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REVIEW

The Acute Effects of Caffeine on OCT and OCTA Parameters: A Systematic Review and Meta-Analysis

Davi Marçola Veiga[1], Yuri Aleksander Ivanov[2], Alexandre Yamada Fujimura Júnior[1], Maria Eduarda Figueiredo Rebolho[1], Beatriz Gonçalves da Silva Miroski Gerente[3], Dillan Cunha Amaral[4], Raíza Jacometti[5], Jaime Guedes[6], Mário Luiz Ribeiro Monteiro[5], Ricardo Noguera Louzada[4,5]

[1]Faculty of Medicine, Marilia Medical School, Marília, SP, Brazil; [2]Faculty of Medicine, University of the Extreme South of Santa Catarina, Criciúma, SC, Brazil; [3]Faculty of Medicine, University of Southern Santa Catarina, Florianópolis, SC, Brazil; [4]Department of Ophthalmology and Otorhinolaryngology, Faculty of Medicine, Federal University of Rio de Janeiro, Rio de Janeiro, RJ, Brazil; [5]Division of Ophthalmology and the Laboratory for Investigation in Ophthalmology (LIM-33), Faculty of Medicine, Universidade de São Paulo, São Paulo, SP, Brazil; [6]Aran Eye Associates, Coral Gables, FL, USA

Correspondence: Jaime Guedes, Aran Eye Associates, 1097 S Lejeune Road, Coral Gables, FL, 33134, USA, Email jaimeguedes@gmail.com

Purpose: This systematic review and meta-analysis aimed to comprehensively assess the acute effects of caffeine and caffeinated beverages on ocular microvasculature measured by optical coherence tomography (OCT) and optical coherence tomography angiography (OCTA) parameters, explicitly focusing on subfoveal choroidal thickness (SFCT) and superficial capillary vessel density (SVD), and deep capillary vessel density (DVD).

Methods: A systematic search was conducted across PubMed, the Cochrane Database, and Embase for trials evaluating the acute effects of caffeine or caffeinated beverages on SFCT, SVD, and DVD, as measured by OCTA. Pooled mean differences (MD) were calculated using random-effects models, with heterogeneity assessed by I^2 statistics. Subgroup analyses were performed by study design, intervention type, and refractive status. The protocol was prospectively registered in PROSPERO (CRD420251091123). Statistical analyses were performed using RStudio 2025.05.1+513.

Results: 18 studies comprising 630 patients were included. Pooled analysis demonstrated a significant reduction in SFCT after caffeine intake (–23.79 μm; 95% CI: –31.43 to –16.15; $p < 0.001$), particularly with coffee and caffeine capsules, whereas no effect was observed with energy drinks or in highly myopic eyes. Regarding SVD, caffeine was associated with significant reductions across foveal, parafoveal, and perifoveal regions, mainly driven by coffee and capsule interventions. In DVD analyses, no overall significant effect was found; however, subgroup analyses indicated significant reductions with caffeine capsules and coffee, while energy drinks showed opposite trends.

Conclusion: Acute caffeine intake, primarily from capsules or coffee, induces significant SFCT reduction and modest reductions in SVD, while changes in DVD were confined mainly to the caffeine-capsule subgroup, suggesting that energy drink ingredients may counteract caffeine-induced vasoconstriction. These findings offer valuable insights into the acute effects of caffeine on ocular microvasculature; however, the modest effect sizes necessitate caution regarding inherent physiological, measurement, and bioactive components variability. This study establishes a foundation for future investigations into the clinical significance of acute ocular microvascular fluctuations following caffeine intake.

Keywords: caffeine, coffee, subfoveal choroidal thickness, optical coherence tomography, optical coherence tomography angiography, systematic review

Introduction

Caffeine is the most widely consumed psychoactive substance worldwide, with approximately 80% of the Western population consuming it regularly.[1] Its popularity is due to its wide availability, legal status, and rapid absorption in the

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gastrointestinal tract, reaching peak plasma levels in approximately 30 minutes.[2,3] The primary dietary sources of caffeine include coffee, tea, energy drinks, and cola-based soft drinks.[1,4] Once ingested, caffeine stimulates the central nervous system, increasing blood pressure and heart rate through antagonism of adenosine receptors, particularly A1 and A2A.[5–7]

Caffeine's vasoconstrictive effects are well documented. However, its impact on ocular blood flow has been less extensively investigated and has been associated with transient choroidal vasoconstriction and reduction in subfoveal choroidal thickness (SFCT).[8] Studies assessing retinal vessel caliber have reported decreases in both arteriolar and venular diameters following caffeine intake, with corresponding changes in ocular hemodynamic parameters.[9,10]

These findings support the hemodynamic influence of caffeine on ocular circulation and provide a physiological framework for interpreting structural and vascular changes detected by Optical Coherence Tomography (OCT) and optical coherence tomography angiography (OCTA).[11]

More recently, OCT and OCTA have been employed to further evaluate these vascular effects, reporting reductions in SFCT following caffeine consumption.[12] SFCT is defined as the vertical distance between Bruch's membrane and the inner scleral boundary beneath the fovea.[13] These noninvasive imaging modalities allow detailed structural and microvascular assessment of the retina and choroid and have facilitated investigation of the relationship between caffeine intake and SFCT.[14]

These changes typically begin between 5 and 30 minutes after the intake of approximately 200 mg of caffeine and may persist for up to 4 hours, peaking around 1 hour post-ingestion.[15] Choroidal thinning has been attributed to reduced ocular blood flow associated with the vasoconstrictive effect of caffeine.[8,12,16] However, ocular autoregulatory mechanisms are thought to maintain overall perfusion within physiological limits.[15]

The choroid is one of the most highly vascularized tissues in the human body and plays a fundamental role in supplying oxygen and nutrients to the outer retina, particularly the photoreceptors and the retinal pigment epithelium (RPE).[17,18] Owing to its rich vascular supply, the choroid is sensitive to hemodynamic changes induced by vasoactive substances.[17,19] OCT and OCTA imaging have also been used to evaluate the vascular and structural effects of other substances on the retina and choroid. For instance, nicotine has been reported to exert ischemic effects on retinochoroidal and vascular structures.[20] Conversely, specific agents have been associated with increased choroidal thickness, including intraocular pressure–lowering medications, topical atropine, and the systemic administration of β-blockers and ethanol.[21]

Accordingly, several studies have investigated the effects of caffeine on choroidal circulation, reporting reductions in ocular blood flow and choroidal thickness. Changes in SFCT, macular flow area, and macular vessel density have also been described following caffeine intake, and investigations assessing superficial, deep, and choriocapillaris vessel density using OCTA have yielded variable findings.[16]

Given these observations, variations in choroidal thickness should be interpreted within the context of physiological and methodological variability.[16,22,23] Epidemiological investigations have also explored associations between caffeine intake and ocular conditions, although findings remain heterogeneous.[24]

Therefore, a systematic evaluation of the available evidence is warranted to quantify the acute effects of caffeine and caffeinated beverages on structural and microvascular parameters assessed by OCT and OCTA.

Methods

Protocol and Registration

This study was conducted and reported according to the guidelines of the Cochrane Collaboration Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement.[25] The protocol was prospectively registered in the International Prospective of Systematic Reviews (PROSPERO) under protocol number CRD420251091123.

Data Source and Search Strategy

We systematically searched PubMed, Embase, and Cochrane databases. References of eligible papers and systematic reviews were also searched for additional studies of interest. Our search was last updated in June 2025. Two authors independently assessed all records, and decisions on full-text retrieval were reached by consensus. Full texts were

retrieved from all databases, and inclusion and exclusion criteria were discussed. The full search strategy for all databases was (caffeine OR energy drink OR coffee OR tea OR cola) AND ("Optical Coherence Tomography" OR OCT[Title/Abstract] OR "Optical Coherence Tomography Angiography" OR "OCTA" OR "vessel density" OR "foveal avascular zone" OR "FD-300" OR "optic nerve head" OR "retinal nerve fiber layer thickness" OR "retinal vessel" OR "choroidal thickness"). Conference abstracts and prospective trials were also searched. Data were collected independently by two authors. Following data collection, the extracted information was cross-checked, and any discrepancies were discussed until consensus was reached. No automation tools were used at any stage of the data extraction process.

Eligibility Criteria

There were no restrictions on the publication date or language. We considered studies eligible for inclusion if they (1) assessed OCT or OCTA at baseline and after caffeine or caffeinated beverages ingestion (2) reported on outcomes of interest. The exclusion criteria were as follows: (1) in vitro studies; (2) case reports, abstracts, editorials, letters, and conference proceedings without sufficient data.

Endpoints and Subanalyses

The clinical outcomes of interest in our study were: (1) SFCT; (2) Foveal DVD;

(3) Parafoveal DVD; (4) Perifoveal DVD; (5) Foveal SVD; (6) Parafoveal SVD; (7) Perifoveal SVD. Additionally, baseline characteristics of included studies and participants were also collected and summarized in Table 1. The variables collected included reported outcomes, intervention type, number of participants, and number of eyes analyzed. Participant-level characteristics included age, sex, refractive error, spherical equivalent, eye axial length, body mass index, and systolic and diastolic blood pressure.

Quality Assessment

Risk of bias was assessed independently by two authors using the Cochrane Risk of Bias tool for randomized controlled trials (RoB 2),[39] and the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool.[40] Any discrepancies were resolved through discussion until consensus was reached. Visual representations of the assessments were generated using the *RobVis* tool.

Statistical Analysis

All statistical analyses were performed using R (RStudio version 2025.05.1+513) with the *meta* package. Study characteristics were tabulated to decide which studies were eligible for each synthesis. For continuous outcomes, mean and standard deviation (SD) values were extracted from the intervention groups' baseline and post-intervention data. When studies reported medians and interquartile ranges (IQR), these values were converted to means and SDs using the method proposed by Wan et al (2014) via the Meta-Analysis Accelerator tool.[41,42] When standard deviations (SDs) were not reported, they were imputed using the *P-value to SD in 2 Groups* conversion method. When no conversion was feasible, SDs were assumed from studies with similar methodology and comparable populations, in accordance with recommendations from the *Cochrane Handbook for Systematic Reviews of Intervention*.[43]

All meta-analyses were conducted under a random-effects model, using the inverse-variance method with the restricted maximum likelihood (REML) estimator for the between-study variance (τ^2). Pooled MD and their corresponding 95% confidence intervals (CI) were calculated for each continuous outcome. A two-sided p-value of < 0.05 was considered statistically significant. Between-study heterogeneity was assessed using Cochrane's Q test (Chi^2) and quantified with the I^2 statistic; $p \leq 0.10$ indicated significant heterogeneity. To explore possible causes of heterogeneity among study results, subgroup meta-analyses according to intervention type, refractive status, and study design were conducted when sufficient data were available.

Results

Study Selection

As shown in Figure 1, the search strategy initially identified 770 studies. After removing 155 duplicates, 615 records remained for title and abstract screening. Of these, 39 were selected for full text, resulting in 18 studies being

Table 1 Baseline Characteristics of the Studies Included

Author (Year)	Study Design	Outcomes of Interest	Intervention	Control	Participants	E. Eyes	C. Eyes	E. Mean age ± SD	C. Mean age ± SD	E. M/F	C. M/F	E. SE (SD)	C. SE ± SD	BCVA ± SD	E. AL ± SD	C. AL ± SD	E. BMI ± SD	C. BMI ± SD	E. SBP ± SD	C. SBP ± SD	E. DBP ± SD	C. DBP ± SD
Jacobs (2024)[26]	Randomized, double-blind, placebo-controlled	VD	200mg caffeine capsule	Placebo capsule	59	42	17	23 ± 3.66	23.2 ± 3.62	13/29	6/11	NA	NA	NA	R: 23.8 ± 1.24; L: 23.8 ± 1.08	R: 23.3 ± 1.07; L: 23.4 ± 1.32	24.1 ± 3.19	25.2 ± 4.84	122 ± 7.57	119 ± 8.07	81.7 ± 6.56	77.4 ± 5.81
Tugan (2022)[27]	Randomized, double-blind, placebo-controlled	VD	200mg caffeine capsule	Placebo capsule	120	60	60	37.5 ± 18.23	36.17 ± 25.07	16/44	16/44	−0.75 ± 3.23	−0.25 ± 4.37	1	24.01 ± 3.25	23.32 ± 3.13	NA	NA	111.67 ± 37.98	113.33 ± 37.98	66.67 ± 22.79	70 ± 15.19
Altinkaynak (2015)[28]	Randomized, placebo-controlled	SFCT	200mg caffeine capsule	Placebo capsule	100	50	50	29.87 ± 6.25	28.72 ± 6.71	28/22	26/24	0.54 ± 0.9	0.38 ± 0.32	1	23.2 ± 0.7	23.2 ± 0.6	NA	NA	NA	NA	NA	NA
Dogan (2022)[29]	Randomized Controlled Trial	VD, SFCT	65-100mg caffeine (Caffeinated coffee)	Decaffeinated coffee	48	24	24	23.45 ± 0.92	22.73 ± 1.13	12/12	12/12	NA	NA	1	21.90 ± 2.07	21.83 ± 2.26	NA	NA	NA	NA	NA	NA
Karti (2018)[30]	Randomized, placebo-controlled	VD	200mg caffeine capsule	Placebo capsule	52	26	26	40.6 ± 8.9	39.5 ± 9.4	14/12	13/13	0.32 ± 0.54	0.24 ± 0.45	NA	23.26 ± 0.33	23.43 ± 0.36	NA	NA	119.4 ± 7.50	117.9 ± 8.30	75.3 ± 3.70	77.3 ± 5.10
Vural (2014)[8]	Randomized Controlled Trial	SFCT	57mg caffeine (100mL coffee)	100mL water	116	62	54	31.61 ± 7.37	32.22 ± 7.71	20/42	22/32	−0.08 ± 0.59	−0.18 ± 0.32	1	22.9 ± 0.5	23.1 ± 0.8	24.55 ± 4.39	22.90 ± 4.82	NA	NA	NA	NA
Zengin (2014)[12]	Randomized, placebo-controlled	SFCT	200mg caffeine capsule	200mg placebo	36	18	18	30 ± 6.84	32.50 ± 7.04	8/10	8/10	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Dervişoğulları (2015)[31]	Randomized, placebo-controlled	SFCT	200mg caffeine capsule	200mg placebo	34	17	17	23.75 ± 1.39	25.25 ± 1.39	12/5	11/6	−0.79 ± 1.71	−0.46 ± 0.81	NA	23.74 ± 2.11	23.78 ± 1.2	NA	NA	NA	NA	NA	NA
Law (2022)[32]	Randomized, crossover, placebo-controlled	VD, SFCT	200mg caffeine capsule	Placebo capsule	18	18	18	24.3 ± 3.1	24.3 ± 3.1	6/12	6/12	−8.05 ± 1.71	−8.05 ± 1.71	NA	26.78 ± 0.97	NA	20.1 ± 4.3	NA	101.4 ± 9.0	101.9 ± 7.7	61.8 ± 5.8	61.8 ± 8.1
Zhu (2022)[33]	Randomized crossover	VAD	72mg caffeine (300mL coffee)	300mL water	27	27	NA	22.7 ± 3.1	NA	12/15	NA	−1.1 ± 1.5	NA	1	23.9 ± 1.0	23.9 ± 1.0	22 ± 4.5	NA	114.18 ± 11.33	118.00 ± 14.32	69.36 ± 6.82	73.75 ± 8.07
Dogan (2021)[34]	Prospective placebo-controlled	VD	51.9mg caffeine* (250mL black tea)	250mL water	60	30	30	33.27 ± 7.92	31.00 ± 7.30	19/11	15/15	NA	NA	1	21.18 ± 1.92	21.80 ± 2.75	NA	NA	NA	NA	NA	NA
Koçak (2022)[14]	Prospective, placebo-controlled	SFCT	75mg caffeine (200mL coffee)	200mL water	56	28	28	32.57 ± 3.52	31.38 ± 3.13	16/12	16/12	0.38 ± 0.18	−0.60 ± 0.32	NA	21.83 ± 0.73	22.05 ± 0.75	23.50 ± 2.93	24.07 ± 21.63	118.8 ± 8.3	117.9 ± 7.9	74.3 ± 4.2	73.6 ± 3.9

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Dogan (2020)[35]	Prospective, cross-over	VD, SFCT	37.5mg caffeine (250mL energy drink)	250mL water	42	42	42	20.58 ± 0.71	20.58 ± 0.71	25/17	25/17	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Toprak (2023)[36]	Prospective crossover	SFCT	37.5mg caffeine (250mL coffee) / 37.5mg caffeine (250mL energy drink)	250mL water	30	30	NA	26.10 ± 1.61	26.10 ± 1.61	30/0	30/0	−1.14 ± 1.08	NA	1	23.85 ± 0.99	NA	23.18 ± 2.35	NA	< 140	NA	< 90	NA
Nagasato (2021)[15]	Prospective cross-sectional	SFCT	148mg caffeine (185mL coffee)	185mL water	81	49	32	30.3 ± 4.9	30.6 ± 4.5	19/30	15/17	−3.02 ± 2.12	−2.64 ± 2.02	NA	24.65 ± 1.09	24.51 ± 1.08	NA	NA	NA	NA	NA	NA
Alotaibi (2024)[37]	Prospective cross-sectional	SFCT	200mg caffeine capsule	NA	45	45	NA	E: 21.08 ± 2.47; M: 20.56 ± 1.12; HM: 21.0 ± 0.71	NA	24/21	NA	E: −0.17 ± 0.16; M: −1.49 ± 0.99; HM: −6.10 ± 0.14	NA	NA	E: 23.49 ± 0.82; M: 24.35 ± 0.77; HM:25.42 ± 0.29	NA	NA	NA	NA	NA	NA	NA	NA
Arej (2020)[4]	Prospective single-arm cohort	SFCT	37.5mg caffeine (250mL energy drink)	NA	20	40	NA	27.9 ± 4.7	NA	7/13	NA	NA	NA	R: 1.14 ± 0.14; L: 1.12 ± 0.12	NA	NA	NA	NA	NA	NA	NA	NA
Shoeibi (2022)[38]	Interventional case series	SFCT, VD	130mg caffeine (450 mL coffee)	NA	22	22	NA	34 ± 6.8	NA	13/9	NA	NA	NA	NA	NA	NA	NA	NA	104.82	NA	72.91	NA

Notes: *Caffeine dose approximation for 250mL of black tea. Source: Mitchell DC, Hockenberry J, Teplansky R, Hartman TJ. Assessing dietary exposure to caffeine from beverages in the US population using brand-specific versus category-specific caffeine values. *Food and Chemical Toxicology.* 2015;80:247–252. doi:10.1016/j.fct.2015.03.024.

Abbreviations: SFCT, subfoveal choroidal thickness; VD, Vessel density; VAD, Vessel area density; SD, standard deviation; NA, not available; E, emmetropes; M, myopes; HM, high myopes; R, right eye; L, left eye; E. eyes, number of eyes in intervention group; C. eyes, number of eyes in control group; E. Mean age, mean age in intervention group in years; C. Mean age, Mean age in control group in years; E. M/F, Male/Female participants in intervention group; C. M/F, Male/Female participants in control group; E.SE, mean spherical equivalent in diopters in intervention group; C.SE, mean spherical equivalent in diopters in control group; BCVA, mean best corrected visual acuity in Snellen decimal scale; E. AL, mean axial length in intervention group in millimeters; C. AL, mean axial length in control group in millimeters; E. BMI, mean body mass index in intervention group; C. BMI, mean body mass index in control group; E. SBP, mean systolic blood pressure in intervention group in mmHg; C. SBP, mean systolic blood pressure in control group in millimeters of mercury; E. DBP, mean diastolic blood pressure in intervention group millimeters of mercury; C. DBP, mean diastolic blood pressure in control group.

included.[4,8,12,14,15,26–38] Altogether, these studies involved 630 participants with a mean age of 28.8 years. Among them, 276 received caffeine in capsule form, 212 consumed coffee, 30 consumed black tea, and 82 consumed an energy drink. One study with 30 participants used a mixed intervention, in which the same individuals ingested coffee, followed by an energy drink.[36] Regarding refractive status, 76 patients were classified as myopes, 23 as high myopes, and the remainder as emmetropes. The detailed baseline characteristics of the included studies are presented in Table 1.

Subfoveal Choroidal Thickness

Regarding the SFCT outcome, a pooled analysis of 13 studies demonstrated a significant reduction in SFCT following caffeine intake compared with baseline. The overall MD was –23.79 micrometers (95% confidence interval [CI]: –31.43 to –16.15; $p < 0.001$), indicating a consistent thinning of the subfoveal choroid after caffeine administration.

In the subgroup analysis by type of intervention, distinct effects were identified (Figure 2). Among the 238 participants who ingested coffee, a marked and significant reduction in SFCT was observed one hour after intake, with a MD of –29.48 micrometers (95% CI: –40.11 to –18.86; $p < 0.001$). In the subgroup of 103 participants who received caffeine capsules, a significant reduction was also demonstrated, with a MD of –20.24 micrometers (95% CI: –

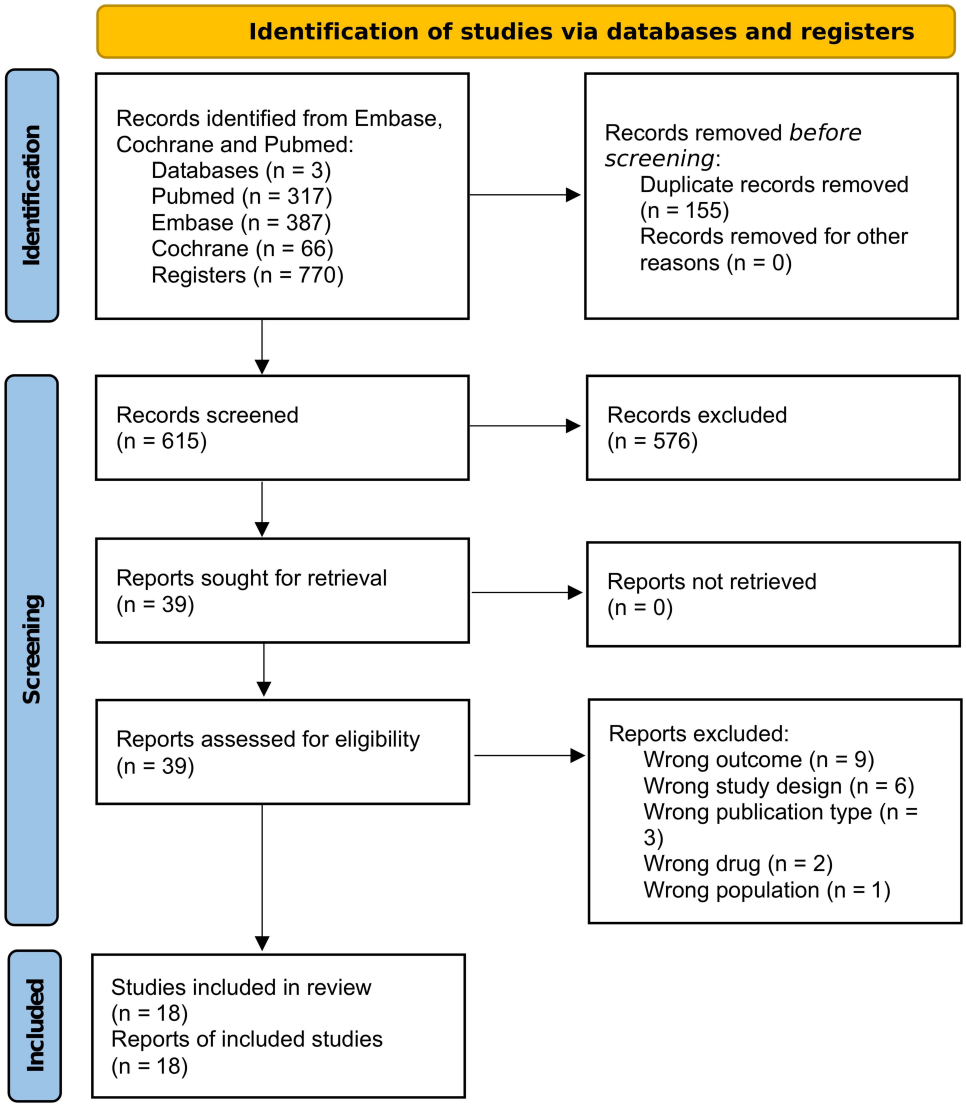

Figure 1 PRISMA flow diagram.

39.92 to –3.56; p = 0.018). Conversely, in the subgroup of participants who consumed energy drinks, no significant effect was observed, with an MD of –9.49 micrometers (95% CI: –28.64 to 9.72; p = 0.33).

This outcome was further analyzed by refractive status (Figure 3). In the emmetropic group (324 participants), caffeine intake was associated with a significant reduction of –28.47 micrometers (95% CI: –38.03 to –18.90; p < 0.001). A similar effect was observed among myopic patients, with a reduction of –32.86 micrometers (95% CI: –53.14 to –12.58; p = 0.002). However, in the subgroup of high myopes, caffeine intake did not demonstrate effectiveness, with a non-significant MD of –0.13 micrometers (95% CI: –27.82 to 27.56; p = 0.99).

Additionally, subgroup analysis by study design was conducted (Supplementary Figure 1), encompassing 423 eyes (224 in the non-randomized subgroup and 199 in the randomized subgroup). For both subgroups, a significant reduction in SFCT at 1 h post-ingestion was observed. Nevertheless, this trend was greater in the randomized subgroup (MD = –32.52; 95% CI: –44.29 to –20.75; p < 0.0001) compared to the non-randomized subgroup (MD = –17.33; 95% CI: –28.40 to –6.25; p = 0.002).

Deep Capillary Vessel Density

The evaluation of DVD was performed across three retinal regions: foveal, parafoveal, and perifoveal. Thus, the study by Jacobs et al (2024)[26] was not included in the meta-analysis, as DVD was reported only for 3×3 mm and 6×6 mm scans centered on the fovea. In that study, no significant differences in DVD at 1 hour post-intervention were observed between the caffeine and placebo groups for either the 3×3 mm (p = 0.760) or the 6×6 mm (p = 0.242) scans.

A total of 204 participants were included in the foveal region. No statistically significant alteration in DVD was observed, with a pooled MD of –0.94% (95% CI: –2.26 to 0.38; p = 0.16). The analysis further revealed a substantial

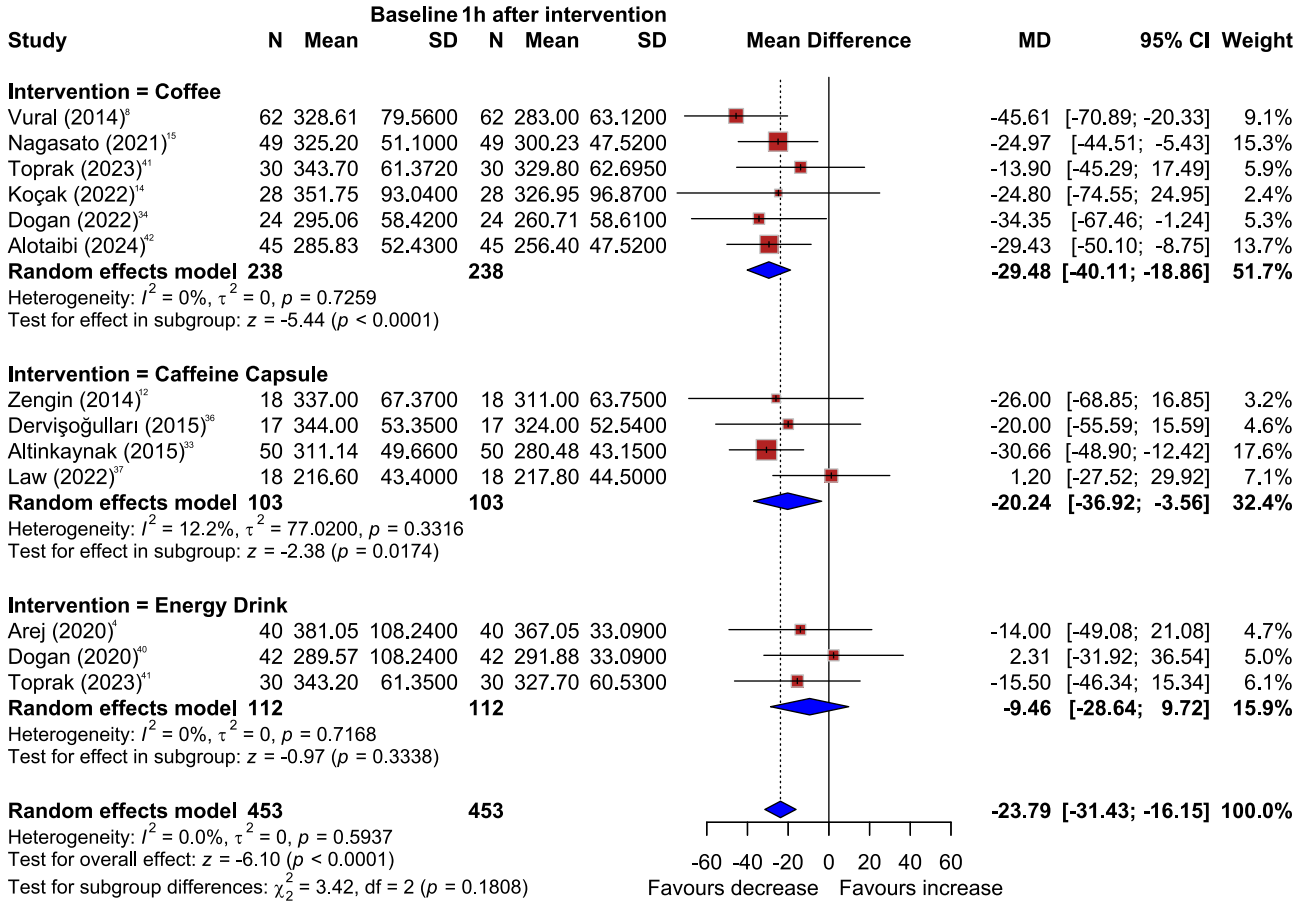

Figure 2 SFCT subgroup analysis, according to type of intervention.

Abbreviations: SFCT, subfoveal choroidal thickness; Baseline, before intervention; 1h after intervention, 1 hour after intervention; N, number of participants; Mean, Mean SFCT (μm); MD, mean difference; SD, standard deviation; 95% CI, 95% Confidence Interval; I^2, heterogeneity; p, p-value.

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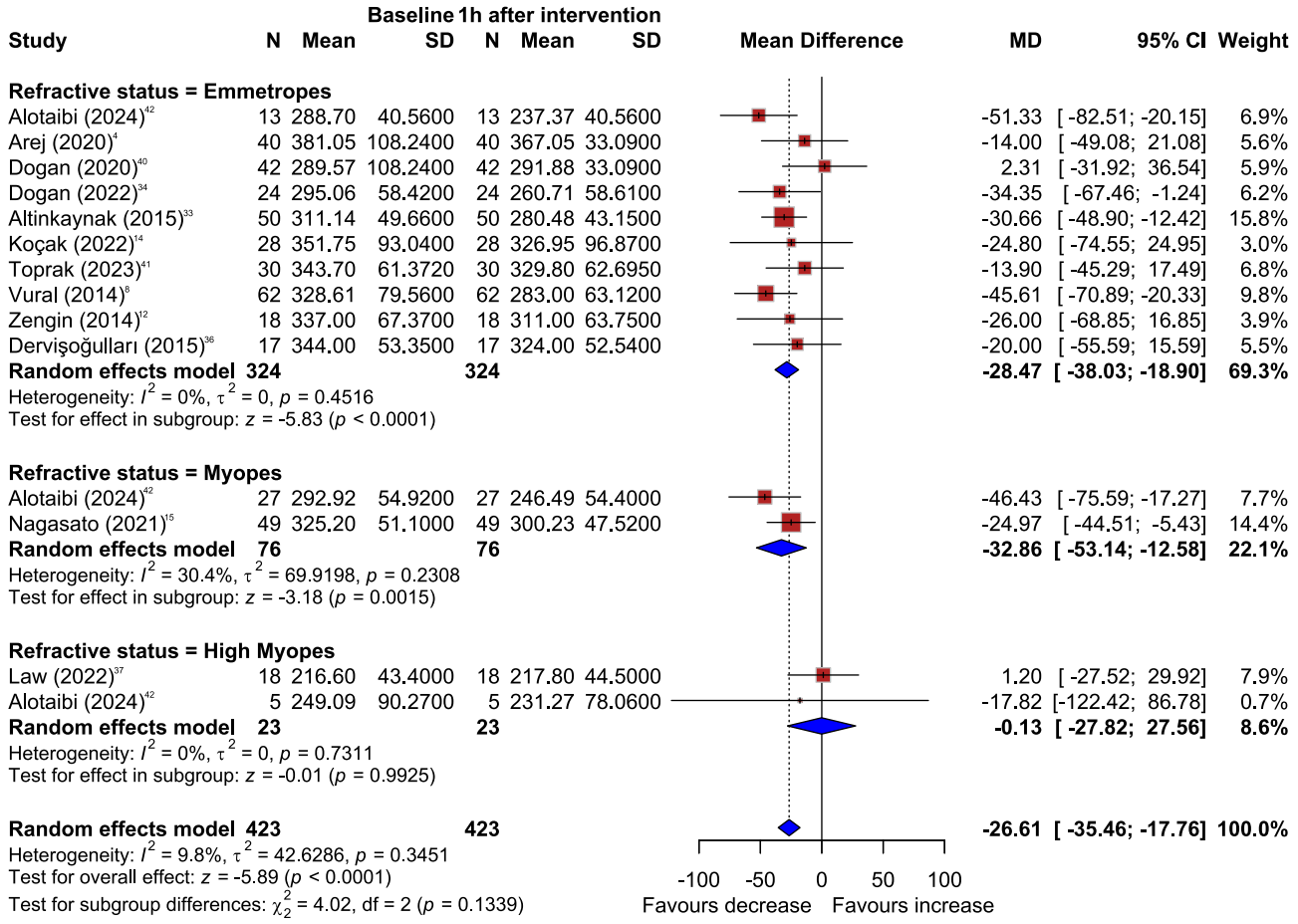

Figure 3 SFCT subgroup analysis, according to refractive status.
Abbreviations: SFCT, subfoveal choroidal thickness; Baseline, before intervention; 1h after intervention, 1 hour after intervention; N, number of participants; Mean, Mean SFCT (μm); MD, mean difference; SD, standard deviation; 95% CI, 95% Confidence Interval; I^2, heterogeneity; p, p-value.

heterogeneity of 59.2%, indicating variability among the included studies. A subgroup analysis was performed to identify potential factors contributing to heterogeneity and to provide a more specific assessment (Figure 4). The use of caffeine capsules demonstrated a statistically significant reduction in foveal DVD, with a pooled MD of –2.23% (95% CI: –3.70 to –0.76; p = 0.003) and no heterogeneity (I^2 = 0%). In contrast, other types of interventions, including coffee, energy drinks, or black tea, did not show statistically significant effects on this outcome. These subgroup differences were statistically significant (p = 0.007).

In the parafoveal region, a total of 204 participants were evaluated. No statistically significant overall difference was observed, with a pooled MD of –0.39% (95% CI: –2.45 to 1.66; p = 0.71) and a substantial heterogeneity of 84.9%, suggesting considerable variability across studies. In the subgroup, participants who ingested caffeine capsules demonstrated a statistically significant reduction in parafoveal DVD (Figure 5), with a pooled MD of –2.18% (95% CI: –3.13 to –1.24; p < 0.001) and no heterogeneity (I^2 = 0%). Similarly, in the subgroup of patients who consumed caffeinated coffee, a significant reduction of –1.83% (95% CI: –3.17 to –0.50; p = 0.007) was also observed. In contrast, studies evaluating energy drinks and black tea showed an increase in parafoveal DVD.

A total of 178 participants were evaluated in the perifoveal region. The combined analysis did not reveal a statistically significant change in DVD, with a pooled MD of –1.18% (95% CI: –4.08 to 1.71%; p = 0.42). In the subgroup analysis, distinct patterns emerged (Supplementary Figure 2). The study assessing caffeine capsules demonstrated a statistically significant reduction in perifoveal DVD (95% CI: –6.84 to –3.00), whereas interventions with coffee (95% CI: –3.93 to 0.74) and black tea (95% CI: –4.39; 1.68) did not show statistically significant results. Conversely, the study evaluating

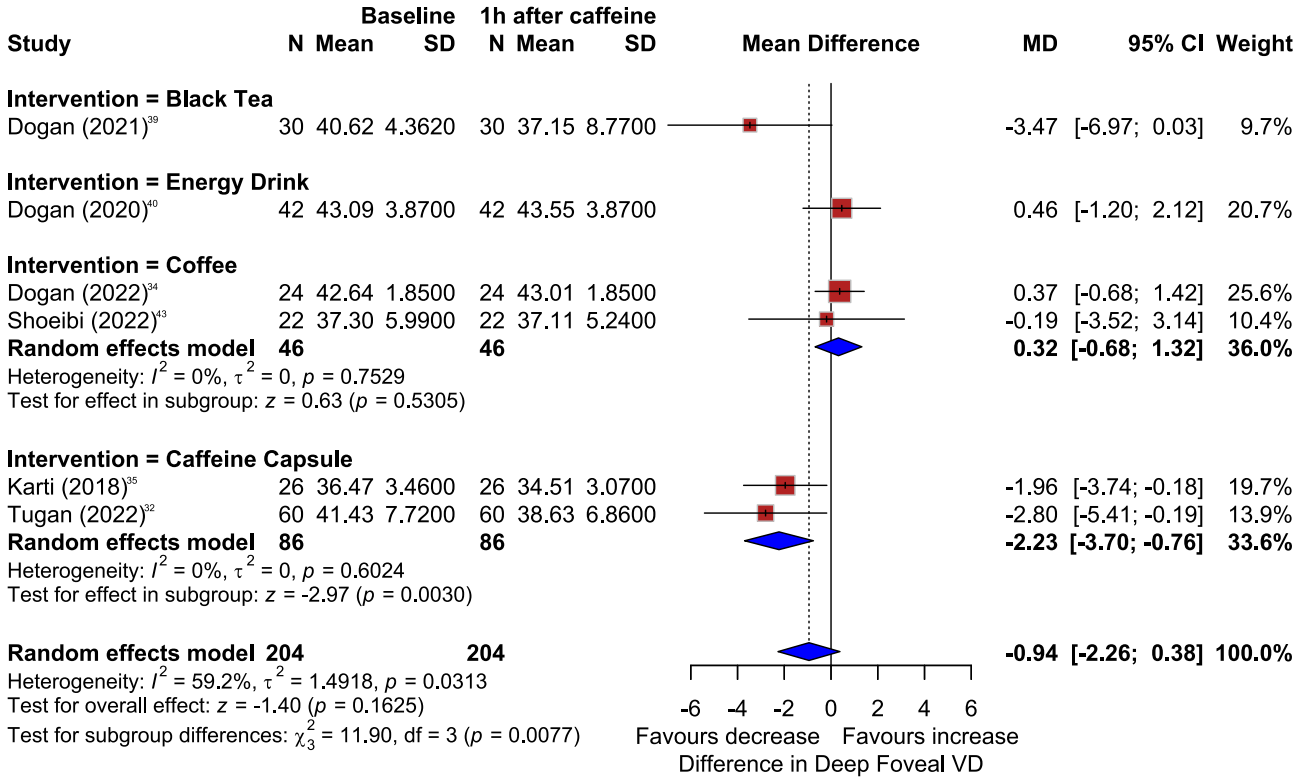

Figure 4 Foveal DVD subgroup analysis, according to intervention.
Abbreviations: VD, vessel density; Baseline, before intervention; 1h after caffeine, 1 hour after intervention; N, number of participants; Mean, mean VD (%); MD, mean difference; SD, standard deviation; 95% CI, 95% Confidence Interval; I^2, heterogeneity; p, p-value.

energy drinks observed a substantial increase in perifoveal DVD (MD = 3.41%; 95% CI: 1.09 to 5.73). Consequently, subgroup differences were statistically significant (p < 0.0001).

Superficial Capillary Vessel Density

SVD was analyzed across the same retinal regions as in the DVD assessment. The study by Jacobs et al (2024)[26] was again excluded from the meta-analysis due to the previously referred difference in measurement reporting. Consistently, this study found no statistically significant differences SVD at 1 hour post-ingestion between the caffeine and control groups for either the 3×3 mm (p = 0.460) or 6×6 mm (p = 0.175) scans.

In the foveal region, a total of 222 participants were analyzed. The combined analysis of studies evaluating caffeine intake through different forms, including coffee, caffeine capsules, black tea, and energy drinks, demonstrated a statistically significant reduction in SVD, with a pooled MD of –0.87% (95% CI: –1.60 to –0.14; p = 0.02). The analysis revealed no heterogeneity (I^2 = 0%), indicating highly consistent results across the included interventions (Figure 6). In the subgroup analysis, both specific interventions showed reductions in foveal SVD; however, these reductions did not reach statistical significance individually and became significant only when the studies were pooled.

In the parafoveal region, the pooled analysis demonstrated a statistically significant reduction in SVD, with a MD of –1.39% (95% CI: –2.36 to –0.43; p = 0.005) and a substantial heterogeneity of 79.4%. In the subgroup analysis, studies evaluating caffeine capsules and coffee maintained the same pattern (Figure 7), showing statistically significant reductions in parafoveal SVD (MD = –1.80% and –1.74%; 95% CI: –2.36% to –0.31 and –3.18 to –0.31, respectively). In contrast, studies that investigated black tea and energy drinks did not report significant alterations in this parameter within the parafoveal region.

In the perifoveal region, the results were consistent with the observations in the parafoveal areas. The pooled analysis revealed a statistically significant reduction in SVD, with a MD of –1.04% (95% CI: –1.90 to –0.19; p = 0.017) and moderate heterogeneity (I^2 = 52.8%). Subgroup analysis (Supplementary Figure 3A) indicated that the reduction was

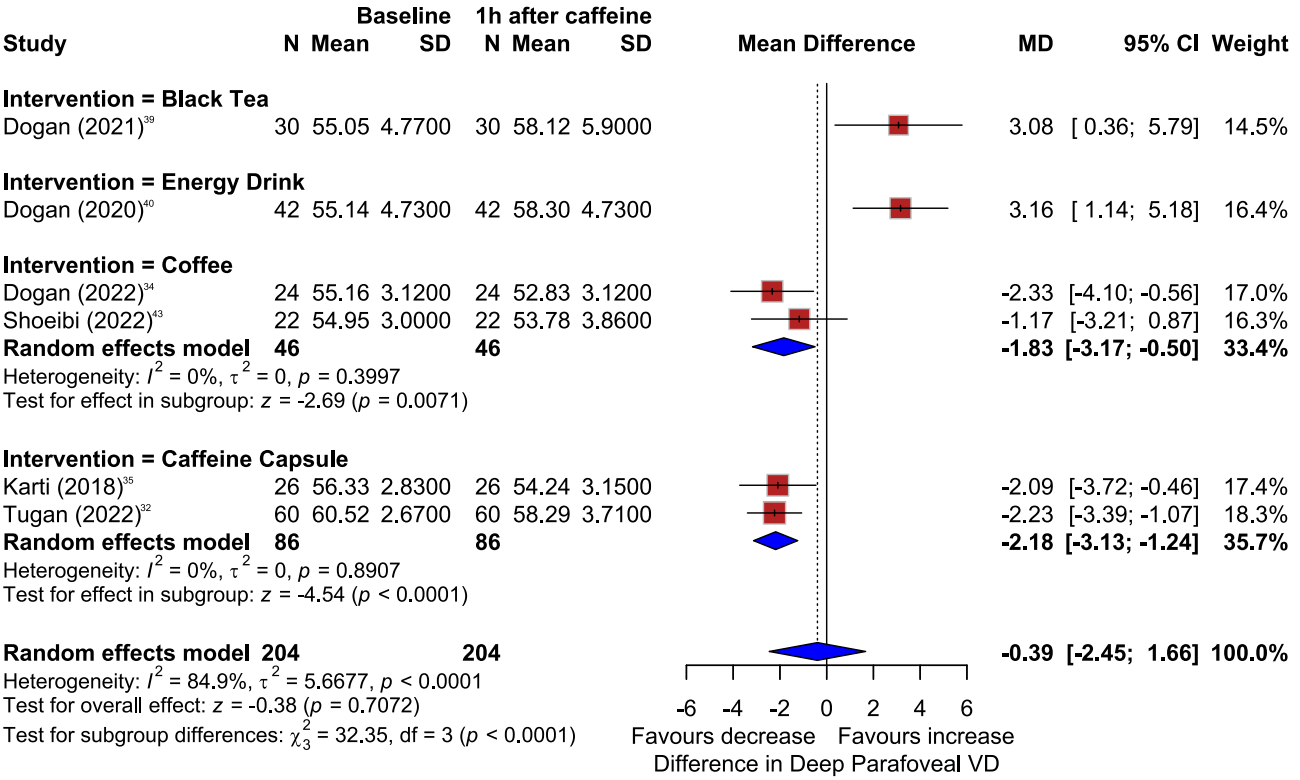

Figure 5 Parafoveal DVD subgroup analysis by intervention.
Abbreviations: VD, vessel density; Baseline, before intervention; 1h after caffeine, 1 hour after intervention; N, number of participants; Mean, mean VD (%); MD, mean difference; SD, standard deviation; 95% CI, 95% Confidence Interval; I^2, heterogeneity; p, p-value.

significant for the caffeine capsule intervention (MD = –1.84%; 95% CI: –2.55 to –1.13), but not for the coffee intervention alone (MD = –1.48%; 95% CI: –3.23 to 0.28; p = 0.1). However, when coffee and caffeine capsule subgroups were combined (Supplementary Figure 3B), significance was reached (MD = –1.79%; 95% CI: –2.45 to –1.13; p < 0.0001). In contrast, interventions with energy drinks and black tea did not demonstrate significant reductions in this region (MD: –0.45%, 95% CI: –1.29 to 0.39; and MD: –0.05%, 95% CI: –1.67 to 1.57, respectively).

Risk of Bias

Figure 8A and 8B (RoB-2 and ROBINS-I, respectively) illustrate the risk of bias assessment for each study. Among the randomized studies, four were well-designed and classified as low risk of bias, while another four raised some concerns due to issues with randomization and population selection. For ROBINS-I, two studies were judged to have a critical overall risk of bias: Shoeibi et al, as it was a case series with inherent methodological limitations, and Nagasato et al, which introduced critical bias by selecting both study groups. Studies by Aloitabi et al (2024), Altinkaynak et al (2015), Dogan et al (2021), and Toprak Sr et al (2023) were rated as having a serious risk of bias due to lack of randomization or failure to account for important confounders such as habitual caffeine consumption. The remaining studies (Arej et al 2021; Dervişoğullari et al 2015; Dogan et al 2020, Dogan et al 2022) were classified as having a moderate overall risk of bias, primarily due to concerns related to randomization, missing data, and misclassification of interventions.

Discussion

In this systematic review and meta-analysis of 18 studies involving 966 patients, we evaluated the acute impact of caffeine on ocular microvasculature using OCT and OCTA imaging. Our analysis identifies a significant and consistent thinning of the subfoveal choroid following caffeine ingestion, regardless of whether it was administered via capsules or energy drinks. In the retinal circulation, we observed a general reduction in SVD across the foveal and extrafoveal regions. However, the response of the deep capillary plexus was markedly more heterogeneous, appearing sensitive to the

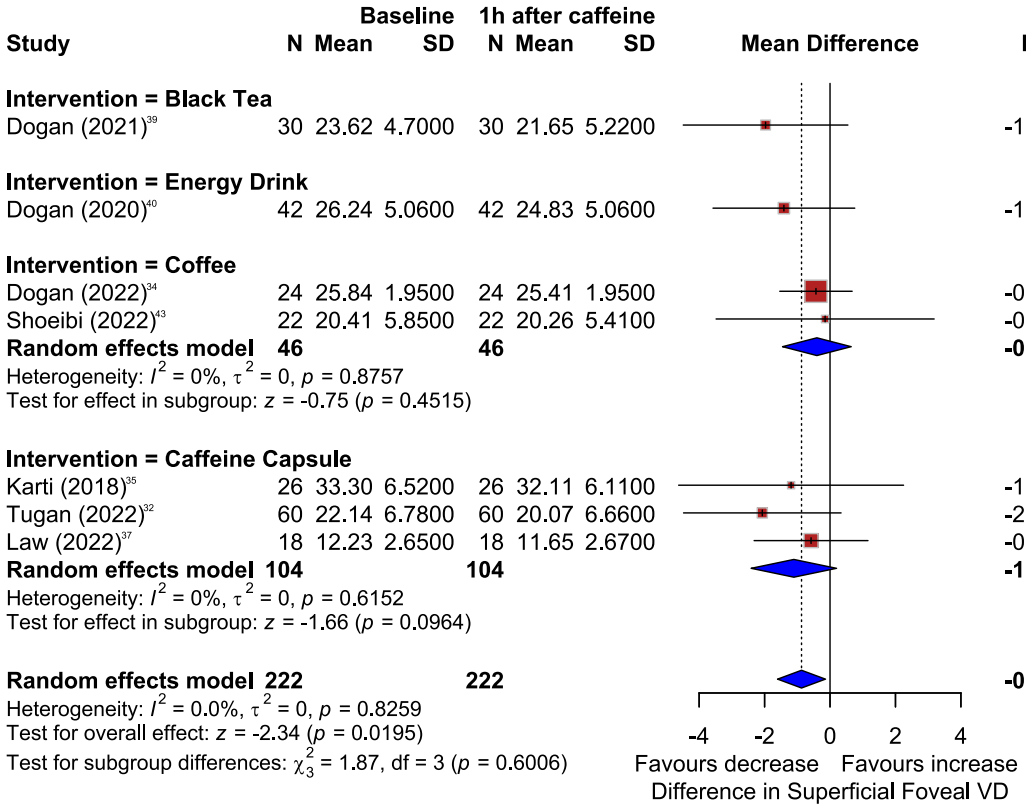

Figure 6 SVD subgroup analysis, according to intervention.
Abbreviations: VD, vessel density; Baseline, before intervention; 1h after caffeine, 1 hour after intervention; N, number of participants; Mean, mean VD (%); MD, mean difference; SD, standard deviation; 95% CI, 95% Confidence Interval; I^2, heterogeneity; p, p-value.

specific source of caffeine. While caffeine capsules and coffee tended to reduce DVD, energy drinks and tea often showed negligible or even opposing effects. These findings suggest that while caffeine generally promotes ocular vasoconstriction, the net vascular response is influenced by the delivery vehicle and the specific retinal layer being measured.

The consistent thinning of the choroid identified in this meta-analysis reinforces the physiological role of caffeine as a potent adenosine receptor antagonist.[1,44] By blocking adenosine receptors, caffeine inhibits the vasodilation typically maintained by endogenous adenosine, thereby promoting vasoconstriction within the highly vascularized choroidal tissue.[1,7] To ensure accuracy in these measurements, several included studies employed Enhanced Depth Imaging (EDI), which provides improved visualization of the choroidal layers and allows for more precise demarcation of the chorioretinal interface.[13,45] These findings quantitatively corroborate numerous observational studies reporting reduced thickness following caffeine ingestion.[8,12,14,15] While this vasoconstrictive effect extends to the retinal circulation, the response in the deep capillary plexus remains more variable.[20,27] This discrepancy may be influenced by the type of OCT technology used; for instance, Jacobs et al observed significant effects using swept-source OCTA (SS-OCTA), which offers faster acquisition and reduced susceptibility to motion artifacts compared to the spectral-domain platforms (SD-OCTA) used by Tugan et al[26,27] Such technical differences may partly explain the variations in reported effect sizes across the literature. Compared with Tugan et al, who used SD-OCT, Jacobs et al observed a significant effect, although of lesser magnitude. A clinically relevant finding from our subgroup analysis is the differential impact of caffeine source on ocular hemodynamics. Coffee elicited a stronger reduction in SFCT (–29.48 µm) compared with pure caffeine capsules (–20.24 µm), suggesting that additional bioactive compounds in coffee may exert synergistic vasoconstrictive effects.[46] In contrast, energy drinks did not produce significant changes in SFCT, despite containing higher caffeine concentrations. This divergence from the consistent effects observed with coffee and caffeine capsules[8,12,14,15] supports the hypothesis that other ingredients commonly present in energy drinks, such as taurine or L-carnitine, may exert

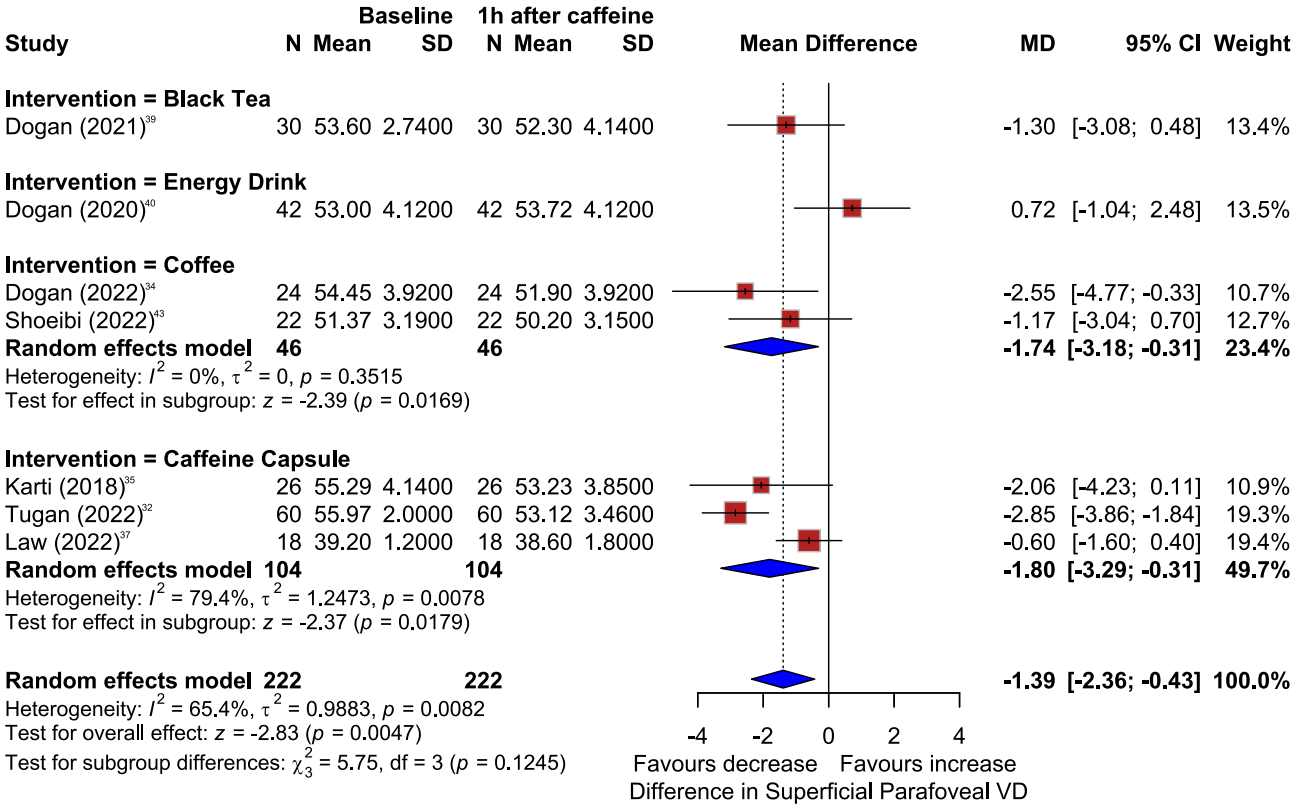

Figure 7 Parafoveal SVD subgroup analysis, according to intervention.
Abbreviations: VD, vessel density; Baseline, before intervention; 1h after caffeine, 1 hour after intervention; N, number of participants; Mean, mean VD (%); MD, mean difference; SD, standard deviation; 95% CI, 95% Confidence Interval; I^2, heterogeneity; p, p-value.

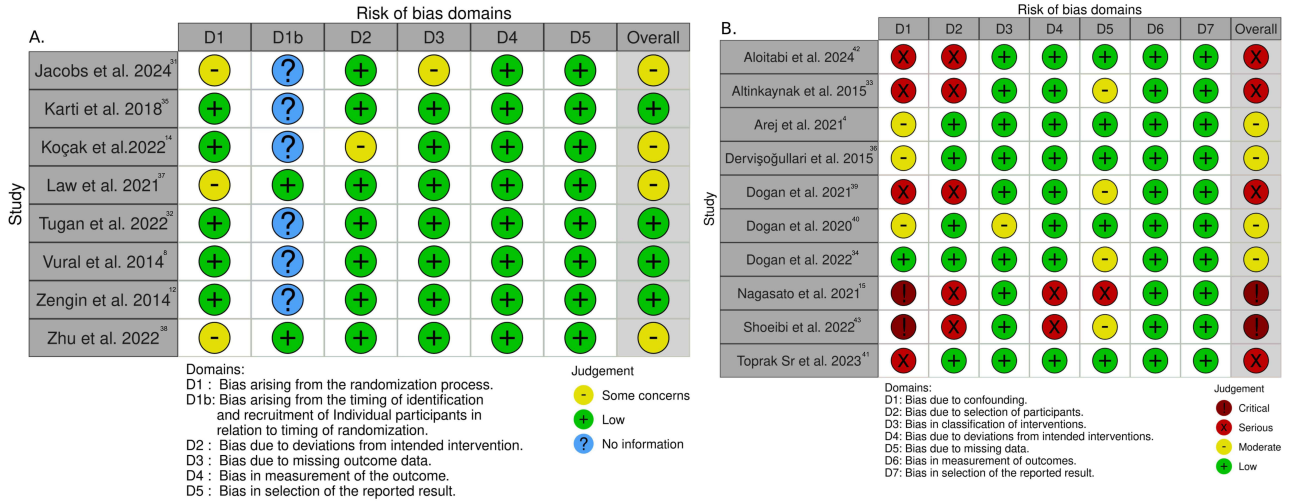

Figure 8 (**A**) RoB-2 risk of bias. (**B**) ROBINS-I risk of bias.

vasodilatory effects,[47,48] that counteract the primary vasoconstrictive action of caffeine. This complex interaction suggests that caffeine may not be the sole causal factor in the hemodynamic response to these specific formulations. Furthermore, given the modest magnitude of the observed changes, it is possible that a portion of the report effects reflects inherent physiological variability or measurement noise rather than a definitive pharmacological event.

Acknowledging these confounding factors is fundamental to the conceptual validity of the findings, as it characterizes the retinal and choroidal response to a multifactorial process.

Caffeine, a methylxanthine-class central nervous system stimulant, influences both cerebral and ocular blood flow.[1,49] Its primary mechanism of action involves antagonism of adenosine receptor subtypes and the indirect release of catecholamines, which inhibit adenosine-mediated vasodilation and promote vasoconstriction.[1] OCT and OCTA enable detailed assessment of these effects using markers such as vessel length, perfusion density, the foveal avascular zone, and choroidal thickness.[50] However, interpreting these changes requires caution, as the choroid is a highly dynamic tissue. Its thickness is influenced by a wide array of confounding factors, including age, refractive error, diurnal variation, and perfusion pressure.[45,50–58] Therefore, studies assessing this outcome should thoroughly specify patient characteristics to account for heterogeneous populations, particularly concerning these confounding factors. However, several of the included studies did not adequately address these variables, limiting the ability to determine whether observed differences in choroidal thickness were attributable to caffeine itself or to underlying individual variation.

The transient vasoconstrictive effect of caffeine, though generally benign in healthy individuals, may become clinically relevant in the presence of ocular pathologies such as degenerative myopia, age-related macular degeneration (AMD), and diabetic retinopathy (DR).[45,59–63] While our findings of reduced SFCT in emmetropic and myopic eyes are consistent with prior,[4,8,14,15] the absence of this effect in high myopia is a novel observation. In highly myopic eyes, where choroidal thinning is a well-established predictor of visual acuity loss,[49–51] unique anatomical alterations could plausibly blunt the vascular response to caffeine.[45,59,62] However, given the limited sample sizes in these subgroups, the lack of significance may equally reflect insufficient statistical power rather than a true physiological resistance to caffeine. In DR, reductions in vessel and perfusion density and enlargement of the foveal avascular zone correlate with disease severity.[64] Thus, additional vasoconstrictive stress from caffeine may further reduce perfusion, exacerbating ischemic risk. Similarly, in dry AMD, caffeine-induced microvascular constriction could aggravate ischemic compromise, consistent with the ischemic hypothesis of pathogenesis.[63,65,66]

This study has important limitations. First, the inclusion of both randomized and non-randomized studies introduces heterogeneity in study design, quality, caffeine dosage, and the timing of post-ingestion measurements, which may affect the reliability of pooled estimates. Second, the patient populations differed in their physiological adaptation to caffeine, with some regular coffee/caffeine drinkers and others not, which could influence choroidal thickness measurements and limit the generalizability of the findings. Finally, although OCT and OCTA are established methods for measuring choroidal thickness and vessel density, differences in imaging modality, device, algorithm, and acquisition protocols across studies may have contributed to measurement variability. Random effects, quality assessment, and sensitivity analysis were used to try to mitigate these limitations.

Conclusion

This meta-analysis found consistent evidence that caffeine intake induces measurable, acute changes in the posterior eye segment, specifically through a temporary decrease in SFCT and SVD, but not DVD. These alterations are short-term, with most parameters returning to baseline within hours of ingestion. The subgroup analyses reveal that this effect is complex and is significantly modulated by the delivery vehicle and refractive status of the eyes. These findings underscore the importance of controlling caffeine intake in both clinical and research settings to ensure the accurate interpretation of advanced ocular imaging.

Data Sharing Statement

All relevant data are within the manuscript and Supplementary Data.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no affiliations with or involvement in any organization or entity with any interest in the subject matter or materials discussed in this manuscript.

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