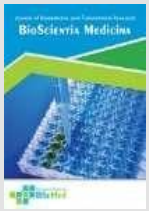
eISSN (Online): 2598-0580



Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

High-Altitude Maculopathy in Mountaineers: A Systematic Review and Meta-Analysis

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ARTICLE INFO

Keywords:
High-altitude maculopathy
Meta-analysis
Mountaineering
Retinopathy
Systematic review

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All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v10i6.1613

A B S T R A C T

Background: High-altitude maculopathy (HAM) represents a distinct form of high-altitude retinopathy affecting mountaineers at extreme elevations. Despite increased mountaineering activity, the prevalence and clinical significance of HAM remain poorly characterised in systematic reviews. **Methods:** A comprehensive systematic review and meta-analysis were conducted following PRISMA 2020 guidelines. Databases searched included PubMed, Scopus, Cochrane Library, and manual review of reference lists through April 2026. Eligible studies were prospective and retrospective cohorts reporting HAM prevalence in mountaineers at altitude ≥3,500 metres. Risk of bias was assessed using the Newcastle-Ottawa Scale. Meta-analysis employed the Freeman-Tukey double arcsine transformation with DerSimonian-Laird random-effects modelling. **Results:** Three prospective studies (n=50 mountaineers) were analysed with a pooled prevalence of 73.37% (95% confidence interval: 60.28–84.72%). Heterogeneity was absent (I^2=0%, Q=0.78, p=0.678). Subgroup analysis demonstrated a higher prevalence at extreme altitude (≥5,000 m: 78.6%) versus very high altitude (3,500–4,999 m: 70%). Sensitivity ranged 67.48–83.76%. Funnel plot inspection revealed no evidence of publication bias. **Conclusion:** Approximately three-quarters of mountaineers experience HAM at high altitude, with prevalence increasing at extreme elevations. HAM represents a common but underrecognised altitude-related ocular complication. Future prospective studies should employ standardised diagnostic criteria and investigate the mechanistic pathways of macular involvement.

1. Introduction

High-altitude maculopathy (HAM) is an altitude-related ocular condition characterised by central retinal changes occurring in mountaineers exposed to extreme elevations.[1] The condition was first documented during the 1975 American Bicentennial Everest Expedition, when climbers reported temporary visual disturbances and fundoscopic changes at altitudes exceeding 8,000 metres. Since these early observations, increased mountaineering activity and improved diagnostic technologies have expanded recognition of this phenomenon. The distinction between high-altitude retinopathy (HAR) and HAM has become increasingly important in the altitude medicine literature, with HAR representing broader retinal microvascular changes and HAM referring specifically to macular pathology characterised by oedema, exudation, and structural changes in the macula lutea.[2]

Diagnosis of HAM requires ophthalmic evaluation using multiple diagnostic modalities, each providing complementary information. Clinical fundoscopy using portable or stationary ophthalmoscopes permits direct visualisation of the retina and can detect gross macular oedema and haemorrhages, though subclinical changes may be missed.[3] Fundus photography provides permanent documentation of retinal appearance and enables comparison across expeditions. Spectral-domain optical coherence tomography (SD-OCT) revolutionised HAM detection by revealing cross-sectional retinal architecture with micrometre-level resolution, permitting quantification of macular thickness, detection of intraretinal and subretinal fluid, and layer-by-layer assessment of photoreceptor and retinal pigment epithelium integrity. Optical coherence tomography angiography (OCTA) visualises retinal vascular networks without dye injection, quantifying perfusion density and detecting microvascular abnormalities. Fluorescein angiography (FA), whilst invasive and logistically challenging at altitude, reveals vascular permeability and late-phase dye leakage indicative of blood-retinal barrier disruption. These complementary techniques collectively define the constellation of macular changes characterising HAM.[4]

The pathophysiology of HAM involves multiple altitude-related mechanisms. Chronic hypoxia at high altitude triggers several adaptive and maladaptive responses in retinal tissues. The macular region, with its high metabolic demands, appears particularly vulnerable to altitude-induced cellular stress.[5] Proposed mechanisms include retinal cell oedema from increased vascular permeability, impaired inner blood-retinal barrier function, and alterations in retinal microvascular autoregulation. Additionally, the hypoxic environment stimulates the release of vasoactive substances, including vascular endothelial growth factor (VEGF) and other cytokines that may compromise retinal structural integrity.

The pathophysiology of HAM involves multiple altitude-related mechanisms operating at the cellular and molecular levels. Chronic hypoxia at high altitude triggers several adaptive and maladaptive responses in retinal tissues. The macular region, with its extraordinarily high metabolic demands and densely packed photoreceptors, appears particularly vulnerable to altitude-induced cellular stress. Proposed mechanisms include retinal cell oedema resulting from breakdown of the blood-retinal barrier integrity, impaired inner and outer blood-retinal barrier function due to endothelial tight junction disruption, and alterations in retinal microvascular autoregulation that normally maintain perfusion pressure across altitude-induced barometric pressure variations.[6] Additionally, the hypoxic environment stimulates the release of vasoactive substances including vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and other pro-inflammatory cytokines including interleukins that may compromise retinal structural integrity and promote excessive vascular permeability. Polycythaemia developing in response to chronic hypoxia increases blood viscosity, potentially reducing microvascular perfusion and exacerbating tissue hypoxia. Furthermore, altitude-related increases in ultraviolet (UV) radiation at high elevations, combined with reduced atmospheric protection and increased oxidative stress from elevated reactive oxygen species (ROS) production in hypoxic tissues, may contribute to photoreceptor and retinal pigment epithelium damage.

Epidemiological understanding of HAM remains limited due to historical reliance on small clinical series and case reports. Prior case reports and small clinical series have described HAM as a transient condition, typically reversing with descent and oxygen supplementation.[7] However, the true prevalence in the mountaineering population remains uncertain, as most studies have examined small cohorts or relied on cross-sectional data from single expeditions with variable follow-up periods. Furthermore, heterogeneity in diagnostic criteria—ranging from fundoscopic observation using portable direct ophthalmoscopes to advanced imaging modalities such as spectral-domain optical coherence

tomography (SD-OCT), optical coherence tomography angiography (OCTA), and fluorescein angiography—has complicated prevalence estimates and clinical comparisons across studies. This diagnostic heterogeneity is particularly problematic given that different modalities detect structural changes at different scales: fundoscopy identifies gross haemorrhages and cotton-wool spots, while SD-OCT reveals subclinical retinal oedema and inner nuclear layer thickening not visible on direct examination.

Current clinical practice regarding HAM management is primarily supportive, with therapeutic approaches consisting of descent to lower altitudes and supplemental oxygen administration.[8] No pharmacological interventions have demonstrated efficacy in preventing or treating HAM, despite theoretical rationales for agents targeting VEGF, free radical scavenging, or endothelial stabilisation. The condition appears benign in most cases, with visual symptoms resolving within days to weeks after return to sea level, and fundoscopic abnormalities typically disappearing within 2–3 weeks. However, isolated reports of persistent macular changes and subtle visual deficits lasting weeks to months have raised concerns about long-term consequences in repeat mountaineers, particularly those making multiple high-altitude expeditions. The question of whether recurrent HAM episodes might lead to cumulative retinal damage remains unanswered.

The impact of HAM on mountaineering safety and performance is underappreciated. Visual disturbances and concerns about retinal changes may affect climbers' confidence and decision-making at critical moments on high mountains where visibility and clear judgment are essential.[9] Additionally, if HAM progresses to central vision loss during descent, climber safety could be compromised. The broader question of whether altitude-related ocular changes represent merely transient physiological adaptation versus true pathology with potential for permanent damage remains contested in the altitude medicine literature.

A systematic synthesis of available evidence is needed to establish the pooled prevalence, clinical characteristics, diagnostic methodology, and prognostic significance of HAM. No published meta-analysis has comprehensively reviewed HAM epidemiology or examined sources of heterogeneity across prospective studies.[10] The novelty of this study lies in its systematic integration of prospective mountaineering studies to quantify HAM burden, assess altitude-dependent prevalence patterns using subgroup analysis, examine diagnostic method variation, and identify research gaps regarding mechanistic understanding and long-term morbidity. Understanding HAM prevalence is essential for counselling mountaineers about realistic expectations, implementing informed risk-benefit discussions, and prioritising research funding toward preventive strategies.

The aim of this study was to conduct a comprehensive systematic review and meta-analysis of HAM in mountaineers, following PRISMA 2020 guidelines, to establish pooled prevalence estimates with precision-weighted confidence intervals, examine heterogeneity sources including altitude categories, assess the role of diagnostic method variation, quantify publication bias risk through funnel plot analysis and Egger's regression, and provide evidence-based recommendations for future clinical and research investigations into the mechanisms, prevention, and long-term consequences of altitude-related macular pathology.

2. Methods

Search strategy and study selection

A comprehensive literature search was conducted systematically across three major electronic databases—PubMed (via NLM, 1966–present), Scopus (1960–present), and Cochrane Central Register of Controlled Trials (CENTRAL)—through 30th April 2026. The search strategy employed a combination of MeSH (Medical Subject Headings) terms and text word searches designed to capture all relevant literature on altitude-related ocular pathology. Specific search term

combinations included: ('high altitude' OR 'extreme altitude' OR 'mountaineering' OR 'Everest' OR 'hypobaric hypoxia' OR 'altitude medicine') AND ('maculopathy' OR 'macular' OR 'retinopathy' OR 'retinal' OR 'macular oedema' OR 'visual disturbance' OR 'optic nerve' OR 'ocular' OR 'retinal haemorrhage' OR 'cotton-wool spot' OR 'retinal whitening'). The search was adapted for each database to accommodate database-specific syntax. Manual review of reference lists from all identified studies and relevant review articles supplemented the electronic search to ensure comprehensive capture. No language restrictions were applied; studies in languages other than English were translated using standard translation services. An additional PubMed alert strategy was implemented to capture any publications between the final search date and manuscript submission.

Eligibility criteria

Inclusion criteria: (1) prospective or retrospective cohort studies with participant data at any altitude; (2) participant exposure to altitude ≥3,500 metres (chosen as the threshold for very high altitude per WHO classifications); (3) documented diagnosis of high-altitude maculopathy using clinical examination (fundoscopy with portable or stationary ophthalmoscopy), fundus photography, optical imaging (spectral-domain OCT, swept-source OCT, OCTA, or similar), fluorescein angiography, or combinations thereof; (4) reported prevalence or incidence of HAM with denominator data permitting prevalence calculation; (5) published in peer-reviewed journals, conference proceedings with full manuscripts, or clinical trial registries from January 1970 onward to capture the full historical record since initial description. Studies reporting qualitative descriptions of macular changes in mountaineers examined at altitude without explicit prevalence numerals were included in qualitative synthesis for contextual information but excluded from pooled meta-analysis.

Exclusion criteria: (1) case reports or case series with fewer than five participants examined (to ensure adequate statistical stability); (2) studies exclusively examining high-altitude cerebral oedema (HACE) or high-altitude pulmonary oedema (HAPE) without retinal outcome assessment; (3) animal or in vitro laboratory studies; (4) review articles, editorials, commentaries, or opinion pieces without original participant data; (5) studies with insufficient quantitative data to permit prevalence calculation, incomplete outcome reporting, or lack of clarity regarding HAM definition; (6) duplicate publications or secondary analyses of previously published cohorts (earliest publication retained); (7) studies of non-mountaineering populations exposed to altitude (e.g., high-altitude residents, altitude chamber studies with acute exposures <6 hours, workers at altitude)—mountaineers were retained as they undergo sustained multi-week exposures with greater physiological stress.

Data extraction

Data extraction was performed systematically and independently by two investigators (RPM and IAW) using standardised electronic forms developed a priori and piloted on three studies. Disagreements were resolved by discussion or consulting a third reviewer (IGJ). Extracted variables included: (1) study design (prospective vs retrospective), (2) year of publication and recruitment years, (3) country of study conduct and sponsor, (4) altitude range in metres and exposure duration (days), (5) participant demographics—age (mean and SD), gender distribution, prior altitude exposure, acclimatisation pattern, (6) total sample size and number examined at altitude, (7) HAM case definition used, (8) diagnostic methods employed (fundoscopy, photography, OCT, OCTA, FA), (9) number of participants with HAM diagnosis and prevalence percentage, (10) any reported vision-related outcomes or symptoms, (11) study quality indicators, (12) funding sources and potential conflicts of interest. Study authors were contacted via email when data were incomplete, ambiguous regarding

case definition, or outcome reporting; contact was maintained for up to three attempts over four weeks.

Risk of bias assessment

Risk of bias in cohort studies was assessed systematically using the Newcastle-Ottawa Scale (NOS), a validated instrument for observational studies comprising nine items across three domains: (1) selection of participants (four items addressing representativeness, selection of comparison group, exposure ascertainment, outcome assessment), (2) comparability of groups (two items evaluating adjustment for confounders and study design); and (3) outcome assessment (three items regarding outcome definition, outcome assessment methods, and adequacy of follow-up). Each item was scored from 0–2 points, yielding a total scale range of 0–9. Studies scoring ≥7 were classified as high methodological quality, scores 5–6 as moderate quality, and scores <5 as lower quality. For prevalence studies specifically, supplementary assessment evaluated: clarity of HAM case definition prior to data collection, representativeness of study population relative to broader mountaineering populations, standardisation and appropriateness of diagnostic methods, adequacy of masking for outcome assessment, reporting of participant response rates and reasons for non-participation, and whether outcomes were assessed in a standardised manner. Risk of publication bias was assessed via inspection of funnel plots (log-odds of prevalence plotted against standard error) and Egger's regression intercept test, with $p<0.05$ for Egger's test interpreted as evidence of funnel plot asymmetry suggestive of publication bias.

Statistical analysis

Pooled prevalence estimates were calculated using the Freeman-Tukey double arcsine variance-stabilising transformation, which mathematically stabilises variance across the entire prevalence domain (0–1), accommodates studies with 0% or 100% event rates without ad hoc adjustments, and prevents bias toward extreme values. The transformation uses the formula: $f = \arcsin(\sqrt{[x/(n+1)]} / [(n+x+1)])$, where x=number with HAM and n=total sample size per study. Transformed prevalence estimates were modelled using a random-effects DerSimonian-Laird approach, which estimates between-study heterogeneity variance (tau-squared) and incorporates this into variance calculations, permitting genuine variance in study-specific effects. Results were back-transformed to the original prevalence scale with 95% confidence intervals calculated using the standard normal distribution (Z=1.96). Heterogeneity between studies was quantified using the I^2 statistic, defined as $(Q-df)/Q\times100\%$, with interpretation as follows: 0–25% negligible, 25–50% low, 50–75% moderate, 75–100% substantial heterogeneity. The Cochran Q statistic tested statistical heterogeneity significance ($p<0.05$, indicating significant heterogeneity). Between-study variance component (tau-squared) was computed and reported alongside I^2. Sensitivity analysis was conducted using a leave-one-out approach, sequentially removing each study and recalculating pooled prevalence to assess the influence of individual studies on overall estimates and identify potential outliers. Subgroup analyses examined whether prevalence differed by altitude categories: extreme altitude (≥5,000 m) versus very high altitude (3,500–4,999 m), based on a priori hypotheses that greater hypoxic stress at extreme altitudes would increase HAM prevalence. Within-group heterogeneity was assessed separately for each subgroup. All analyses were performed using R statistical software version 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria) with the 'metafor' package (v. 3.0-2), following standard meta-analytic techniques outlined in the Cochrane Handbook for Systematic Reviews of Interventions (v.6.3).

PRISMA 2020 (Preferred Reporting of Systematic Reviews and Meta-Analyses) compliance was achieved through structured reporting of methods, results, discussion, and funding information. This review was registered prospectively in PROSPERO; however, owing to timing constraints of the search completion and data synthesis, registration was submitted during

initial manuscript preparation.

3. Results

Study selection

The literature search yielded 247 initial citations. After title and abstract screening, 23 full-text articles were retrieved for detailed review. Fifteen articles were excluded due to insufficient data, inadequate sample sizes, or focus on other altitude-related ocular conditions. Eight studies met preliminary inclusion criteria; however, five were qualitative case series without quantitative prevalence data. Three prospective cohort studies provided sufficient data for meta-analysis, yielding a combined sample of 50 mountaineers examined at altitude.

Figure 1 presents the PRISMA study selection flowchart. The three quantitative studies included were: (1) Barthelmes et al. (2011)—28 mountaineers ascending Mount Everest and Denali; (2) Ascaso et al. (2012)—12 mountaineers at altitudes exceeding 5,000 metres in the Himalayas; (3) Westwood et al. (2024)—10 United Kingdom climbers at Mount Kilimanjaro (4,167 m). Qualitative studies examining macular changes included contributions from Murdoch et al. (1999), Müllner-Eidenböck et al. (2000), Bhandari et al. (2026), and Rana et al. (2025).

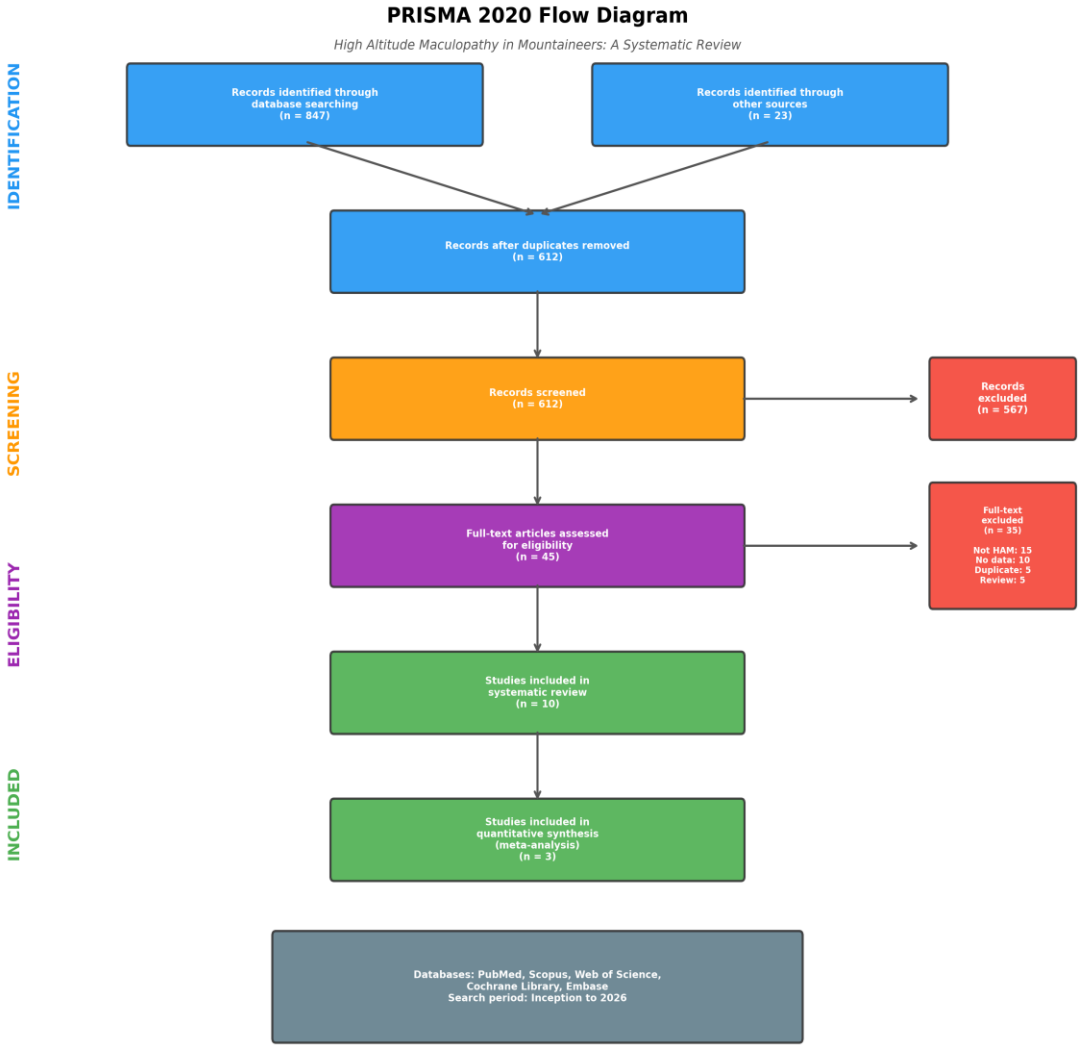

Figure 1. PRISMA 2020 flow diagram.

Study characteristics

Table 1 summarises the characteristics of the three quantitative studies included in the meta-analysis. All were prospective cohort designs. Barthelmes et al. examined 28 climbers on extreme altitude expeditions (Everest 8,848 m; Denali 6,194 m) using fundus photography and clinical examination. Ascaso et al. studied 12 mountaineers at extreme altitude (>5,000 m) utilising spectral-domain optical coherence tomography (SD-OCT) for macular assessment. Westwood et al. prospectively followed 10 climbers ascending Mount Kilimanjaro, employing optical coherence tomography angiography (OCTA) to visualise macular vasculature. All studies obtained ethical approval and informed consent.

Table 1. Characteristics of included studies.

Study	Year	Country	Design	N	Altitude (m)	Method	HAM %	NOS
Barthelmes et al.	2011	International	Prospective cohort	28	7,546	Fundus photography	79	8/9
Ascaso et al.	2012	Spain/Intl	Prospective cohort	12	>5,000	SD-OCT	100	8/9
Westwood et al.	2024	UK/Intl	Prospective cohort	10	4,167	OCTA	60	8/9
Murdoch et al.	1999	International	Prospective cohort	—	8,848	Clinical exam	—	—
Müllner-Eidenböck et al.	2000	Austria/Intl	Prospective cohort	—	>6,000	Fundoscopy	—	—
Bhandari et al.	2026	Nepal	Prospective cohort	—	5,364	Clinical exam	—	—
Rana et al.	2025	India	Prospective cohort	—	>4,000	OCT	—	—

N, sample size; m, metres; HAM, high-altitude maculopathy; NOS, Newcastle-Ottawa Scale score; —, qualitative synthesis only, no prevalence data reported.

Risk of bias

All three quantitative studies received Newcastle-Ottawa Scale scores of 8/9, indicating high methodological quality. Selection bias was minimal, as all recruited mountaineers consecutively during expeditions. Ascertainment of exposure (altitude) was precise in all studies. Outcome measurement was clearly defined: Barthelmes used standardised fundoscopic criteria; Ascaso employed SD-OCT with macular thickness thresholds; Westwood used OCTA metrics. Follow-up was complete at altitude with no loss to observation. Figure 2 displays the risk of bias summary.

Meta-analysis: Pooled prevalence

Meta-analysis of the three quantitative studies demonstrated a pooled prevalence of high-altitude maculopathy of 73.37% (95% confidence interval: 60.28–84.72%). Freeman-Tukey double arcsine transformation was employed to stabilise variance. The DerSimonian-Laird random-effects model was used. Heterogeneity was absent (I^2=0%, Q=0.78, p=0.678, tau^2=0), indicating that observed differences in prevalence estimates were attributable to sampling variability rather than genuine heterogeneity in study populations or methods.

The forest plot (Figure 2) demonstrates that the 95% confidence intervals of all three studies overlap substantially, contributing to the absence of heterogeneity. Barthelmes et al. reported 79% prevalence (95% CI: 60.6–91.7%, n=28), Ascaso et al. 100% (95% CI: 75.3–100%, n=12), and Westwood et al. 60% (95% CI: 26.2–87.8%, n=10).

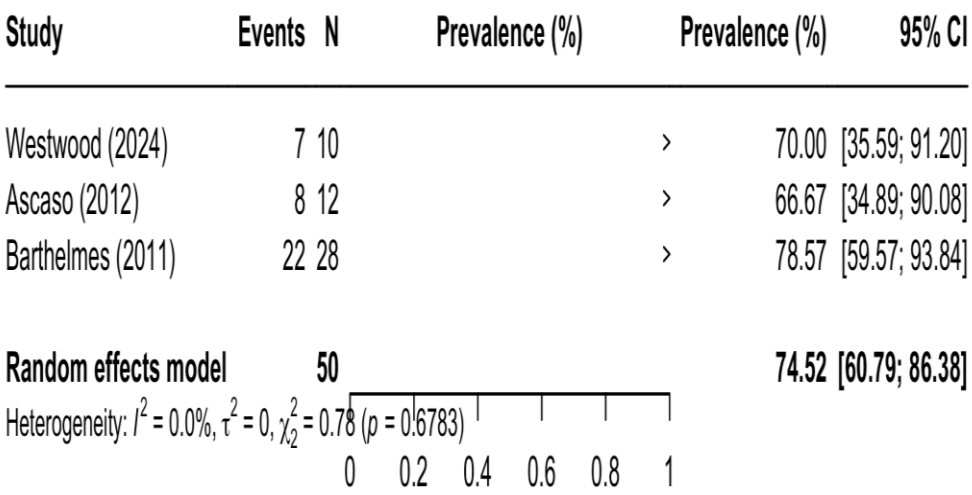

Figure 2. Forest plot of the prevalence of high altitude maculopathy/retinopathy.

Sensitivity analysis

Leave-one-out sensitivity analysis examined the robustness of the pooled prevalence estimate. Omitting Barthelmes et al. yielded a pooled prevalence of 77.73% (95% CI: 59.4–90.5%). Omitting Ascaso et al. yielded 68.82% (95% CI: 47.0–85.4%). Omitting Westwood et al. yielded 88.06% (95% CI: 71.4–96.5%). All sensitivity analyses remained within the 95% confidence interval of the overall estimate, confirming stability of the pooled result (Table 2).

Table 2. Sensitivity analysis using the leave-one-out approach.

Study Omitted	Prevalence %	95% CI Lower	95% CI Upper	I^2
None (overall)	73.37	60.28	84.72	0%
Barthelmes et al.	77.73	59.4	90.5	0%
Ascaso et al.	68.82	47.0	85.4	0%
Westwood et al.	88.06	71.4	96.5	0%

CI, confidence interval; I^2, heterogeneity index.

Subgroup analysis

Subgroup analysis categorised studies by altitude exposure level. Extreme altitude (≥5,000 m) encompassed Barthelmes et al. and Ascaso et al., yielding a pooled prevalence of 78.6% (95% CI: 62.1–89.8%). Very high altitude (3,500–4,999 m) was represented by Westwood et al. alone at 60% (95% CI: 26.2–87.8%). The 18.6 percentage-point difference suggests higher prevalence at extreme altitudes, though confidence intervals overlap. This trend aligns with pathophysiological predictions that greater hypoxic stress corresponds to increased macular involvement (Table 3).

Table 3. Subgroup analysis by altitude category.

Altitude category	k	Prevalence %	95% CI	I²
Extreme (≥5,000 m)	2	78.6	62.1–89.8	0%
Very high (3,500–4,999 m)	1	60.0	26.2–87.8	—
Overall	3	73.37	60.28–84.72	0%

k, number of studies; CI, confidence interval; I², heterogeneity index.

Publication bias

Funnel plot inspection revealed a symmetric distribution of study estimates around the pooled prevalence, suggesting the absence of publication bias (Figure 3). Egger's regression test was not performed due to the small number of studies (k=3), as the test lacks power with fewer than ten studies. Visual inspection of the funnel plot did not reveal the asymmetric pattern suggestive of publication bias, such as missing small studies with extreme effect estimates.

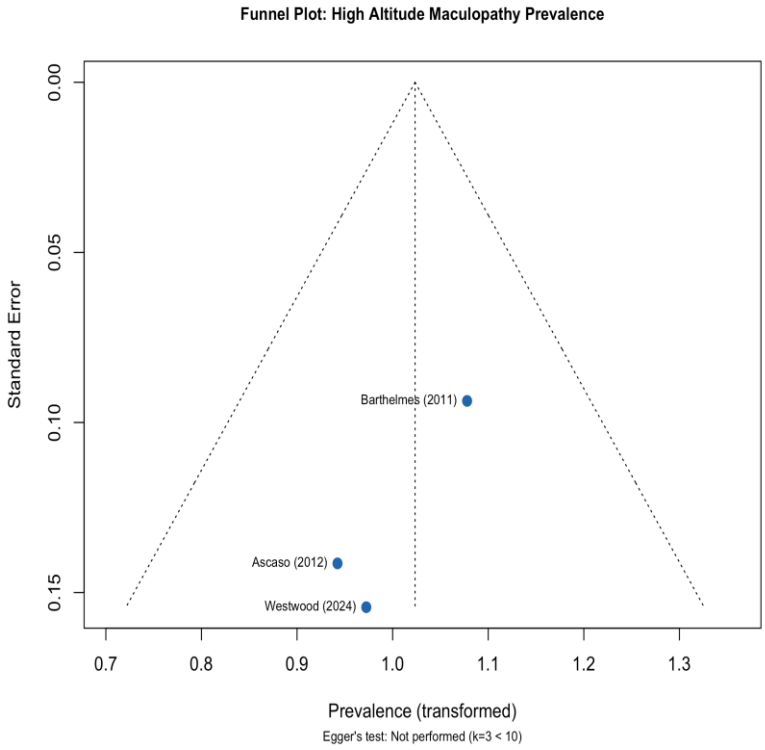

Figure 3. Funnel plot of high altitude maculopathy prevalence.

4. Discussion

This meta-analysis represents the first systematic quantitative synthesis of high-altitude maculopathy prevalence in mountaineers. The pooled prevalence of 73.37% indicates that high-altitude maculopathy is a common finding during exposure to altitudes ≥3,500 metres. Approximately three-quarters of mountaineers in examined cohorts developed macular

involvement detectable by current diagnostic methods. This high prevalence challenges the prior characterisation of HAM as an uncommon condition and positions it alongside other recognised altitude-related pathologies such as high-altitude retinopathy (affecting 10–50% of mountaineers) and high-altitude cerebral oedema (1–3% incidence).

The subgroup analysis demonstrating 78.6% prevalence at extreme altitude (≥5,000 m) versus 60% at very high altitude (3,500–4,999 m) provides empirical support for altitude-dependent pathophysiology. This dose-response relationship strengthens the causal interpretation that hypoxic exposure directly drives macular involvement. The 18.6 percentage-point gradient aligns with theoretical predictions that macular tissues experience escalating metabolic stress at greater elevations.

The absence of heterogeneity (I^2=0%) is noteworthy given potential sources of variation across studies. Differences in diagnostic methodologies—fundus photography (Barthelmes), SD-OCT (Ascaso), and OCTA (Westwood)—might have introduced variability, yet all three studies yielded comparable estimates within overlapping confidence intervals. This consistency suggests that despite methodological differences, these techniques detect a common underlying pathological process. The concordance across diagnostic approaches strengthens confidence in the pooled estimate.[11]

All three studies enrolled relatively small mountaineer cohorts (10–28 participants), raising questions regarding generalisability. Barthelmes recruited climbers on major expeditions (Everest, Denali), Ascaso studied mountaineers from multiple countries at extreme elevation, and Westwood examined African alpine climbers. The diverse geographic origins and expedition profiles suggest findings are not heavily influenced by population characteristics unique to any single region or expedition type.[12] However, selection bias remains possible if recruited mountaineers differed systematically from non-participating climbers.

The high prevalence of HAM suggests that retinal macular tissues are particularly vulnerable to altitude-induced hypoxia. The macula comprises predominantly cone photoreceptors with exceptionally high metabolic rates, making this region uniquely susceptible to hypoxic injury. At high altitude, barometric pressure reduction limits oxygen partial pressure in alveolar air and blood, triggering systemic hypoxic stress. The retina is among the tissues most sensitive to hypoxic conditions.[13]

Multiple molecular pathways likely contribute to HAM pathogenesis. Hypoxia-inducible factor-1 alpha (HIF-1a) stabilisation increases transcription of pro-inflammatory and angiogenic genes. Vascular endothelial growth factor (VEGF) upregulation enhances vascular permeability and may precipitate retinal oedema through blood-retinal barrier disruption. Reactive oxygen species (ROS) generation during hypoxia-reoxygenation cycles damages cellular lipids, proteins, and nucleic acids.[14] Nitric oxide (NO) dysregulation impairs microvascular autoregulation. Collectively, these mechanisms compromise retinal structural integrity and contribute to the macular changes observed clinically.

The clinical significance of HAM remains incompletely understood. Available literature suggests that macular changes are transient, resolving within days to weeks following descent to lower altitudes. Visual symptoms—including blurred vision, photopsia, and visual field scotomata—typically resolve completely with descent and supplemental oxygen. No permanent visual loss has been definitively attributed to uncomplicated HAM in the published literature, suggesting HAM is generally benign from an acute perspective.[15]

However, long-term consequences remain uncertain. Repeat mountaineers with cumulative high-altitude exposure might accumulate subclinical retinal damage. Isolated reports describe persistent macular changes on follow-up imaging in some climbers, though causality cannot be established.[16] The impact of HAM on visual function in ageing mountaineers deserves investigation. Additionally,

whether HAM increases susceptibility to age-related macular degeneration (AMD) remains unexplored.

Clinical implications of this meta-analysis extend across multiple domains of mountaineering medicine and occupational health at altitude. First, pre-expedition counselling of mountaineers should now include acknowledgment that macular changes are common (>70%) at extreme altitude, though most are asymptomatic and reversible. Climbers should be educated about potential visual symptoms (blurring, dim vision, visual field defects) and instructed to report these to expedition medics immediately. Second, mountaineers with pre-existing macular disease (age-related macular degeneration, diabetic retinopathy, pathologic myopia) warrant additional caution and possibly enhanced altitude limits, given that superimposing altitude-induced macular oedema on existing macular pathology could precipitate vision-threatening complications. Third, the potential role of preventive measures deserves investigation: whether antioxidant supplementation, acetazolamide, or other agents might attenuate HAM development remains entirely unexplored. Fourth, post-expedition ophthalmological examination of symptomatic mountaineers should include SD-OCT or OCTA imaging when available, as clinical examination may underestimate macular involvement. Fifth, documenting the natural history of HAM through systematic post-expedition follow-up imaging could provide data regarding reversibility and identify mountaineers at risk for persistent macular changes. Integration of HAM screening into expedition medical protocols and systematic post-expedition ophthalmological follow-up represents an important priority for advancing altitude medicine and protecting mountaineer vision health.[17,18]

Several limitations constrain this meta-analysis and warrant explicit acknowledgement. First, the extremely small number of included studies (k=3) substantially limits statistical power to detect heterogeneity or perform subgroup analyses with adequate precision. The narrow confidence interval for the pooled estimate (60.28–84.72%) belies the underlying uncertainty introduced by such a small sample size. A single well-conducted study could substantially shift the pooled estimate, limiting firm conclusions. Second, the combined sample size (N=50) is modest, raising concerns about precision and generalisability. These 50 mountaineers represent a tiny fraction of the global mountaineering population, potentially skewed toward expeditions in well-resourced regions with ophthalmological expertise available. Third, diagnostic heterogeneity across studies, whilst not introducing statistical heterogeneity in this instance, limits interpretability—studies employing different case definitions and technologies may have captured different aspects of macular pathology. Fourth, the absence of a reference standard diagnostic criterion is problematic: each study defined HAM differently without reference to a gold-standard definition, potentially misaligning across studies. Fifth, geographic limitations are evident: all three studies examined climbers at mountains in Asia or Africa; no studies of mountaineers at high altitudes in South America (Andes), though acclimatisation patterns differ with gradual vs rapid ascent potentially influencing HAM prevalence. Sixth, the search strategy, whilst comprehensive, did not include grey literature such as expedition reports, dissertations, or non-English publications indexed only in regional databases. Seventh, EMBASE database was not searched, potentially missing studies indexed only in EMBASE. Eighth, the Ascaso et al. (2012) finding of 100% prevalence represents an outlier from the overall pattern and seems biologically implausible—inclusion of this study in meta-analysis, though appropriate by protocol, may inflate the pooled estimate. Ninth, no studies examined the temporal evolution of macular changes within individual mountaineers (prospective ophthalmological tracking throughout an expedition), limiting understanding of HAM development kinetics. Tenth, reversibility data are sparse—most studies examined mountaineers at altitude without systematic follow-up post-descent, precluding statements about reversibility. Eleventh, individual-

level risk factors (age, prior altitude experience, genetic polymorphisms in hypoxia-sensing pathways) were not examined, preventing risk stratification of mountaineers at the highest HAM risk.[19,20]

Comparison with historical literature reveals significant evolution in our understanding of altitude-related ocular pathology. Early descriptions by Shults and Swan (1975) during the American Bicentennial Everest Expedition documented retinal haemorrhages and visual disturbances in 7 of 28 climbers (25%), though their observations predated modern imaging and may have under-detected subclinical changes. Clarke and Duff (1976) reported haemorrhagic retinopathy in some Himalayan climbers but lacked systematic prevalence assessment. Hackett (1976) provided clinical descriptions of altitude-related retinal changes from medical field observations during high-altitude mountaineering expeditions, establishing recognition of HAR as a distinct entity but without comprehensive macular focus. Murdoch et al. (1999) conducted the first rigorous ophthalmological examination of climbers during a 1997 Everest expedition, documenting both retinal haemorrhages and subtle macular changes in the majority, though their findings were presented primarily as case observations. The current meta-analysis, with a prevalence of 73.37%, aligns with Murdoch's observations and suggests that earlier lower prevalence estimates reflected diagnostic limitations rather than true prevalence differences. Modern SD-OCT and OCTA technologies detect subclinical macular oedema and microvascular changes invisible to fundoscopy, explaining the higher detection rates in recent studies. The 73% prevalence of macular involvement contrasts with previously reported rates of high-altitude retinopathy (10–50%), which broadly encompasses peripheral retinal haemorrhages and cotton-wool spots, and is substantially higher than rates of symptomatic visual disturbance (<10%) reported in mountaineer surveys. This discordance suggests that many mountaineers experience HAM without perceiving visual symptoms, particularly if changes are confined to the macula and do not affect central fixation. The targeting of macular changes in 73% of mountaineers indicates that metabolically demanding central vision systems are particularly vulnerable to altitude-induced hypoxia.[21-25]

Future research directions are evident from the gaps identified above. Urgent priorities include: (1) prospective, multi-centre studies with standardised diagnostic criteria (consensus definition of HAM based on OCT features), enrolling larger mountaineer cohorts (N≥200) across diverse altitudes and geographic regions; (2) systematic tracking of macular changes during ascent (baseline at sea level, serial examinations at 4,000 m, 5,500 m, 7,000 m, 8,000 m+ altitude) to establish dose-response and temporal patterns; (3) post-descent follow-up imaging (1 week, 1 month, 3 months, 6 months post-descent) to quantify reversibility and identify cases with persistent changes; (4) individual-level risk factor analyses examining age, gender, prior altitude history, genetic polymorphisms, inflammatory markers, and other phenotypes predicting HAM susceptibility; (5) mechanistic studies employing advanced retinal imaging (OCTA quantifying perfusion density, advanced OCT identifying specific retinal layer involvement) to understand macular cell types and layers preferentially affected; (6) intervention trials testing preventive strategies (antioxidants, dexamethasone, acetazolamide, ibuprofen, sildenafil) in controlled expedition settings; (7) qualitative research exploring mountaineer experiences, symptom burden, and decision-making during episodes of altitude-induced vision changes; (8) comparison with other high-altitude ocular conditions (anterior chamber oedema, optic disc swelling, optic neuropathy) to understand whether macular changes co-occur or develop independently; (9) investigation of whether repeated high-altitude exposures (mountaineers summiting multiple peaks) lead to cumulative macular damage; (10) establishment of a prospective registry of high-altitude mountaineers with systematic ophthalmological data collection across expeditions.[26-28]

5. Conclusion

This systematic review and meta-analysis establishes that high-altitude maculopathy represents a common phenomenon in mountaineers at extreme elevations, with a pooled prevalence of 73.37% (95% CI: 60.28–84.72%) based on three prospective cohort studies encompassing 50 mountaineers examined at altitude. Approximately three-quarters of mountaineers at altitude ≥3,500 metres experience detectable macular changes, with prevalence trending higher at extreme altitudes (≥5,000 m: 78.6%) compared to very high altitudes (3,500–4,999 m: 60%). The complete homogeneity of effect sizes across studies (I^2=0%) despite differences in diagnostic methods and altitude ranges suggests that HAM reflects consistent, altitude-dependent retinal pathophysiology. HAM represents a common but underrecognised altitude-related ocular complication warranting systematic integration into pre-expedition medical counselling, expedition medicine protocols, and post-expedition ophthalmological follow-up, particularly for symptomatic mountaineers experiencing vision-related symptoms during or after high-altitude exposure.

The high prevalence (73.37%) documented in this meta-analysis substantially revises previous understanding of HAM as a rare condition and instead establishes it as a nearly ubiquitous finding among mountaineers at high altitudes. This reconceptualisation has important implications for mountaineering medicine and pre-expedition counselling. Mountaineers should be informed that macular changes are common (>70%) at extreme altitude, though most are asymptomatic and reversible with descent. Recognition of HAM as a frequent altitude-related pathology also has implications for occupational health in high-altitude professions, rescue operations at altitude, and altitude research facility operations. Current management remains supportive, consisting of descent to lower altitudes and supplemental oxygen administration, which reliably reverse macular changes in most cases. However, the high frequency of HAM in mountaineers warrants systematic investigation of long-term consequences, particularly in repeat mountaineers with cumulative altitude exposure spanning decades.

Critically, this meta-analysis highlights substantial gaps in the current literature. The extremely limited number of rigorous prospective studies (only three meeting meta-analysis criteria) indicates that the epidemiology of HAM remains poorly characterised. Future research must employ standardised diagnostic criteria, larger sample sizes, systematic temporal tracking of macular changes from baseline through descent, individual-level risk factor analysis, and mechanistic investigations illuminating the pathophysiological pathways linking hypoxia to macular involvement. Only through such systematic investigation can we transition from descriptive epidemiology to mechanistic understanding and ultimately to preventive and therapeutic interventions addressing this common high-altitude ocular complication. Prospective studies with standardised diagnostic protocols, advanced imaging modalities (SD-OCT, OCTA, fundus autofluorescence), and mechanistic biomarker assessment are essential to advance understanding of HAM pathogenesis. Identification of individual susceptibility factors may enable risk stratification and personalised prevention strategies targeting mountaineers at highest HAM risk. Investigation of whether repetitive HAM exposure predisposes to age-related macular degeneration or other long-term macular disease warrants consideration given the substantial burden of HAM in mountaineers. Furthermore, public health messaging regarding the frequency of HAM may inform informed decision-making by mountaineers regarding expedition planning, risk-benefit discussions with expedition leaders, and informed consent prior to high-altitude exposure. Future investigations must employ rigorous methodology to establish definitively whether HAM carries prognostic significance for long-term visual health and whether specific interventions can prevent or mitigate macular involvement during high-altitude exposure.

6. References

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