≤20 g/d= 15.4<br>>20 g/d= 19.5 |

*Abbreviations: BMI, body mass index; HTN, hypertension; DM, diabetes mellitus; DLP, dyslipidemia; SES, socioeconomic status; M, male; F, female; EX, past smoker*

*Table S4b: Cohort studies*

| Author/Year | Title | Country | Age (years, mean or range) | Male sex (%) | Smoking (%) | BMI (kg/m2) | HTN (%) | DM (%) | DLP (%) | Alcohol (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| **Zeng X. et al. (2025)** | Associations between a healthy lifestyle score and retinal neurovascular health | UK | 56.40±8.08 | 47.77 | 45.55 | _ | _ | _ | _ | Moderate: 64.75 |
| **Chen Q. et al. (2025)** | Associations of Retinal Microvascular Density and Fractal Dimension with Glaucoma: A Prospective Study from UK Biobank | UK | Glaucoma: 55.22 (8.20)<br>Non-glaucoma: 60.92 (6.21) | Glaucoma: 44.9<br>Non-glaucoma: 50.4 | Glaucoma: 42.9<br>Non-glaucoma: 43.6 | _ | Glaucoma: 49.3<br>Non-glaucoma: 63.7 | Glaucoma: 5.1<br>Non-glaucoma: 10 | _ | Glaucoma:<br>Low: 20.2 ,<br>Moderate: 59.6 ,<br>High: 20.1 ,<br>Not answer: 0.1<br>Non-glaucoma:<br>Low: 24.9 ,<br>Moderate: 51.7 ,<br>High: 23.4 ,<br>Not answer: 0 |
| **Van der Heide F. et al. (2023)** | Alcohol consumption and microvascular dysfunction: a J-shaped association: The Maastricht Study | Netherlands | None: 59.0 ± 8.6<br>Light alcohol consumption: 59.1 ± 8.8<br>Moderate alcohol consumption: 60.1 ± 8.2<br>Hight alcohol consumption: 61.0 ± 7.2 | None: 32.7<br>Light alcohol consumption: 57.6<br>Moderate alcohol consumption: 57.6<br>Hight alcohol consumption: 49.5 | None: 17.7<br>Light alcohol consumption: 10.9<br>Moderate alcohol consumption: 11.5<br>Hight alcohol consumption: 12.8 | None: 28.2 ± 5.5<br>Light alcohol consumption: 27.5 ± 4.6<br>Moderate alcohol consumption: 26.4 ± 3.9<br>Hight alcohol consumption: 26.3 ± 4.0 | – | None: 45.2<br>Light alcohol consumption: 29.3<br>Moderate alcohol consumption: 22.1<br>Hight alcohol consumption: 20.5 | – | None: 16.02<br>Light alcohol consumption: 31.02<br>Moderate alcohol consumption: 19.95<br>Hight alcohol consumption: 32.99 |
| **Tano T. et al. (2016)** | Retinal vessel diameters in a Japanese population: the Locomotive Syndrome and Health Outcome in Aizu Cohort Study | Japan | 64.5±0.2 | 44.8 | 16.1 | 23.8±0.1 | 39.6 | 6.6 | _ | 72.1 |
| **Klein R. et al. (2012)** | Relationship of Blood Pressure and Other Factors to Serial Retinal Arteriolar Diameter Measurements Over Time | USA | 1st exam= 61.3±10.9,<br>2nd exam= 64.4±10.1,<br>3rd exam= 67.5±9.2,<br>4th exam= 70.5±8.3 | 1st exam= 44.1,<br>2nd exam= 44,<br>3rd exam= 43.1,<br>4th exam= 42.3 | 1st exam= 20.3,<br>2nd exam= 15,<br>3rd exam= 10.4,<br>4th exam= 9.3 | 1st exam= 28.7±5.4,<br>2nd exam= 29.5±5.5,<br>3rd exam= 29.9±5.9,<br>4th exam= 30.5±6 | – | 1st exam= 7.1,<br>2nd exam= 8.3,<br>3rd exam= 9.5,<br>4th exam= 12.9 | – | 1st exam= 2.4,<br>2nd exam= 2.0,<br>3rd exam= 1.5,<br>4th exam= 0.8 |

*Abbreviations: BMI, body mass index; HTN, hypertension; DM, diabetes mellitus; DLP, dyslipidemia*

*Table S4c: Interventional studies.*

| Author/Year | Title | Country | Age (years, mean or range) | Male sex (%) | Smoking (%) | BMI (kg/m2) | HTN (%) | DM (%) | DLP (%) | Alcohol (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| **Zhu X. et al. (2025)** | Acute effects of daily red wine consumption on retinal and cerebral blood flow in healthy young adults and an animal model | Shanghai | 22.7±3.1 | 44.4 | 0 | 22±4.5 | 0 | 0 | 0 | 0 |

*Abbreviations: BMI, body mass index; HTN, hypertension; DM, diabetes mellitus; DLP, dyslipidemia*

***Moderate alcohol intake:***
Two cohort studies with 32.226 participants from the UK Biobank [32] and 1787 from the Aizu Cohort Study [15] and a cross-sectional study with 5034 participants from the ARIC study [10] (all middle-aged and older participants) examined the possible association between moderate alcohol intake level and CRVE, with only the ARIC study showing a positive association ($p<0.05$ for Liew et al.) and the cohort study with participants from the UK Biobank showing a positive trend ($p=0.058$ for Zeng et al.), while three cross-sectional studies with 737 participants from the Rotterdam study [12], 1641 from the Thessaloniki Eye study [33] and 3457 from the MESA study [13], examined the same possible association, only the MESA study showed a negative association ($p<0.001$ for Wong et al.).

***High alcohol intake:***
A cross-sectional study with 930 middle-aged and older participants from the Rotterdam study, examined the possible association between high levels of alcohol intake and CRVE, however there was not any association ($p>0.05$) [12].

***Alcohol as a continuous variable:***
In two observational studies (one cohort [9] and one cross-sectional study [34]) including 3120 middle-aged and older participants from the Maastricht study [9] and 181 adults at increased risk but free of CVD [34], the possible association between alcohol consumption (as a continuous variable) and CRAE was examined, however there was no association (both $p>0.05$).

**AVR:**
***Low alcohol intake:***
In a cross-sectional study including 2158 middle-aged and older participants from the Rotterdam study, the possible association between low alcohol intake level and AVR was examined, however there was not any association ($p>0.05$) [12].

***Moderate alcohol intake:***
A cohort study with 32.226 middle-aged and older participants from the UK Biobank showed a positive association between moderate alcohol intake level and AVR ($p<0.001$) [32], while three cross-sectional studies with 566 participants from the African-Predict study [14], 737 from the Rotterdam study [12] and 1641 from the Thessaloniki Eye study [33], examined the same association with only the African-Predict study showing a negative association ($p=0.033$ for Maugana et al.).

***High alcohol intake:***
A cross-sectional study with 930 middle-aged and older participants from the Rotterdam study, showed an inverse association between high alcohol intake level and AVR ($p<0.05$) [12].

***FD:***
Two observational studies based on individuals from the UK biobank (477 with glaucoma - 1908 glaucoma-free individuals [35] and 32.226 general population individuals [32]), provided contrasting results, with the first one showing a negative association between alcohol consumption -irrespectively of alcohol quantity- and both arteriolar and venular fractal dimension ($p\leq0.05$; before matching glaucoma and control group) [35], while the second one revealed a positive assocation between alcohol intake and vessel fractal dimension ($p<0.001$) (multivariate adjusted model) [32].

***Vascular tortuosity:***
A population-based cross-sectional study based on 3280 middle-aged and older participants from the Singapore Malay Eye Study, showed that alcohol consumption has a statistically non-significant negative trend with retinal arteriolar tortuosity ($p=0.099$) (multivariate adjusted model) [36].

***VSD:***
The UK biobank population based prospective study, including 477 glaucoma and 1908 glaucoma-free individuals, showed an inverse association between alcohol intake and both arteriolar and venular vascular skeleton density [35]. Specifically, alcohol consumption – irrespectively of alcohol quantity - has a statistically significant inverse association with arterial and venular vascular skeleton density before matching glaucoma individuals with control group ($p<0.001$). The same association remained after matching glaucoma individuals with control group, being statistically significant only in moderate alcohol consumption (from once monthly to maximum 4 times weekly) (arteriolar VSD: $p=0.02$ and venular VSD: $p=0.01$). Moreover there was a similar trend in the case of arteliolar VSD in low and high alcohol intake consumption levels after matching glaucoma individuals with control group ($p=0.09$ and $p=0.08$, respectively) [35].

***VDI:***
A randomised self-controlled interventional study with 27 healthy young adults (non-smokers, non-drinkers and not heavy coffee drinkers), showed that VDI significantly increased 0.5h after red wine consumption and then decreased after 2h (superficial retinal layer: $p<0.05$, deep retinal layer: $p>0.05$ and overall retinal layer: $p<0.05$) [37].

**Flicker light-induced dilation in retinal microvascular diameters:**
The Maastricht cohort study which was based on 3120 middle-aged and older individuals, showed a statistically significant inverse association only between moderate alcohol consumption and flicker-light induced increase in retinal arteriolar diameters, despite adjustment for cofounders ($p<0.05$) [9].

No studies examining the association between alcohol consumption and other structural (WCSA and WLR) and functional (RBF and RBFV) biomarkers were available.

**Meta-analysis of studies - Quantitative synthesis of retinal microvascular biomarkers**
***Alcohol consumption and CRAE:***
Alcohol consumption had a statistically significant inverse association with CRAE when only individuals with high levels of alcohol intake (>20g/day) were included in the meta-analysis (Beta Coefficient [β]: -1.525, 95% confidence interval [CI]: -2.812 to -0.238, p-value= 0.020 - fully adjusted model from Klein et al. study included **(Figure 2a)**; β: -1.616, 95% CI: -2.737 to -0.495, p-value=0.005 - least adjusted model from Klein et al. study included) **(Figure 2b)** [11,12]. On the contrary, there was a statistically significant positive association when individuals with low levels of alcohol intake were included in the meta-analysis (β: 0.125, 95% CI: 0.011 to 0.240, p-value=0.032 - unadjusted model from Van der Heide et al. study included) **(Figure 2c)**, however lost its significance when the adjusted models from each study included (β: 0.042, 95% CI: -0.117 to 0.200, p-value= 0.606 - adjusted model from

Van der Heide et al. study included) **(Figure S1a)** [9,12]. There was an inverse association when only studies with alcohol intake as a continuous variable were included (β: -0.059, 95% CI: -0.087 to -0.031, p-value<0.001 - unadjusted model from Van der Heide et al. study included) **(Figure 2d)**, however lost its significance when the adjusted models from each study included (β: -0.015, 95% CI: -0.043 to 0.014, p-value= 0.313 - adjusted model from Van der Heide et al. study included) **(Figure S1b)** [9,34]. Lastly, taking into consideration the limitation of data heterogeneity, there was no association between CRAE and alcohol intake when including all available studies expressing alcohol as a binary variable (YES/NO) (β: -0.132, 95% CI: -0.464 to 0.201, p-value= 0.438 - fully adjusted model from Zeng et al. and Tano et al. studies included) **(Figure S1c)** [10,14,15,32].

***Alcohol consumption and CRVE:***

Alcohol consumption was not associated with CRVE when individuals only with low levels of alcohol intake were included in the meta-analysis (β: 0.013, 95% CI: -0.101 to 0.128, p-value= 0.821 - adjusted model from Van der Heide et al. study included) **(Figures S2a)** [9,12], but also when only studies with alcohol intake as a continuous variable were included (β: 0.015, 95% CI: -0.014 to 0.043, p-value= 0.304 - adjusted model from Van der Heide et al. study included) **(Figure S2b)** [9,34]. In the same direction, when taking into consideration the limitation of data heterogeneity, alcohol consumption was not associated with CRVE when all available studies (adjusted and unadjusted) expressing alcohol as a binary variable (YES/NO) were included (β: 0.407, 95% CI: -0.313 to 1.127, p-value= 0.268 - fully adjusted model from Zeng et al. study included) **(Figure S2c)** [10,15,32], but also when only the adjusted studies were included (β: 0.438, 95% CI: -0.370 to 1.246, p-value= 0.288 - fully adjusted model from Zeng et al. study included) **(Figure S2d)** [9,10,12,32]. In all above cases due to the similarity of the results, we opted for the most adjusted models of both Zeng et al. and Van der Heide et al. studies.

***Alcohol consumption and AVR:***

Taking into consideration the limitation of data heterogeneity, there was no association between alcohol consumption and AVR when all available studies expressing alcohol as a binary variable (YES/NO) without specifying frequency (regular intake) or amount of alcohol intake were included (β: -0.032, 95% CI: -0.128 to 0.065, p-value= 0.521 -fully adjusted model from Zeng et al. included) **(Figure S3)** [14,32].

It is important to highlight that two cross-sectional studies [13,33] were omitted from the meta-analysis due to lack of necessary data for statistical analysis. Moreover, despite having available data, due to heterogeneity of them, a meta-analysis for FD could not be performed.

**Meta-regression analysis**

Based on the above results, meta-regression analysis was performed regarding the effect of gender and age on the associations of the retinal vessel diameter biomarkers CRAE and CRVE and alcohol consumption. Due to the limited number of available data, the results were statistically non-significant (p>0.05) [9,10,12,14,15,32,34,35,38] **(Figures S4–S5)**. For the meta-regression analysis we opted for the most adjusted model in each Zeng et al. study [32].

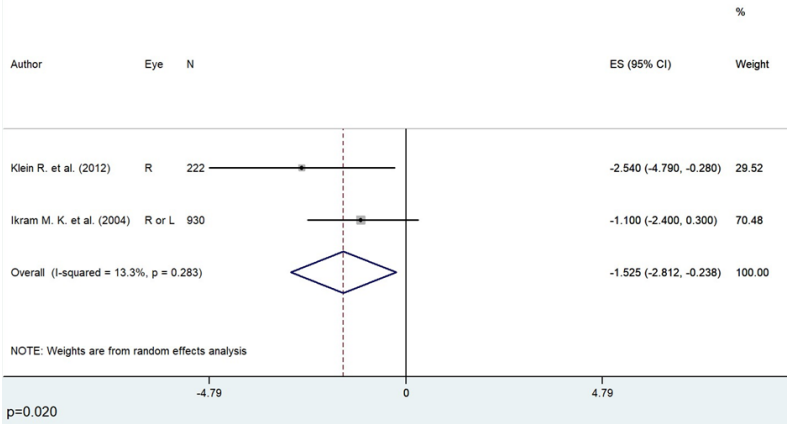



*Figure 2a: High alcohol intake (fully adjusted for Klein et al.)*
*Abbreviations: N, number; ES, effect size; CI, confidence intervals; R, right eye; L, left eye; p, p-value*

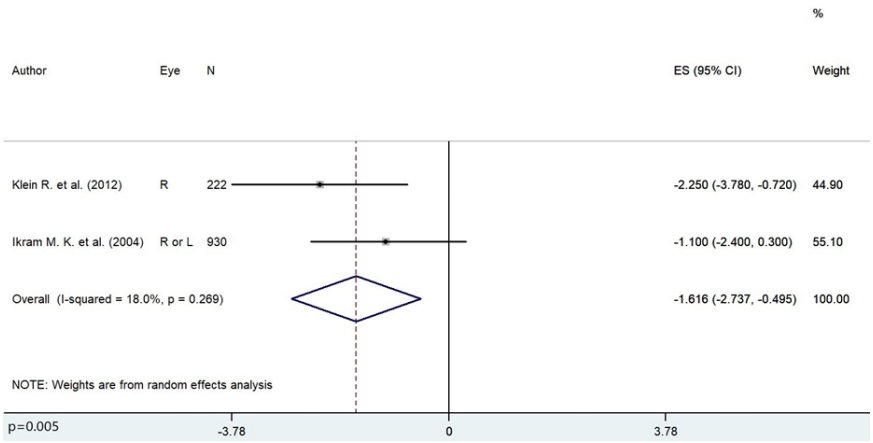



*Figure 2b: High alcohol intake (least adjusted for Klein et al.)*
*Abbreviations: N, number; ES, effect size; CI, confidence intervals; R, right eye; L, left eye; p, p-value*

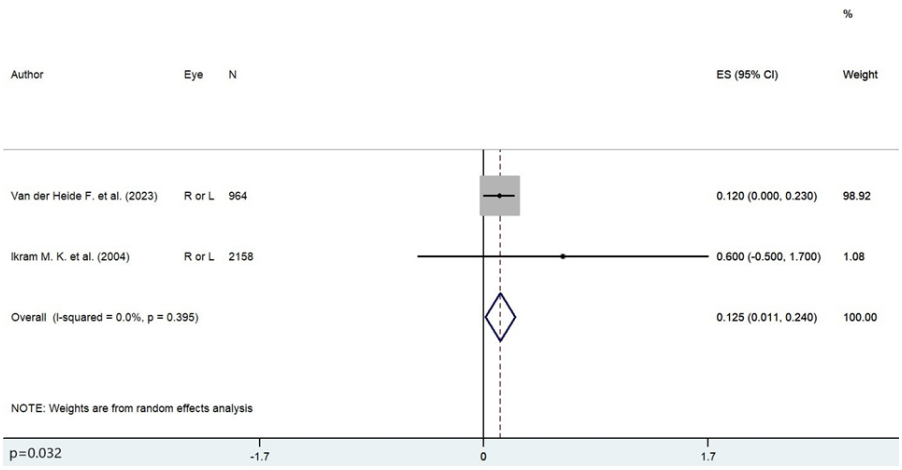



*Figure 2c: Low alcohol intake (unadjusted for Van der Heide et al.)*
*Abbreviations: N, number; ES, effect size; CI, confidence intervals; R, right eye; L, left eye; p, p-value*

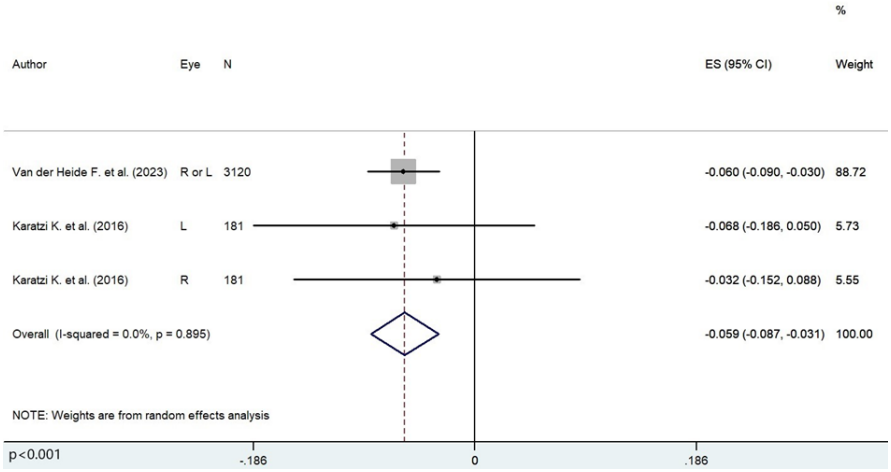



*Figure 2d: Alcohol as a continuous variable (unadjusted for Van der Heide et al.)*
*Abbreviations: N, number; ES, effect size; CI, confidence intervals; R, right eye; L, left eye; p, p-value*

*Figure 2: Forest plot of the meta-analysis between alcohol and CRAE: (2a) studies with high alcohol intake – fully adjusted for Klein et al.; (2b) studies with high alcohol intake – least adjusted for Klein et al.; (2c) studies with low alcohol intake – unadjusted for Van der Heide et al.; (2d) all available studies expressing alcohol as a continuous variable – unadjusted for Van der Heide et al.*

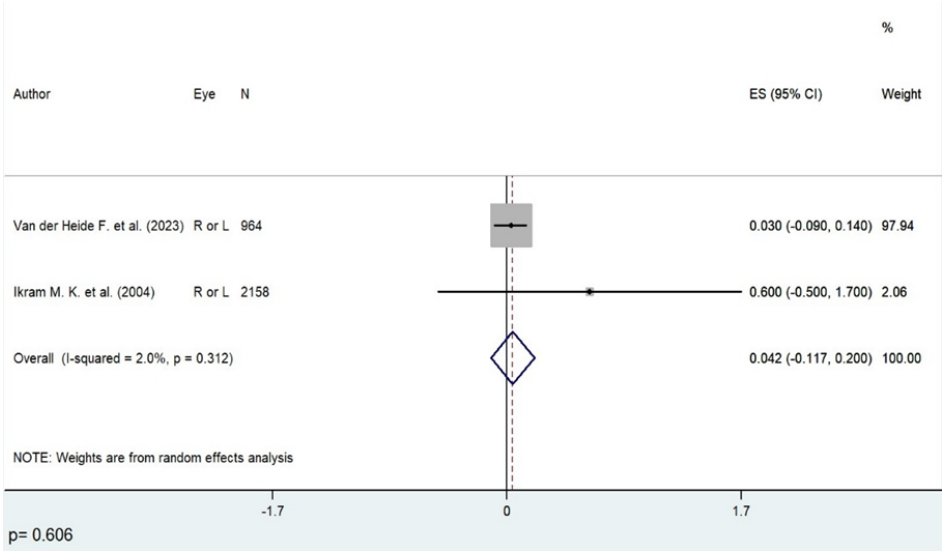



*Figure S1a: Low alcohol intake (adjusted model from Van der Heide et al. study included)*
*Abbreviations: N, number; ES, effect size; CI, confidence intervals; R, right eye; L, left eye; p, p-value*

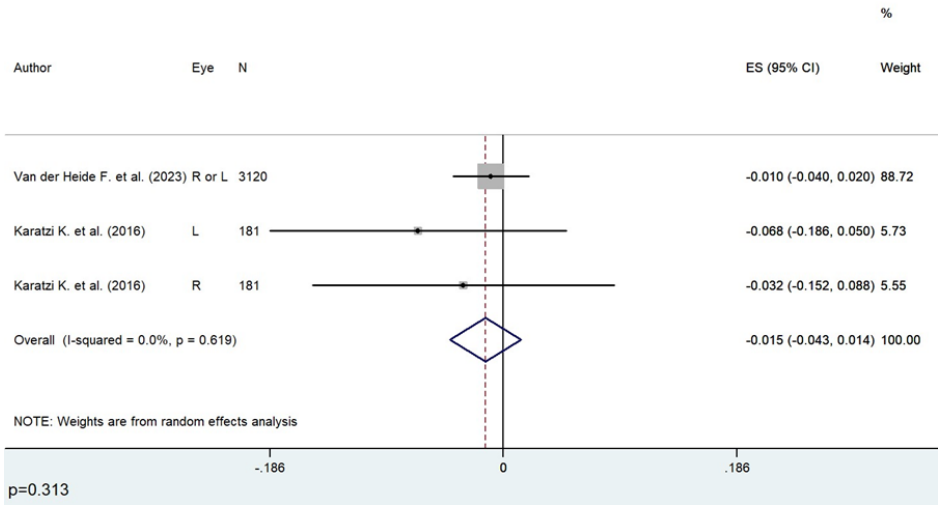



*Figure S1b: Alcohol as a continuous variable (adjusted model from Van der Heide et al. study included)*
*Abbreviations: N, number; ES, effect size; CI, confidence intervals; R, right eye; L, left eye; p, p-value*

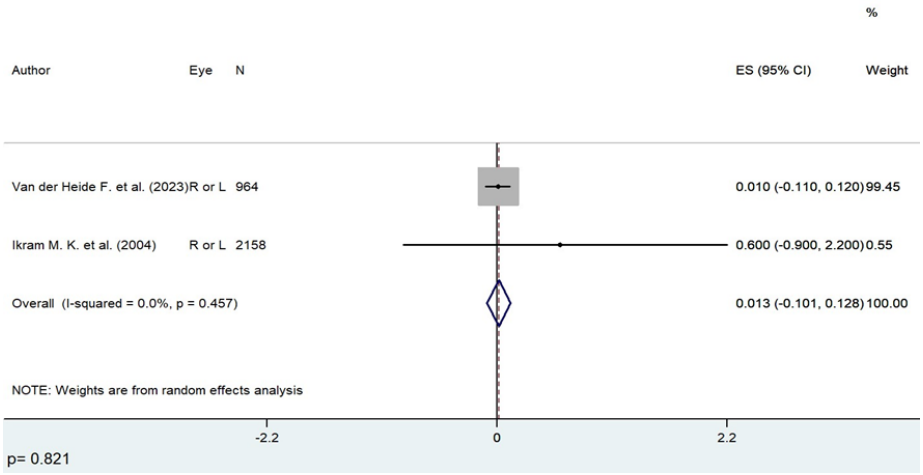



*Figure S1c: Alcohol as a binary variable (fully adjusted model from Zeng et al. included)*
*Abbreviations: N, number; ES, effect size; CI, confidence intervals; R, right eye; L, left eye; p, p-value*

*Figure S1: Forest plot of the meta-analysis between alcohol and CRAE: (S1a) studies with low alcohol intake; (S1b) all available studies expressing alcohol as a continuous variable; (S1c) all available studies expressing alcohol as a binary variable (YES/NO)*

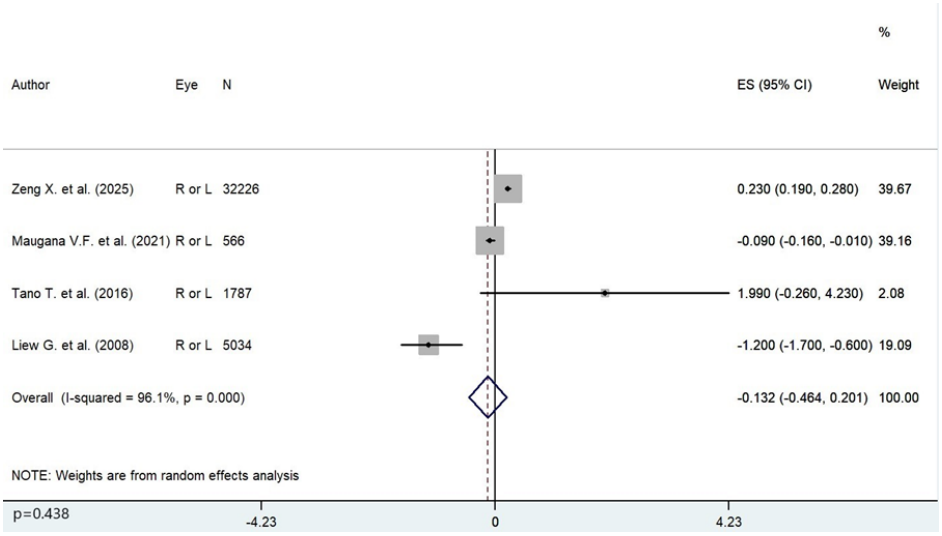



*Figure S2a: Studies with low alcohol intake (adjusted model from Van der Heide et al. included).*
*Abbreviations: N, number; ES, effect size; CI, confidence intervals; R, right eye; L, left eye; p, p-value*

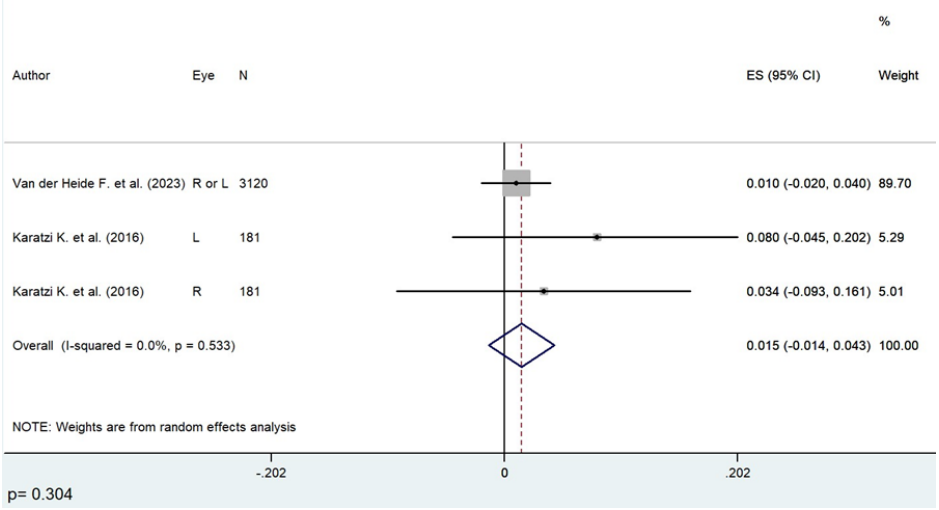



*Figure S2b: All studies with alcohol intake as continuous variable (adjusted model from Van der Heide et al. included). Abbreviations: N, number; ES, effect size; CI, confidence intervals; R, right eye; L, left eye; p, p-value*

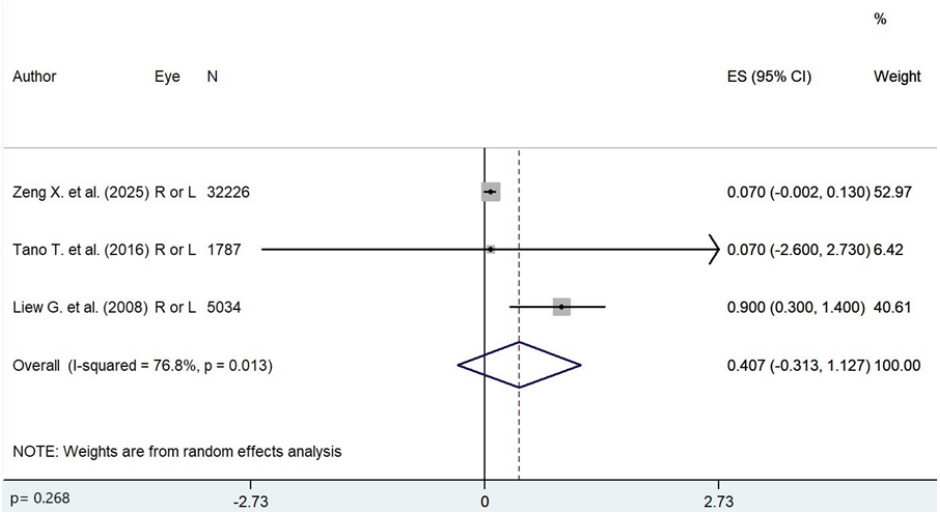



*Figure S2c: Alcohol as a binary variable (fully adjusted model from Zeng et al. included). Abbreviations: N, number; ES, effect size; CI, confidence intervals; R, right eye; L, left eye; p, p-value*

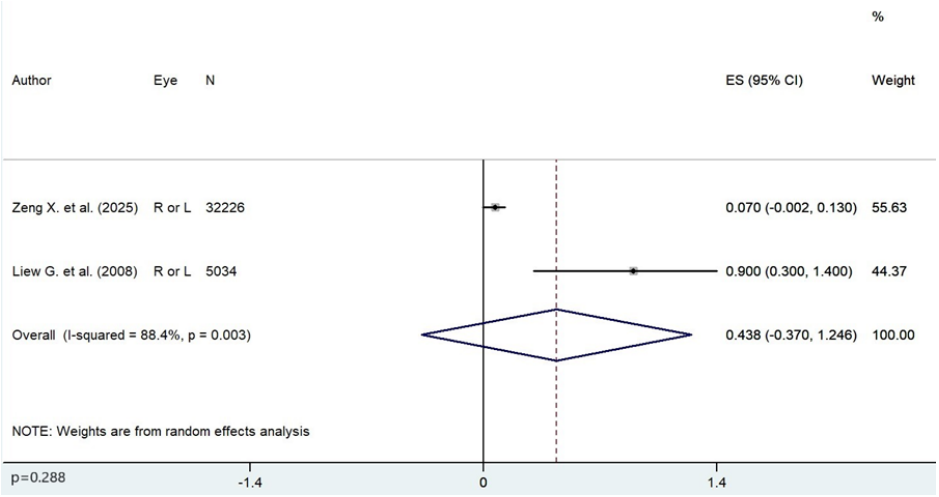



*Figure S2d: Only adjusted studies (fully adjusted model from Zeng et al. included). Abbreviations: N, number; ES, effect size; CI, confidence intervals; R, right eye; L, left eye; p, p-value*

*Figure S2: Forest plot of the meta-analysis between alcohol and CRVE: (S2a) studies with low alcohol intake; (S2b) all available studies expressing alcohol as a continuous variable; (S2c) all available studies expressing alcohol as a binary variable (YES/NO); (S2d) only adjusted studies included*

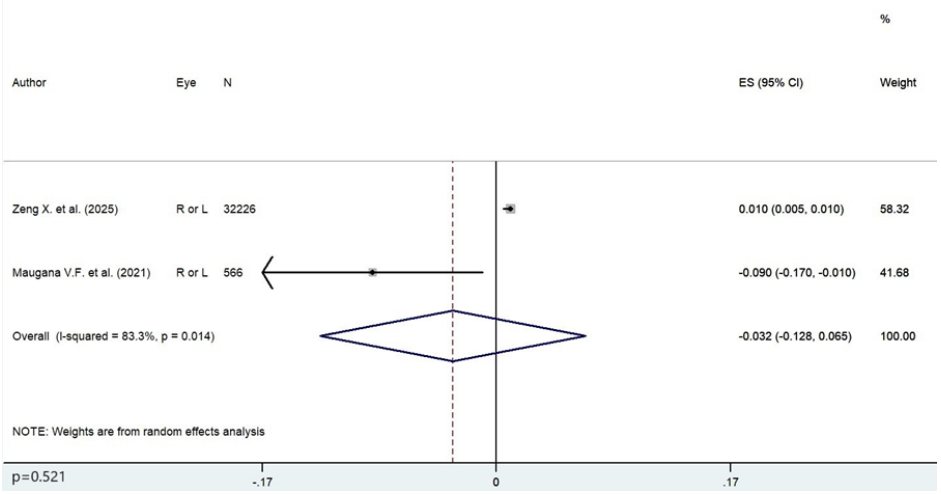



*Figure S3: Forest plot of the meta-analysis between alcohol and AVR: Alcohol as a binary variable (fully adjusted model from Zeng et al. included).*
*Abbreviations: N, number; ES, effect size; CI, confidence intervals; R, right eye; L, left eye; p, p-value*

```
Meta-regression                                   Number of obs   =         4
REML estimate of between-study variance           tau2            =         0
% residual variation due to heterogeneity         I-squared_res   =    77.60%
Proportion of between-study variance explained    Adj R-squared   =   100.00%
With Knapp-Hartung modification
```

| b | Coef. | Std. Err. | t | P>\|t\| | [95% Conf. | Interval] |
|---|---|---|---|---|---|---|
| sexmale | .428086 | .1198121 | 3.57 | 0.070 | -.0874239 | .943596 |
| _cons | -20.21796 | 5.696294 | -3.55 | 0.071 | -44.72714 | 4.291211 |

*Figure S4a: Male sex.*

```
Meta-regression                                   Number of obs   =         4
REML estimate of between-study variance           tau2            =     1.571
% residual variation due to heterogeneity         I-squared_res   =    91.99%
Proportion of between-study variance explained    Adj R-squared   =  -132.93%
With Knapp-Hartung modification
```

| b | Coef. | Std. Err. | t | P>\|t\| | [95% Conf. | Interval] |
|---|---|---|---|---|---|---|
| age | .0097718 | .0460489 | 0.21 | 0.852 | -.1883604 | .2079041 |
| _cons | -.4609728 | 2.406146 | -0.19 | 0.866 | -10.81378 | 9.891837 |

*Figure S4a: Age.*

*Figure S4: Meta-regression analysis for male between alcohol as a binary variable and CRAE: (S4a) male; (S4b) age.*

```
Meta-regression                                   Number of obs   =         3
REML estimate of between-study variance           tau2            =         0
% residual variation due to heterogeneity         I-squared_res   =     0.00%
Proportion of between-study variance explained    Adj R-squared   =   100.00%
With Knapp-Hartung modification
```

| b | Coef. | Std. Err. | t | P>\|t\| | [95% Conf. | Interval] |
|---|---|---|---|---|---|---|
| sexmale | -.3317473 | .105547 | -3.14 | 0.196 | -1.672849 | 1.009354 |
| _cons | 15.9177 | 5.038366 | 3.16 | 0.195 | -48.10081 | 79.9362 |

*Figure S5a: Male sex.*

```
Meta-regression                                   Number of obs   =         3
REML estimate of between-study variance           tau2            =     .1724
% residual variation due to heterogeneity         I-squared_res   =    37.70%
Proportion of between-study variance explained    Adj R-squared   =    32.31%
With Knapp-Hartung modification
```

| b | Coef. | Std. Err. | t | P>\|t\| | [95% Conf. | Interval] |
|---|---|---|---|---|---|---|
| age | .118833 | .1386427 | 0.86 | 0.549 | -1.64279 | 1.880456 |
| _cons | -6.516137 | 8.079205 | -0.81 | 0.568 | -109.1722 | 96.1399 |

*Figure S5a: Age.*

*Figure S5: Meta-regression analysis for male between alcohol as a binary variable and CRVE: (S5a) male; (S5b) age.*

Despite the fact that retinal microcirculation indices might be used to monitor changes in respect to alcohol consumption habits and thus monitor potentially relevant treatment strategies, this research aim could not be addressed in the present systematic review and meta-analysis due to the fact that the existing literature mainly includes observational studies, which limits the establishment of a cause-effect relationship.

## Discussion

In this systematic review and meta-analysis, we provide a comprehensive synthesis of available evidence on the association between alcohol consumption and retinal microvascular structure and function. The main findings can be summarized as follows: (i) the systematic review showed that higher alcohol consumption is consistently associated with narrowed CRAE and reduced AVR, but also alcohol in general is associated with a trend towards lower vascular tortuosity, impaired flicker light–induced dilation, low VSD (arteriolar and venular) and acutely increased VDI. The one available interventional study showed that acute alcohol intake was associated with increased and then decreased VDI values (0.5 and 2h, respectively), ii) the meta-analysis showed that high alcohol intake and alcohol as a continuous variable are associated with narrowed CRAE, while low alcohol intake is associated with greater CRAE – with only the first association being statistically significant in all levels of adjustment of the included studies. Collectively, these results suggest that alcohol consumption, particularly at higher levels, is associated with unfavorable retinal microvascular phenotypes, while low alcohol intake seems to be associated with a possible protective role on retinal microcirculation; however, the latter association must be further investigated in well-designed studies.

The possible discrepancy between moderate alcohol consumption and CRAE, CRVE, AVR and FD is likely due to the different levels of adjustment, as it is known that adjusting for the alternative vessel can impact the direction of the association between a cardiovascular risk factor and the retinal vessel biomarker (CRAE or CRVE). After meta-analyzing these data, heavy and low alcohol intake were both associated with CRAE, however, CRVE and AVR were not associated with alcohol intake despite the results of the existing literature [9,10,12,14,15,32–34]. In order to meta-analyze the data from the studies included, an attempt was made to categorize them based on the frequency and quantity of alcohol consumption. Despite these efforts, the significant heterogeneity and incomplete reporting of data regarding quantity, frequency of alcohol intake and type of alcohol beverage, substantially limit the reliability of the present results, especially when it comes to meta-analyzing binary data of alcohol intake (YES/NO). Consequently, it is essential to establish universal thresholds for the quantity and frequency of alcohol consumption to facilitate a thorough evaluation of its potential effects on the human body. As for the meta-regression analysis, all the results for both gender and age were statistically non-significant, probably due to the small number of available literature and thus a small amount of data.

Various pathophysiological mechanisms may explain the above associations between alcohol consumption and the different structural and functional biomarkers, with the two most significant being: i) endothelial dysfunction via oxidative stress and inflammation, and ii) systematic hypertension via vascular remodeling/stiffening [18]. Other possible pathophysiological pathways could be the sympathetic nervous system activation (for CRAE) [39], neurodegeneration leading to reduced metabolic demand (for FD and VSD) [40,41], fibrosis and structural simplification (for tortuosity) [42] and impaired neurovascular coupling (for FID) [43]. As far as the pathophysiology behind the acute effect of alcohol intake on VDI, blood ethanol levels seem to affect retinal vasodilation and vasoconstriction via NO expression levels [37]. Moreover, the animal-based model (rat) of the Zhu et al. study, demonstrated that moderate red wine intake may acutely affect vascular endothelial cells via increased oxidative stress and increased ET-1 levels but also by down-regulating claudin-5 expression, resulting in microvascular contraction [37].

The present systematic review and meta-analysis encompass a broad range of existing literature on the association of alcohol consumption with the retinal microcirculation, with all available studies being observational. The retinal microcirculation shares common characteristics with other microcirculations and is, therefore, considered to be a window of the microcirculation in other target organs of the human body [1]. Despite the fact that several studies have shown that narrowed CRAE, dilated CRVE, decreased FD, high retinal vessel tortuosity, smaller VSD and lower FID (both arteriolar and venular) are associated with increased CVD risk (cardiac mortality, incident stroke and incident CHD) [20–26], the "cross-sectional" relationship between the studied retinal biomarkers and alcohol consumption can only be used as an impetus for establishing a cause-and-effect association between the results of the present study and their application to the rest of the cardiovascular system. Through retinal imaging, we can non-invasively evaluate the long-term adverse effects of lifestyle factors - such as alcohol consumption - in retinal microcirculation and potentially use these indices as markers of the effectiveness of lifestyle interventions in the future; the latter hypothesis must be tested in well-designed studies. A recent multicenter, open-label randomized control trial in China (ESPRIT study), examined the reversibility of the retinal vessel indices, showing for the first time that a lower treatment target of SBP (from 130 to 140mmHg) was associated with significant improvements of retinal vessel indices (vessel caliber, density, complexity and tortuosity) [44]. Taking all the above into consideration, studying the fundus may ultimately become an important tool in clinical practice, by contributing to a better choice of treatment and also by playing a key role in cardiovascular prevention strategies.

Alcohol consumption is thought to exert deferential effects on the cardiovascular system, supporting the J-shape theory, varying between different kinds of alcoholic beverages [9,19]. Despite the heterogeneity in the quantity, frequency and type of alcohol drink, alcohol consumption seems to exhibit a non-linear dose-dependent (low -high) inverse effect on the retinal microcirculation, as alcohol intake levels increase, a result consistent with the above theory [9].

Considering the results of the present systematic review and meta-analysis but also taking into account the results of Zhu et al. study [37], there is a need for further and detailed investigation of the possible acute effect of alcohol intake on retinal microcirculation, as acute alcohol consumption might be a possible confounder when evaluating the retinal microcirculation. Despite the fact that some studies have incorporated this potential acute effect in their methodological approach, resulting in

abstaining from alcohol consumption for a reasonable period (at least 2-3 hours [34,45]) before fundoscopy, there is lack of large-scale studies validating the need of alcohol abstinence prior assessing the retinal microcirculation.

This study has several strengths, including a comprehensive and systematic search strategy, adherence to MOOSE guidelines, inclusion of a wide range of retinal structural and functional biomarkers, and quantitative synthesis of retinal vessel caliber outcomes. However, several limitations should be acknowledged. The majority of included studies were observational and cross-sectional, precluding causal inference. The literature retrieved from our review was quite limited, while some studies included a relatively small number of participants. Among the included literature, the majority does not specify the type of alcoholic beverage and the exact quantity in grams, with some studies omitting specifying also the consumption frequency, resulting in significant data heterogeneity. Moreover, these studies utilized only a restricted number of available indices for the evaluation of the retinal microcirculation, while no interventional studies were found. Even though different software packages were used across the studies included for the assessment of retinal indices, no current study exists comparing these different types of software, which constitutes an interesting research area and warrants a dedicated study. Lastly, there was a diversity regarding the adjustment of confounders between the studies included in this systematic review, with lack of fully adjusted models in several studies. All the above may emphasize the need for more studies in this field of research.

## Conclusion

This systematic review and meta-analysis demonstrate that higher alcohol consumption is associated with adverse retinal microvascular alterations, most consistently characterized by retinal arteriolar narrowing, evidence of microvascular dysfunction. While findings regarding low or moderate alcohol consumption were heterogeneous, the available evidence does not indicate a clearly protective effect on retinal microvascular health. Given the established links between retinal microvascular abnormalities and both ocular and systemic vascular disease, alcohol consumption may represent a modifiable factor influencing retinal microvascular integrity. Future longitudinal and interventional studies with standardized exposure assessment and advanced retinal imaging are warranted to clarify causality and to determine whether alcohol reduction may improve retinal microvascular outcomes.

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**Competing Interests of Authors:** None

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