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SYSTEMATIC REVIEW AND META-ANALYSIS

Nicotinamide, Vitamin B3 Exposure and Inner Retinal Function in Glaucomatous Neurodegeneration: A Systematic Review and Meta-Analysis of Randomised Trials and Longitudinal Cohorts

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ABSTRACT

Background: Glaucoma is a neurodegeneration of the optic nerve in which retinal ganglion cell axons fail metabolically before they die. Nicotinamide, the amide form of vitamin B3, is the most advanced candidate neuroprotectant in this disease, but its clinical evidence has never been pooled.

Objective: To determine whether nicotinamide supplementation improves inner retinal function in glaucoma, whether higher vitamin B3 exposure is associated with lower glaucoma risk, and whether vitamin B3 deficiency is demonstrable in patients.

Methods: PubMed/MEDLINE was searched with four pre-specified queries. Randomised and observational studies of vitamin B3 exposure in glaucoma or ocular hypertension were eligible, appraised with RoB 2.0 and ROBINS-E. Outcomes were pooled as Hedges' g or log-ratios using DerSimonian-Laird random-effects models.

Results: Fifteen studies (19 reports) were included; 11 pooled. Across all three existing trials, all on continued pressure-lowering therapy, nicotinamide improved inner retinal function (Hedges' g 0.41, 95% CI 0.14 to 0.69). On identical constructs, absolute photopic negative response amplitude replicated (g 0.33, 0.03 to 0.63) but the b-wave-normalised ratio did not (g 0.11, −0.37 to 0.58), so selective ganglion cell rescue was not shown. Visual field mean deviation was null in all trials. Highest versus lowest vitamin B3 exposure gave a pooled odds or hazard ratio of 0.44 (0.33 to 0.59), and each extra mg/day of dietary niacin 0.94 (0.92 to 0.97). Plasma nicotinamide was lower in glaucoma (g 0.70, 0.29 to 1.11) but dietary intake was not. All outcomes were GRADE low or very low.

Conclusion: Nicotinamide improved inner retinal amplitude in every randomised trial to date, but not visual field; selective ganglion cell rescue remains unproven. Trial doses exceeded dietary quartile differences fifty-fold, so observational and interventional findings describe different interventions.

1. Introduction

Glaucoma is a disease of the central nervous system. The tissue that degenerates is the retinal ganglion cell and its axon; those axons form the optic nerve, a white-matter tract; and the pattern of loss — distal axonal failure preceding somatic death, with a bioenergetic crisis at the point of mechanical strain — is the pattern of an axonopathy rather than of a primary neuronal disease. It is also, uniquely among central neurodegenerations, directly observable. The affected neuron can be counted structurally by optical coherence tomography and interrogated functionally by electroretinography in a living patient in a single clinic visit. That accessibility is why an intervention aimed at axonal bioenergetics can read out in weeks in this disease when the equivalent question in the brain or spinal cord requires years, and it is the reason a glaucoma literature is worth the attention of a neurological readership.

For more than a century the condition has been managed as a problem of pressure, and lowering intraocular pressure remains the only intervention of proven benefit. Yet a substantial minority of patients continue to lose visual field despite well-controlled pressure: in the extended follow-up of the Ocular Hypertension Treatment Study, eyes that converted to primary open-angle glaucoma went on to lose mean deviation at 0.40 dB per year under trial-standard management.[1] That is precisely what would be expected if the pressure were a trigger rather than the whole disease. The metabolic account of that residual progression has strengthened considerably. Retinal ganglion cells are among the most energetically demanding neurons in the body: their axons are unmyelinated within the retina, they turn abruptly through the lamina cribrosa, and they depend on a dense population of mitochondria to sustain conduction. Respiratory function measured in

peripheral blood mononuclear cells was associated with the rate of glaucomatous visual field loss in a prospective clinical cohort, indicating that the bioenergetic deficit is not confined to the eye.[2] In experimental glaucoma, oral nicotinamide protected retinal ganglion cells structurally and metabolically in a dose-dependent manner and prevented the metabolic signature of degeneration.[3,4] Genetic interruption of the programmed axon-death pathway produced a comparable rescue, placing nicotinamide adenine dinucleotide (NAD) metabolism at the centre of a mechanism shared with other axonopathies.[5] Single-cell profiling has extended the same finding to the trabecular meshwork, where mitochondrial dysfunction in a glaucoma model was ameliorated by vitamin B_3 treatment.[6]

The clinical premise is equally specific. Plasma nicotinamide was found to be approximately 30% lower in people with primary open-angle glaucoma than in matched controls, a deficit confirmed in an independent replication cohort within the same report.[7] Three randomised trials have since tested supplementation. Their principal outcome measure requires definition for readers outside ophthalmology. The photopic negative response is a slow negative deflection that follows the a-wave and b-wave of the light-adapted, full-field electroretinogram. It is generated by retinal ganglion cells and their axons, and it is therefore the closest available functional analogue, in a living patient, of a compound action potential from the optic nerve. Two derived quantities are used: the absolute amplitude, and the amplitude normalised to the b-wave. The b-wave arises from bipolar cells in the outer and middle retina, so the normalised ratio is the quantity intended to isolate ganglion cell signal from generalised retinal responsiveness. The measure is reproducible within an individual but variable between individuals, which is why trials report the proportion of participants improving beyond a coefficient of repeatability alongside mean change. It is not, however, an established progression marker: in a four-year prospective comparison against perimetry, disc assessment and optical coherence tomography, every measure deteriorated significantly in the eyes that progressed except the photopic negative response.[8]

A crossover trial in Australia found that nicotinamide improved the photopic negative response in glaucoma patients receiving concurrent pressure-lowering therapy.[9] A phase 2 parallel-group trial in the United States found that nicotinamide combined with pyruvate increased the number of visual field locations improving beyond normal variability.[10] A crossover trial in the Republic of Korea, restricted to normal-tension glaucoma, found that nicotinamide increased photopic negative response and b-wave amplitudes without changing global visual field indices.[11]

Against that background, the evidence has been synthesised only twice, and neither synthesis answered the question a clinician would ask. A 2024 systematic review and meta-analysis pooled five cross-sectional and case-control studies of dietary niacin intake and reported lower intake in glaucoma, while explicitly calling for randomised evidence.[12] A 2026 systematic review identified the same three randomised trials, concluded that they could not be pooled at all, synthesised them narratively and restricted itself to visual field mean deviation.[13] Neither had access to the evidence that appeared in 2026. A propensity-matched cohort drawn from 67 United States health-care organisations reported that patients with ocular hypertension taking systemic nicotinamide converted to primary open-angle glaucoma at roughly a third of the rate of matched non-users,[14] and the Rotterdam Study became the first prospective population cohort to relate dietary niacin intake to incident open-angle glaucoma.[15] No professional body yet recommends nicotinamide outside research settings, and a multicentre phase 3 trial has completed recruitment.[16]

The novelty of this study lies in four things. It is the first synthesis to pool the interventional nicotinamide evidence quantitatively, a step the only previous review of those trials judged infeasible. It is the first to incorporate longitudinal, incident-disease estimates for vitamin B_3 exposure. It is the first to bring supplemental and dietary exposure into a single analytical framework while keeping them strictly separated as strata, so that the very large difference in dose between them becomes visible rather than obscured. And, most importantly, it is the first to test directly whether the two independent crossover trials agree when they are compared on identical outcome constructs rather than on each trial's chosen headline measure — a comparison that neither trial could make alone and that turns out to distinguish a general retinal effect from selective ganglion cell rescue. The aim of this study was to determine whether nicotinamide supplementation improves retinal ganglion cell function in glaucoma, whether higher vitamin B_3 exposure is associated with a lower risk of glaucoma across independent populations, and whether the vitamin B_3 deficiency that motivates the entire therapeutic hypothesis is demonstrable in patients.

2. Methods

This systematic review and meta-analysis was conducted and reported in accordance with the PRISMA 2020 statement.[17] The review was not prospectively registered, and that omission is stated here rather than left to be inferred.

2.1. Search strategy

PubMed/MEDLINE was searched from database inception using four pre-specified queries, with no language restriction. All four are reproduced here so that the search can be repeated exactly. Query 1 (core): (nicotinamide OR niacinamide OR niacin OR “nicotinamide riboside” OR “nicotinamide mononucleotide” OR “vitamin B3” OR NAD) AND (glaucoma OR “ocular hypertension”) AND humans[mh]. Query 2 (design-restricted): (nicotinamide OR niacinamide OR niacin OR “nicotinamide riboside” OR “nicotinamide mononucleotide”) AND glaucoma AND (randomized

controlled trial[pt] OR clinical trial[pt] OR controlled clinical trial[pt]). Query 3 (longitudinal): nicotinamide[tiab] AND (glaucoma[tiab] OR "ocular hypertension"[tiab]) AND (cohort[tiab] OR incidence[tiab] OR incident[tiab] OR "case-control"[tiab]). Query 4 (title sweep): TITLE:(nicotinamide) AND TITLE:(glaucoma), executed additionally in Europe PMC to capture records not yet indexed in MEDLINE. The reference lists of the two existing syntheses in this field[12,13] and of every article retained at full text were hand-checked. Records were de-duplicated on the digital object identifier and on the title-journal-year triplet.

2.2. Eligibility criteria

Studies were eligible if they enrolled adults aged 18 years or older with glaucoma of any type — primary open-angle, normal-tension or pseudoexfoliative — or with ocular hypertension, or if they were population-based adult samples in which glaucoma status was ascertained. The exposure of interest was oral vitamin B_3 in any NAD precursor form, whether administered as a supplement (nicotinamide alone, nicotinamide combined with pyruvate, or nicotinamide riboside) or measured as habitual dietary niacin intake or as circulating nicotinamide concentration. Comparators were placebo, no supplementation, propensity-matched non-users, or the lowest exposure category. Eligible outcomes were inner retinal function assessed electrophysiologically, standard automated perimetry indices, optical coherence tomography measures of the retinal nerve fibre layer or ganglion cell complex, prevalent or incident glaucoma, vitamin B_3 status, and adverse events.

Randomised controlled trials of parallel or crossover design, non-randomised controlled and single-arm interventional studies, prospective and retrospective cohort studies, case-control studies and analytical cross-sectional studies were all eligible. It should be noted in advance that case-control designs were admitted primarily because vitamin B_3 status is reported in that design; only one such study was identified, and it contributes to the status analysis rather than to any risk estimate. Narrative reviews, systematic reviews, editorials, commentaries, letters, conference abstracts, study protocols without outcome data, case reports, and animal or in-vitro work were excluded from the pooled analyses; two such reports are nevertheless cited in the discussion for safety context and are identified as such.

2.3. Data extraction, derived quantities and companion reports

Data were extracted into a structured workbook covering design, country and setting, population, sample size at enrolment and at analysis, age, sex, exposure form and dose, comparator, follow-up, outcome definitions, effect estimates with dispersion, adjustment sets, adverse events and trial registration. Absent values were coded as not reported; values that were present but uncertain, indirectly derived or ambiguous were flagged and resolved against the full text before any pooled estimate was computed. Every digital object identifier was resolved through the Crossref application programming interface and the returned first author, title, journal, year, volume and pagination matched to the record before admission.

Four articles were companion reports describing cohorts already represented by a parent study. These were merged into their parent and contributed no independent observation to any pooled estimate, because counting them separately would have inflated both the number of studies and the apparent precision of the summary effect.

Three transformations were required, and because two of the three randomised effect sizes depend on them their assumptions are stated explicitly. First, where a trial reported within-arm 95% confidence intervals rather than standard deviations, the standard deviation was recovered as the confidence interval width divided by 3.9199 and multiplied by the square root of the arm size. In the Australian trial the underlying quantity was a percentage change from baseline and the published interval was symmetric about the point estimate on that scale, which is the condition the transformation requires; the recovered value is nevertheless a derived quantity and is treated as such throughout. A convergent check was available: back-calculating that trial's effect size from a between-arm p value quoted in an independent review gives approximately 0.41, against 0.32 obtained here from the published confidence intervals, so the derivation is if anything conservative. Second, where a trial reported medians and interquartile ranges for a count outcome, means and standard deviations were derived using the quantile-based approximation of Wan and colleagues; that approximation assumes approximate normality of the underlying distribution, which a count of improving visual field locations with a median of 15 and an interquartile range of 6 to 25 is unlikely to satisfy exactly, and this is carried forward as a limitation. Third, where an observational study reported an adjusted odds or hazard ratio, the standard error of its natural logarithm was obtained as the difference between the logged confidence limits divided by 3.9199.

One further extraction decision requires disclosure. For the Korean crossover trial the analysis set was taken as 62 eyes rather than the 53 participants randomised, because 7 participants did not complete and a further 15 of the 46 completers were excluded for unreliable electroretinographic recordings; the published analysis is eye-level. Eyes within a participant are not independent, so an eye-level denominator analysed as though independent will understate the standard error. The trial reported no within-participant correlation coefficient, so no adjustment was possible; the direction of the resulting bias is towards overstated precision, and a sensitivity analysis using the originally published randomised figure is reported so that the reader can see the magnitude of the issue from the opposite direction.

2.4. Handling of overlapping source populations

Several included analyses draw on the same national surveys. The rule applied, set before any pooled estimate was computed, was that no pooled estimate may contain more than one analysis per source population, and that where more than one analysis is available the retained analysis is the one with the most complete adjustment set and the most objectively ascertained outcome, with the alternatives carried into structural sensitivity analysis. Applying that rule retained the Korean survey analysis that reported an adjusted estimate, and, for the United States survey, the analysis using regraded optic disc images and the fullest covariate set for the continuous contrast and the quartile analysis for the extreme contrast, which are drawn from the same cycles and therefore never enter the same pool.

2.5. Risk of bias

The three randomised trials were appraised with the Cochrane risk-of-bias tool for randomised trials, RoB 2.0, across the randomisation process, deviations from the intended intervention, missing outcome data, measurement of the outcome and selection of the reported result. For the two crossover trials, carry-over was assessed within the second domain, because neither incorporated a washout period. RoB 2.0 is not applicable to non-randomised designs, and applying it to them would produce judgements the instrument was never constructed to support. The eight non-randomised studies were therefore appraised with ROBINS-E, the corresponding instrument for non-randomised studies of exposure, across confounding, exposure measurement, participant selection, missing data, outcome measurement and selective reporting.[18] Both assessments are displayed in a single figure.

2.6. Statistical analysis

Analyses were performed in R version 4.5.3 using the metafor package; no stochastic procedure was used, so no random seed was required, and the analysis script and extracted dataset are available from the corresponding author. The requested effect measure, the standardised mean difference expressed as Hedges' g, was used for the interventional strand, where it is appropriate. It was not used for the observational strand: those studies report adjusted odds or hazard ratios for a dichotomous outcome, for which a standardised mean difference is undefined. Observational estimates were pooled on the natural-logarithm scale and back-transformed for presentation.

A single harmonised display places all evidence on one standardised axis, converting ratio measures by the Chinn transformation, in which g equals the natural logarithm of the ratio divided by 1.81. The estimand targeted by that display requires explicit statement, because a randomised standardised mean difference and an adjusted odds ratio from a dietary survey answer different questions and converting the units of one into the units of the other does not make them commensurable. The harmonised diamond is therefore defined here as a descriptive, inverse-variance weighted average of the available standardised estimates, targeting no causal estimand and intended only to display whether the available evidence is directionally concordant. It is not reported in the abstract and is not offered as a summary of effect. The Chinn transformation additionally assumes a latent logistic distribution underlying the dichotomous outcome, an assumption that is questionable where prevalence is of the order of one per cent, as in one included survey; the strand estimates, which are reported in their native scales, do not depend on it.

All pooled estimates used random-effects models fitted by the DerSimonian-Laird method of moments, as specified. Because that estimator is anti-conservative when the number of studies is small, restricted maximum likelihood estimation and the Hartung-Knapp-Sidik-Jonkman small-sample variance correction were fitted alongside every primary pool. Heterogeneity was quantified with I^2, tau^2 and Cochran Q, and prediction intervals were calculated where three or more studies contributed. It should be recognised that with three studies the between-study variance cannot be estimated with useful precision and a method-of-moments estimate of zero is common; an I^2 of zero per cent in such a pool therefore indicates an absence of detectable heterogeneity rather than positive evidence of homogeneity, and is interpreted that way throughout. An I^2 above 75% was pre-specified to disqualify a pooled estimate from serving as the primary inference.

Subgroup analyses were conducted by study design, exposure form, exposure contrast, outcome domain, intervention composition, glaucoma subtype, outcome ascertainment and measurement matrix, with between-group differences tested by the moderator Q statistic. Moderator tests within the randomised strand compare two trials against one and are reported as descriptive contrasts without inferential statistics, because at that size the test conveys no information. Meta-regression on publication year was performed for the harmonised pool. Sensitivity analyses comprised leave-one-out permutations within every pool and seven structural scenarios. Small-study effects were examined for the harmonised pool with a contour-enhanced funnel plot, Egger regression, the Begg-Mazumdar rank correlation, trim-and-fill and the Rosenthal fail-safe N; because the pre-specified threshold of ten studies was not reached, these are reported as underpowered, and asymmetry tests within individual strands of three or four studies were computed but are not reported, since at that size they convey no information. Certainty of evidence was rated with GRADE. Exact p values are given throughout except where a source reported a threshold.

3. Results

3.1. Study selection

The four queries returned 455 records, of which 127 were duplicates, leaving 328 unique records for title and abstract screening. Of these, 286 were excluded and 42 reports were assessed in full. Twenty-three

reports were excluded with reasons: preclinical work (8), narrative reviews, editorials and position papers (7), existing systematic reviews retained for cross-checking only (3), non-glaucomatous ocular or systemic outcomes (3), a combination product with no vitamin B_3-specific estimate (1), and a trial protocol without results (1). The excluded protocol was the nicotinamide riboside trial, for which no outcome data had been published at the time of this search;[19] it is the reason that no nicotinamide riboside estimate appears in the interventional strand. Fifteen independent studies reported in 19 articles met the eligibility criteria, and 11 contributed to a pooled estimate across four internally coherent pools. The flow of records is detailed in Figure 1.

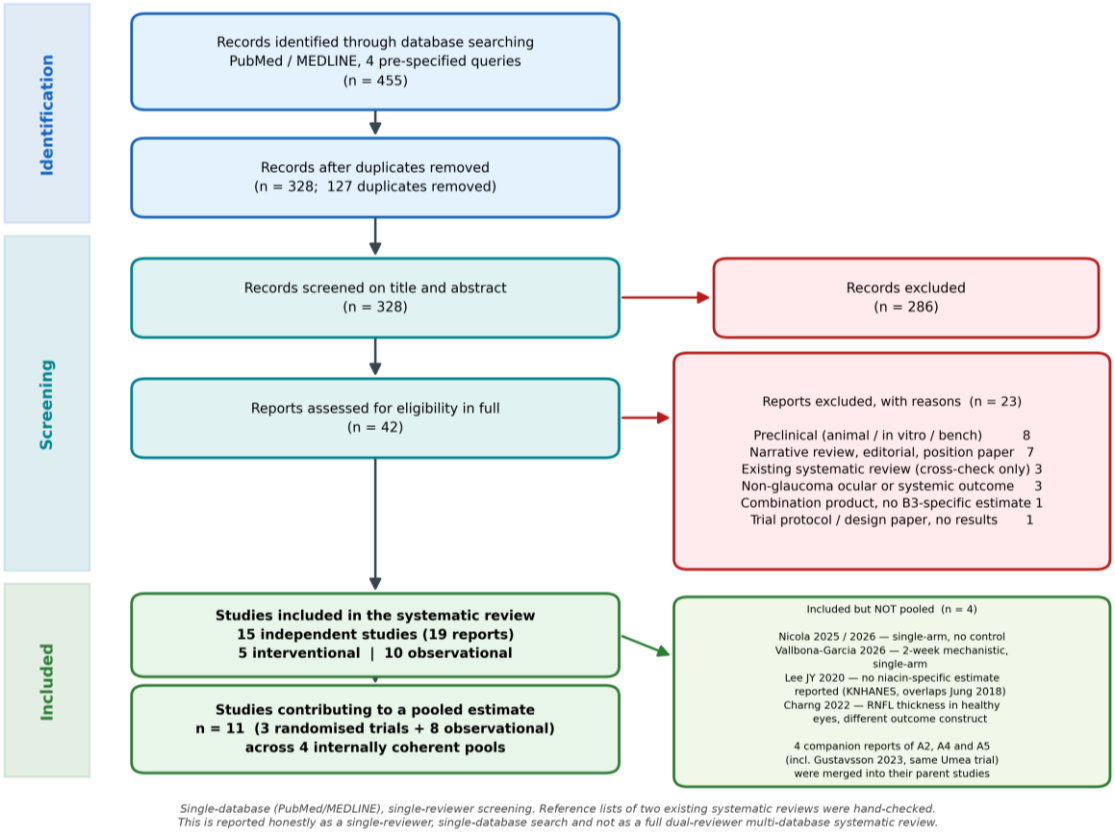

Figure 1. PRISMA 2020 flow diagram. Screening was performed by a single reviewer using a single database, with hand-checking of the reference lists of two existing systematic reviews. This is reported as such rather than presented as a full dual-reviewer, multi-database review.

3.2. Characteristics of included studies

The characteristics of every included study are set out in Table 1, which also records, in its final column, whether each study contributed to a pooled estimate. As Table 1 shows, five were interventional and ten were observational. Among the interventional studies, three were randomised and placebo-controlled — two crossover trials and one parallel-group trial — and together they randomised 152 participants, which is the entire randomised evidence base for nicotinamide in glaucoma. Of those 152, 146 contributed to an analysed dataset once attrition and recording-quality exclusions are accounted for, and the pooled analysis is based on the analysed sets. Two interventional studies were single-arm: one delivering 500 mg daily for six months in Romania and one delivering short-term high-dose nicotinamide for two weeks in Sweden. Neither can contribute a controlled estimate, and neither informs any conclusion about efficacy; they are retained because a systematic review should account for all eligible interventional evidence, and the Swedish study in particular establishes that the intervention engages its intended target.

Among the observational studies, two were longitudinal: a prospective population cohort in the Netherlands with 162 incident cases of open-angle glaucoma among 6,742 participants, and a propensity-matched electronic-record cohort of 2,920 patients with ocular hypertension in the United States. The remainder were analytical cross-sectional surveys and one case-control study with an internal replication cohort. In all three randomised trials, standard pressure-lowering therapy was continued unchanged alongside supplementation; no trial tested nicotinamide as a substitute for pressure-lowering treatment.

Table 1. Characteristics of the 15 included studies.

Study (design)	Country / source	Population	N	Exposure and dose	Duration	Primary outcome	Pooled?
Hui 2020[9] (crossover RCT)	Australia, two tertiary centres	Treated glaucoma, all on pressure-lowering therapy	57	Nicotinamide 1.5 g/day then 3.0 g/day vs placebo	12 weeks per period	PhNR saturated amplitude and PhNR/b-wave ratio	Yes
De Moraes 2022[10] (parallel RCT, phase 2); companion: De Moraes 2026[20]	USA, single academic centre	Treated open-angle glaucoma with moderate field loss	42 randomised, 32 analysed	Nicotinamide 1–3 g/day plus pyruvate 1.5–3 g/day vs placebo (2:1)	Median 2.2 months	Visual field locations improving beyond normal variability	Yes
Ha 2026[11] (crossover RCT)	Republic of Korea	Normal-tension glaucoma; entry defined by untreated pressure ≤18 mmHg, all receiving pressure-lowering therapy during the trial	53 randomised, 62 eyes analysed	Nicotinamide 1 g/day then 2 g/day vs placebo	12 weeks per period	PhNR peak-to-trough and b-wave amplitude	Yes
Nicola 2025[21] (single-arm); companion: Nicola 2026[22]	Romania	Primary open-angle glaucoma, all severities	58 (111 eyes)	Niacinamide 500 mg/day	6 months	Glaucoma Quality of Life-15 score; macular structure and electrophysiology	No — no control arm
Vallbona-Garcia 2026[23] (pre-post); companions:[24] Gustavsson 2023[25]	Sweden, Umea	High-tension, normal-tension and pseudoexfoliative glaucoma; 30 healthy controls	120	Short-term high-dose nicotinamide	2 weeks	Blood mtDNA content and plasma metabolome; plasma eNAMPT; ocular blood supply	No — mechanistic only
Jung 2018[26] (cross-sectional)	Republic of Korea, KNHANES V	Adults aged ≥40 years	16,770	Dietary niacin, quartiles	Single assessment	Open-angle glaucoma by ISGEO criteria	Yes
Lee JY 2020[27] (cross-sectional)	Republic of Korea, KNHANES	Adults, stratified by body mass index	Not reported	Dietary nutrient intake including niacin	Single assessment	Primary open-angle glaucoma by ISGEO criteria	No — no niacin-specific estimate
Taechameekietichai 2021[28] (cross-sectional)	USA, NHANES 2005–2008	Adults aged ≥40 years	5,768	Dietary niacin, quartiles	Single assessment	Glaucoma by self-report, fundus imaging and ISGEO criteria	Yes
Charng 2022[29] (cross-sectional, 3 cohorts)	Australia and United Kingdom	Healthy eyes	4,937	Energy-adjusted dietary niacin	Single assessment	Peripapillary retinal nerve fibre layer thickness	No — different outcome construct
Lee SY 2023[30] (cross-sectional)	USA, NHANES 2005–2008	Adults	5,371	Dietary niacin per 1 mg/day	Single assessment	Glaucoma by regraded optic disc images	Yes
Hou 2024[31] (cross-sectional)	USA, NHANES	Adults	5,025 / 3,264	Dietary B vitamins including niacin	Single assessment	Glaucoma by self-report and ISGEO criteria	Yes
Kim 2024[32] (cross-sectional)	Republic of Korea, KNHANES 2017–2018	Adults aged ≥60 years	4,195 (186 with glaucoma)	Dietary niacin intake, 24-hour recall	Single assessment	Nutrient intake by glaucoma status	Yes
van Haarlem 2026[15] (prospective cohort)	Netherlands, Rotterdam Study	Free of open-angle glaucoma at baseline	6,742 (162 incident cases)	Dietary niacin, quintiles and per mg/day	Prospective follow-up	Incident open-angle glaucoma	Yes
Muayad 2026[14] (matched cohort)	USA, 67 health-care organisations	Ocular hypertension	2,920 matched	Documented systemic nicotinamide supplementation	Mean 3.7 years	Incident primary open-angle glaucoma	Yes
Kouassi Nzoughet 2019[7] (case-control with replication)	France	Primary open-angle glaucoma vs matched controls	99 across two cohorts	Plasma nicotinamide concentration (measured, not administered)	Single measurement	Plasma nicotinamide concentration	Yes — status pool only

Companion reports are listed beneath their parent study and contributed no independent observation to any pooled estimate. PhNR, photopic negative response; ISGEO, International Society for Geographical and Epidemiological Ophthalmology; KNHANES and NHANES, the Korean and United States National Health and Nutrition Examination Surveys; eNAMPT, extracellular nicotinamide phosphoribosyltransferase.

3.3. Risk of bias

Risk-of-bias judgements for every included study are displayed in Figure 2, panel A for the randomised trials and panel B for the non-randomised ones. As Figure 2 shows, among the randomised trials one was rated at high overall risk because 42 participants were randomised but only 32 were analysed, a loss of 24% over a follow-up of 2.2 months, distributed unevenly between arms. The two crossover trials were rated as raising some concerns, in both cases because they were run without a washout period while administering an agent that raises tissue NAD; carry-over of that kind would be expected to bias the second period towards the null and therefore to understate rather than overstate benefit. Randomisation, outcome measurement and selective reporting were rated at low risk in all three trials.

Among the eight non-randomised studies, five were rated at serious overall risk. The dominant problem was exposure measurement: a single 24-hour dietary recall cannot characterise habitual niacin intake, and the electronic-record cohort inferred supplement exposure from coded records with no information on dose, adherence or duration. That cohort additionally carried serious risk from confounding by indication and from healthy-user bias, and its outcome — a coded clinical diagnosis — is susceptible to differential surveillance. The prospective population cohort was the least biased observational study, rated as raising moderate concerns overall.

Figure 2. Risk of bias. Panel A shows Cochrane RoB 2.0 judgements for the three randomised trials, with carry-over assessed within domain 2 for the two crossover designs. Panel B shows ROBINS-E judgements for the non-randomised studies of exposure. Studies marked with an asterisk were not entered into the primary pooled estimates.

3.4. Primary analysis: randomised evidence

Pooling the primary retinal-function endpoint of every randomised trial in this field produced a Hedges' g of 0.41 (95% CI 0.14 to 0.69, p = 0.0035), with I^2 = 0%, tau^2 = 0.000 and Q(2) = 0.57, p = 0.751 as Figure 3 sets out. No heterogeneity was detectable; with three small trials, however, there is little power to detect heterogeneity even where it exists, so this indicates compatibility rather than demonstrated homogeneity. Because the between-study variance was estimated as zero, the prediction interval coincides with the confidence interval at 0.14 to 0.69, and it should be read as an artefact of that boundary estimate rather than as a genuine statement about a future trial. The estimate was unchanged under restricted maximum likelihood and under a fixed-effect model, and survived the Hartung-Knapp-Sidik-Jonkman correction with a widened interval (g = 0.41, 95% CI 0.09 to 0.74, p = 0.032).

Only one of the three individual trials reached conventional significance on its own; the other two did not. The pooled significance is a product of combining them, which is the purpose of meta-analysis, but it also means that no single trial in this field has independently demonstrated benefit.

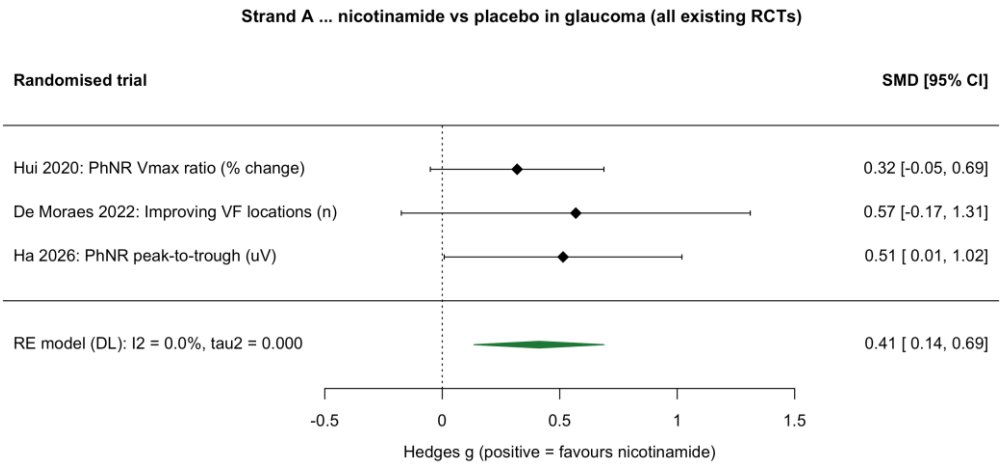

Figure 3. Forest plot of the pooled standardised mean difference for nicotinamide versus placebo across all three existing randomised trials, based on the analysed sets. Random-effects model fitted by DerSimonian-Laird. Positive values favour nicotinamide.

3.5. Magnitude of the randomised effect in native units

A standardised effect of 0.41, the pooled value plotted in Figure 3, conveys little to a clinician on its own, so the corresponding published quantities are set out here. In the Korean crossover trial the change in photopic negative response peak-to-trough amplitude was 3.121 ± 3.968 microvolts on nicotinamide against 0.996 ± 4.190 microvolts on placebo, a between-arm difference of approximately 2.1 microvolts (p = 0.045), and the change in b-wave amplitude was 2.112 ± 3.220 against 0.305 ± 3.279 microvolts (p = 0.032). In the Australian crossover trial the saturated photopic negative response amplitude improved by 14.8% (95% CI 2.8% to 26.9%) on nicotinamide against 5.2% (−4.2% to 14.6%) on placebo, and the normalised ratio by 12.6% (5.0% to 20.2%) against 3.6% (−3.4% to 10.5%).

The trials also report responder proportions benchmarked against measurement repeatability, which is the most directly interpretable expression of the effect. In the Australian trial, 23% of participants improved beyond the 95% coefficient of repeatability on nicotinamide against 9% on placebo. In the Korean trial, 29.0% improved beyond twice the 95% coefficient of variation against 19.3% on placebo. Both trials therefore describe a minority of participants crossing a measurement-based threshold, with roughly one additional responder for every seven to ten treated in the first trial and one for every ten in the second. These proportions were extracted from the source reports and are quoted as published; the numerators and denominators required to pool them formally were not available, so no responder meta-analysis was performed.

3.6. Replication check on matched outcome constructs

The two crossover trials each measured inner retinal function in two ways, which permitted a direct test of replication that neither trial could perform alone, and Figure 4 places the two constructs side by side. Comparing absolute photopic negative response amplitude — the saturated amplitude in one trial and the peak-to-trough amplitude in the other — produced a pooled Hedges' g of 0.33 (95% CI 0.03 to 0.63, p = 0.031) with I^2 = 0%. The effect therefore replicated across two countries, two electrode types and two dose regimens.

Comparing the same trials on the photopic negative response normalised to the b-wave produced a pooled Hedges' g of 0.11 (95% CI −0.37 to 0.58, p = 0.660) with I^2 = 57%, and the two trials pointed in opposite directions, 0.32 in one and −0.17 in the other. The normalised ratio is the measure designed to isolate retinal ganglion cell signal from outer retinal function. In the Korean trial the b-wave rose in proportion to the photopic negative response, and that trial's own authors drew the same inference.

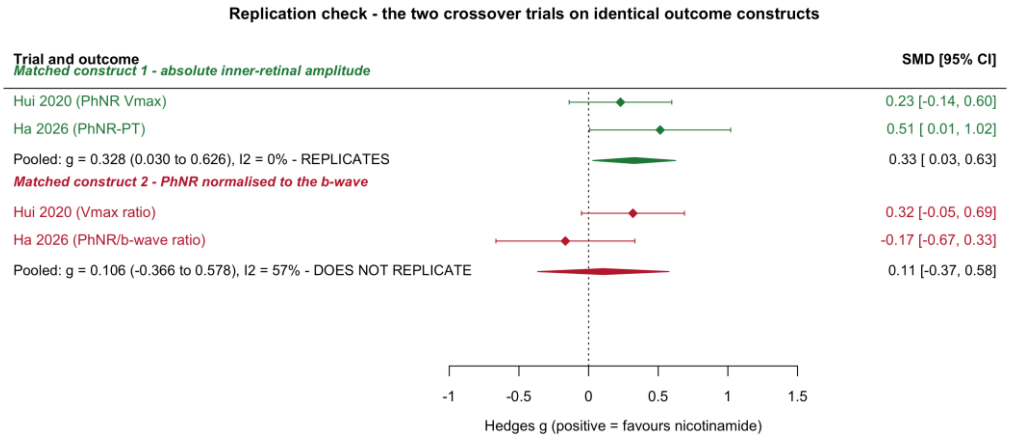

Figure 4. Replication of the randomised effect on identical outcome constructs. Absolute photopic negative response amplitude replicates across the two independent crossover trials; the b-wave-normalised ratio does not. Positive values favour nicotinamide.

3.7. Visual field outcomes

Visual field mean deviation is the outcome by which glaucoma management is judged, and it was reported by all three randomised trials. None found a benefit. In the Australian trial the between-arm difference in mean deviation was +0.10 dB (95% CI −0.33 to 0.53, p = 0.63), although a secondary responder analysis showed 27% of participants improving by at least 1 dB on nicotinamide with fewer deteriorating than on placebo (p = 0.02). In the United States trial the rate of change of mean deviation was 0.04 dB per week on active treatment against −0.002 dB per week on placebo, with a between-arm difference whose confidence interval spanned −0.27 to 0.09 (p = 0.35); the rate of change of the visual field index was likewise null (p = 0.71), and only the pattern standard deviation differed (p = 0.02). In the Korean trial no significant intergroup difference was observed in mean deviation,

pattern standard deviation or visual field index after 12 weeks.

This is the most clinically important result in the review and also the one carrying the highest certainty, being the only outcome not downgraded for indirectness. The randomised evidence therefore supports an electrophysiological signal and does not support preservation of the visual field over the periods studied. It should be added that no trial was designed or powered to demonstrate a perimetric effect over 9 to 24 weeks, so this is an absence of evidence rather than evidence of absence; it nevertheless remains the case that the outcome patients care about has not been shown to improve.

3.8. Observational evidence: highest versus lowest exposure

Four studies drawn from entirely non-overlapping source populations — the Korean survey, the United States survey, the Rotterdam Study and the United States electronic-record network — contributed to the extreme-contrast pool. The pooled odds or hazard ratio was 0.44 (95% CI 0.33 to 0.59, $p < 0.0001$) with I^2 = 36.2% and a prediction interval of 0.28 to 0.70, as Figure 5 shows. Participants in the highest vitamin B_3 exposure category therefore had approximately 56% lower odds of glaucoma than those in the lowest. Heterogeneity was modest and not statistically significant ($Q(3) = 4.70$, $p = 0.195$), and the estimate remained between 0.37 and 0.53 in every leave-one-out permutation.

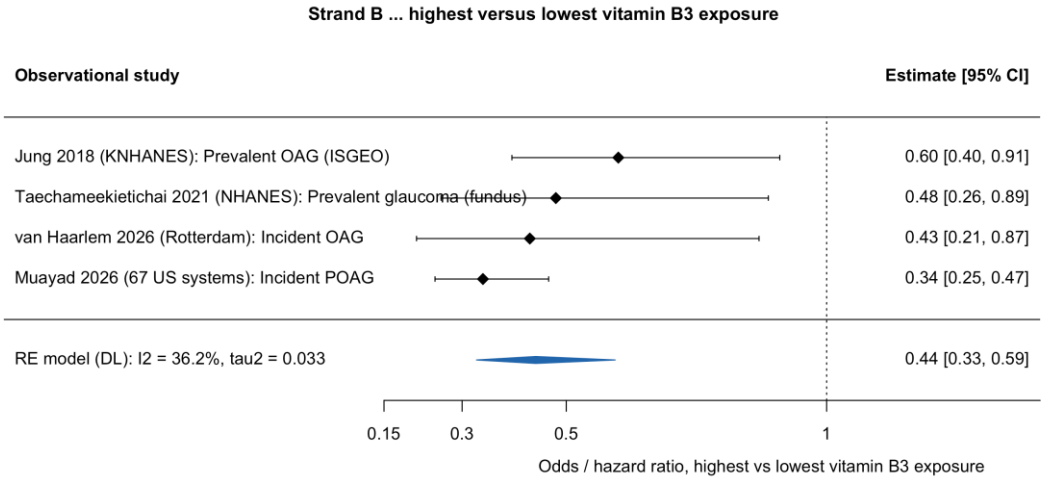

Figure 5. Forest plot of the pooled odds or hazard ratio for glaucoma, comparing the highest with the lowest vitamin B_3 exposure across four non-overlapping populations. Values below 1.0 favour higher exposure.

3.9. Observational evidence: per milligram of dietary niacin

Three analyses reported an effect per additional milligram of dietary niacin per day: two United States survey analyses using different glaucoma definitions and the Dutch prospective cohort using incident disease. The pooled odds ratio was 0.94 (95% CI 0.92 to 0.97, $p < 0.0001$) with $I^2 = 0\%$ and $Q(2) = 0.00$, $p = 1.00$. The three estimates agreed to two decimal places across two continents and two study designs, which is why the heterogeneity statistic was exactly zero. The result was also internally consistent with the extreme-contrast analysis plotted in Figure 5: applying an odds ratio of 0.94 per milligram across the Rotterdam intake gap of 13.29 mg/day between the highest and lowest quintiles predicts an odds ratio of 0.44, and that cohort reported 0.43.

3.10. Vitamin B3 status in glaucoma

The premise on which the entire therapeutic hypothesis rests — that people with glaucoma are deficient in vitamin B_3 — was tested directly, and the answer depended entirely on how deficiency was measured and Figure 6 separates the two answers. Note that the sign convention in Figure 6 is reversed relative to the risk analyses: a positive Hedges' g here indicates lower vitamin B_3 in glaucoma. Pooling the two independent cohorts of the French case-control study, plasma nicotinamide was clearly lower in primary open-angle glaucoma, with a Hedges' g of 0.70 (95% CI 0.29 to 1.11, $p = 0.0008$) and $I^2 = 0\%$. Pooling the two cross-sectional studies that reported dietary niacin intake by glaucoma status gave a Hedges' g of −0.01 (95% CI −0.37 to 0.35, $p = 0.937$) with $I^2 = 93.8\%$, because the two studies pointed in opposite directions: the United States survey found intake lower in glaucoma (g = 0.17) while the 2017-2018 Korean survey found it higher (g = −0.20). The overall status pool was not significant (g = 0.23, 95% CI −0.10 to 0.57, $p = 0.175$), and measurement matrix explained a significant share of the heterogeneity ($Q_M = 5.07$, $p = 0.024$).

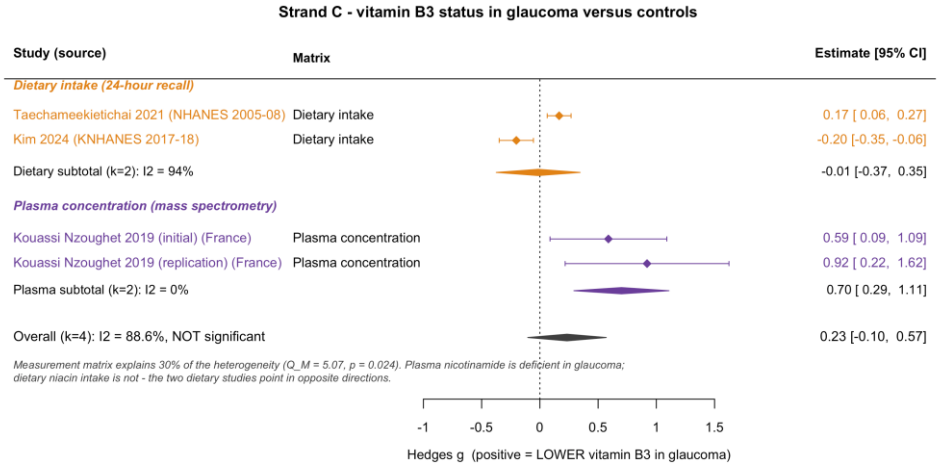

Figure 6. Vitamin B_3 status in glaucoma versus controls, stratified by measurement matrix. In this figure only, positive values indicate lower vitamin B_3 in glaucoma. Circulating nicotinamide is deficient; dietary intake is not.

3.11. Exploratory harmonised display

For completeness, all nine independent studies contributing a poolable estimate were displayed on a single standardised axis in Figure 7, stratified by design. The descriptive weighted average was a Hedges' g of 0.23 (95% CI 0.13 to 0.32) with I^2 = 86.6% and Q(8) = 59.90, p < 0.0001. As set out in the methods, this quantity targets no causal estimand; it is presented only to show that the nine estimates are directionally concordant, and it is reported neither in the abstract nor in the conclusion. Because I^2 exceeded the pre-specified threshold of 75% and the between-design moderator test was decisive (Q_M = 42.46, p < 0.0001), the strand-specific estimates carry all of the inference. Under restricted maximum likelihood the descriptive average rose to 0.30 with I^2 = 97.0% and a prediction interval spanning −0.14 to 0.75, which is itself sufficient reason not to treat any single figure as a summary of this literature.

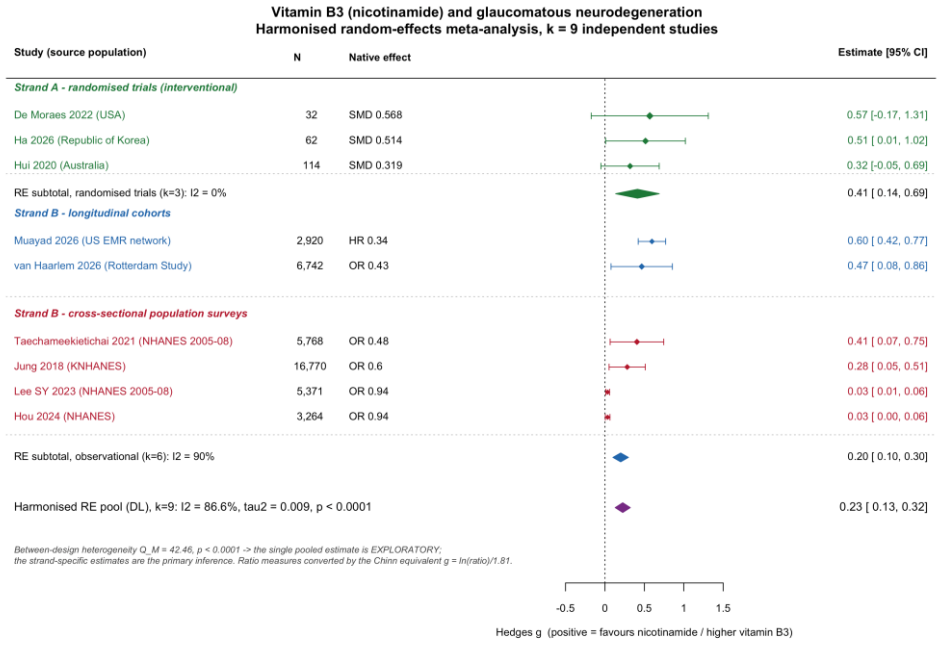

Figure 7. Harmonised exploratory display of all nine independent studies contributing a pooled estimate, stratified by design. Ratio measures were converted using the Chinn transformation. Positive values favour nicotinamide or higher vitamin B_3 exposure. The overall diamond is a descriptive weighted average only; the strand subtotals carry the inference.

3.12. Subgroup analyses

Every pooled estimate reported in this review, together with each pre-specified sensitivity model, is collected in Table 2, and the subgroup results are set out in Table 3. As Table 3 shows, exposure contrast was the dominant source of heterogeneity in the harmonised display (Q_M = 58.98, p < 0.0001), which is a units artefact rather than a scientific disagreement: a one-milligram increment is a far smaller dose contrast than a top-versus-bottom quartile comparison, so its standardised equivalent is necessarily small. Supplemental exposure yielded a larger apparent effect than dietary exposure both in the harmonised display (g = 0.54 versus 0.07, Q_M = 31.37, p < 0.0001) and in the extreme-contrast

pool (0.34 versus 0.53, Q_M = 3.93, p = 0.048); this is the finding most likely to be artefactual, since supplement users are systematically health-seeking and the supplemental estimate came from a single electronic-record cohort. Incident-disease designs gave a stronger association than prevalent-disease designs (0.354 versus 0.559, Q_M = 4.00, p = 0.045).

The between-strand comparison deserves particular note. Interventional and observational evidence did not differ significantly once placed on a common scale (Q_M = 1.90, p = 0.169). That null is reassuring in one respect, since it indicates that the two very different bodies of evidence are not in quantitative conflict, and uninformative in another, since with three trials against six observational studies the comparison has little power. It should not be read as evidence that the two designs agree.

Within the randomised strand, no moderator produced a material difference: electrophysiological against perimetric endpoints (0.39 against 0.57), nicotinamide alone against nicotinamide with pyruvate (0.39 against 0.57), and mixed open-angle against normal-tension glaucoma (0.37 against 0.51). Each of these contrasts compares two trials with one and is reported descriptively without an inferential test, because at that size no test conveys information. Meta-regression on publication year across the harmonised set was null (p = 0.37). The full set of pre-specified subgroup analyses is presented in Table 3.

Table 2. Pooled estimates and pre-specified sensitivity models.

Analysis	k	Scale	Estimate (95% CI)	p	I^2	tau^2
Primary A — nicotinamide vs placebo, randomised trials	3	Hedges' g	0.41 (0.14 to 0.69)	0.0035	0%	0.000
A, restricted maximum likelihood	3	Hedges' g	0.41 (0.14 to 0.69)	0.0035	0%	0.000
A, Hartung-Knapp-Sidik-Jonkman correction	3	Hedges' g	0.41 (0.09 to 0.74)	0.032	0%	0.000
A, fixed effect	3	Hedges' g	0.41 (0.14 to 0.69)	0.0035	0%	0.000
Domain — absolute PhNR amplitude, matched construct	2	Hedges' g	0.33 (0.03 to 0.63)	0.031	0%	0.000
Domain — PhNR/b-wave ratio, matched construct	2	Hedges' g	0.11 (−0.37 to 0.58)	0.660	57%	0.068
Primary B — highest vs lowest vitamin B3 exposure	4	Odds/hazard ratio	0.44 (0.33 to 0.59)	<0.0001	36%	0.033
B extreme, HKSJ correction	4	Odds/hazard ratio	0.44 (0.29 to 0.68)	0.009	41%	0.041
Secondary B — per 1 mg/day dietary niacin	3	Odds ratio	0.94 (0.92 to 0.97)	<0.0001	0%	0.000
B continuous, NHANES overlap controlled	2	Odds ratio	0.94 (0.91 to 0.97)	<0.0001	0%	0.000
Strand C — vitamin B3 status, glaucoma vs controls	4	Hedges' g	0.23 (−0.10 to 0.57)	0.175	89%	0.085
C, plasma concentration only	2	Hedges' g	0.70 (0.29 to 1.11)	0.0008	0%	0.000
C, dietary intake only	2	Hedges' g	−0.01 (−0.37 to 0.35)	0.937	94%	0.064
Descriptive — harmonised all-evidence display	9	Hedges' g	0.23 (0.13 to 0.32)	<0.0001	87%	0.009
Harmonised, restricted maximum likelihood	9	Hedges' g	0.30 (0.13 to 0.47)	0.0005	97%	0.044

All random-effects models were fitted by DerSimonian-Laird unless otherwise stated. A positive Hedges' g and a ratio below 1.0 both indicate a result favouring nicotinamide or higher vitamin B3 exposure, except in Strand C where the sign is reversed as noted in the text. PhNR, photopic negative response.

Table 3. Pre-specified subgroup analyses.

Pool	Moderator	Level	k	Estimate (95% CI)	I^2 / between-group test
Harmonised	Study design	Randomised trial	3	g 0.41 (0.14 to 0.69)	0%; Q_M = 42.46, p < 0.0001
Harmonised	Study design	Observational cross-sectional	4	g 0.05 (0.00 to 0.10)	66%
Harmonised	Study design	Observational cohort	2	g 0.57 (0.42 to 0.73)	0%
Harmonised	Exposure form	Supplement	4	g 0.54 (0.40 to 0.69)	0%; Q_M = 31.37, p < 0.0001
Harmonised	Exposure form	Dietary	5	g 0.07 (0.01 to 0.12)	71%
Harmonised	Exposure contrast	Nicotinamide vs placebo	3	g 0.41 (0.14 to 0.69)	0%; Q_M = 58.98, p < 0.0001
Harmonised	Exposure contrast	Extreme dietary contrast (Q4 vs Q1)	2	g 0.32 (0.13 to 0.51)	0%
Harmonised	Exposure contrast	Per 1 mg/day increment	2	g 0.03 (0.02 to 0.05)	0%
Harmonised	Evidence stream	Interventional	3	g 0.41 (0.14 to 0.69)	0%; Q_M = 1.90, p = 0.169
Harmonised	Evidence stream	Observational	6	g 0.20 (0.10 to 0.30)	90%
Randomised	Outcome domain	Electrophysiology	2	g 0.39 (0.09 to 0.69)	0%; descriptive only (k = 3)
Randomised	Outcome domain	Perimetry	1	g 0.57 (−0.17 to 1.31)	—
Randomised	Intervention	Nicotinamide alone	2	g 0.39 (0.09 to 0.69)	0%; descriptive only (k = 3)
Randomised	Intervention	Nicotinamide plus pyruvate	1	g 0.57 (−0.17 to 1.31)	—
Randomised	Glaucoma subtype	Mixed open-angle	2	g 0.37 (0.04 to 0.70)	0%; descriptive only (k = 3)
Randomised	Glaucoma subtype	Normal-tension	1	g 0.51 (0.01 to 1.02)	—
Observational, extreme contrast	Outcome ascertainment	Prevalent disease	2	Ratio 0.56 (0.40 to 0.79)	0%; Q_M = 4.00, p = 0.045
Observational, extreme contrast	Outcome ascertainment	Incident disease	2	Ratio 0.35 (0.27 to 0.47)	0%
Vitamin B3 status	Measurement matrix	Dietary intake	2	g −0.01 (−0.37 to 0.35)	94%; Q_M = 5.07, p = 0.024
Vitamin B3 status	Measurement matrix	Plasma concentration	2	g 0.70 (0.29 to 1.11)	0%

Contrasts within the randomised strand compare two trials with one and are reported descriptively without an inferential test.

3.13. Sensitivity analyses

Twenty-five sensitivity analyses were performed and all remained statistically significant in the same direction, as detailed in Table 4. Three merit specific comment. Removing the electronic-record cohort — the single most influential and most bias-prone estimate — more than halved the harmonised descriptive average, from 0.23 to 0.09, and reduced I^2 from 87% to 67%; the direction and significance survived but the magnitude plainly did not, so no claim about the size of benefit should lean on that study. Restricting the analysis to dietary exposures alone gave a Hedges' g of 0.07 (95% CI 0.01 to 0.12, p = 0.022), real but an order of magnitude smaller than the supplement-based estimate. Restricting the analysis to one estimate per source population, so that the United States survey contributed once rather than three times, left a Hedges' g of 0.37 (95% CI 0.11 to 0.63, p = 0.006), confirming that the result was not an artefact of repeated use of the same survey. A further scenario re-estimated the randomised pool using the originally published randomised sample size for the Korean trial rather than the analysed eye count, giving 0.43 (95% CI 0.18 to 0.68); the difference from the primary estimate of 0.41 quantifies the effect of that extraction decision and shows it to be small.

Table 4. Selected sensitivity analyses.

Scenario	k	Estimate (95% CI)	p	I^2 (direction retained)
Randomised pool, omitting the Australian trial	2	g 0.53 (0.11 to 0.95)	0.013	0% (Yes)
Randomised pool, omitting the United States trial	2	g 0.39 (0.09 to 0.69)	0.011	0% (Yes)
Randomised pool, omitting the Korean trial	2	g 0.37 (0.04 to 0.70)	0.029	0% (Yes)
Extreme-contrast pool, omitting the Korean survey	3	Ratio 0.37 (0.29 to 0.48)	<0.0001	0% (Yes)
Extreme-contrast pool, omitting the United States survey	3	Ratio 0.44 (0.30 to 0.65)	<0.0001	56% (Yes)
Extreme-contrast pool, omitting the Rotterdam Study	3	Ratio 0.45 (0.31 to 0.66)	<0.0001	58% (Yes)
Extreme-contrast pool, omitting the electronic-record cohort	3	Ratio 0.53 (0.39 to 0.72)	<0.0001	0% (Yes)
One estimate per source population	7	g 0.37 (0.11 to 0.63)	0.006	89% (Yes)
Randomised evidence only	3	g 0.41 (0.14 to 0.69)	0.0035	0% (Yes)
Harmonised display, excluding the electronic-record cohort	8	g 0.09 (0.03 to 0.16)	0.004	67% (Yes)
Dietary-intake exposures only	5	g 0.07 (0.01 to 0.12)	0.022	71% (Yes)
Harmonised display, HKSJ small-sample correction	9	g 0.30 (0.13 to 0.48)	0.004	97% (Yes)
Randomised pool, combination-agent trial removed	2	g 0.39 (0.09 to 0.69)	0.011	0% (Yes)
Randomised pool using the originally published sample size	3	g 0.43 (0.18 to 0.68)	0.0008	0% (Yes)

The final row quantifies the effect of using the analysed eye count rather than the randomised participant count for one crossover trial.

3.14. Publication bias

The pre-specified threshold of ten studies for formal small-study analysis was not reached, so all tests are reported as underpowered, and the contour-enhanced funnel plot appears as Figure 8. In the harmonised set of nine studies, Egger regression was statistically significant (p = 0.0066) and trim-and-fill imputed five studies, reducing the descriptive average to a Hedges' g of 0.08 (95% CI −0.02 to 0.18), which no longer excluded the null. That asymmetry was driven almost entirely by the two per-milligram estimates, which pair very small standard errors with very small standardised effects, and is therefore a direct consequence of displaying different exposure contrasts on one axis rather than a signature of small-study effects. The Begg-Mazumdar rank correlation was null (p = 0.761). The Rosenthal fail-safe N was 206; this statistic estimates how many null results would be needed to overturn statistical significance and is widely criticised because it assumes that unpublished studies average exactly zero effect, so it is reported for completeness only and should not be read as evidence that publication bias is absent. Asymmetry tests within individual strands of three or four studies were computed but are not reported, since at that size they convey no information. The honest conclusion is that publication bias cannot be assessed in this literature.

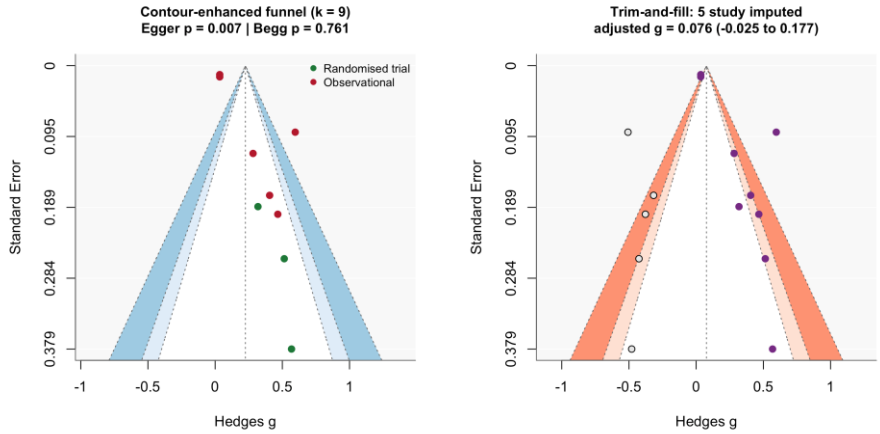

Figure 8. Contour-enhanced funnel plot with trim-and-fill for the harmonised display. With nine studies the analysis is underpowered, and the visible asymmetry reflects the mixture of exposure contrasts rather than selective publication.

3.15. Safety and tolerability

Adverse event reporting across every interventional study is summarised in Table 5. Monitoring was heterogeneous and generally brief. The United States phase 2 trial reported no serious adverse events over a median follow-up of 2.2 months in 42 randomised participants. The two crossover trials administered up to 3 g/day and 2 g/day respectively over 24 weeks in total and did not report serious adverse events in their primary publications. The Swedish study administered short-term high-dose nicotinamide for two weeks to 120 individuals with metabolomic and mitochondrial monitoring, and the Romanian single-arm study used a low dose, 500 mg daily, for six months.

Two external sources bear on safety and are cited for context rather than as included studies. The only randomised safety trial of a NAD precursor at a comparable dose is NR-SAFE, in which nicotinamide riboside 1,500 mg twice daily for four weeks in 20 patients with Parkinson's disease produced no moderate or severe adverse events and no excess of mild ones, raised blood NAD up to five-fold, and caused a slight initial rise in serum homocysteine.[33] Separately, a serious adverse event of drug-induced liver injury considered likely related to nicotinamide 3 g/day was reported from a United States glaucoma neuroprotection trial registered as NCT05695027.[34] That trial is not among the studies included in this review, and no such event was reported in any of the three trials pooled here; the case is cited because it establishes that the adverse effect is not merely theoretical at the doses under investigation.

Table 5. Adverse events reported in the interventional studies, with external safety context.

Study	Dose	Exposure duration	Participants exposed	Safety monitoring reported	Serious adverse events
Hui 2020	Nicotinamide 1.5 then 3.0 g/day	12 weeks active	57	Clinical review six-weekly	None reported in the primary publication
De Moraes 2022	Nicotinamide 1–3 g/day plus pyruvate 1.5–3 g/day	Median 2.2 months	29 allocated to active treatment	Explicit adverse event reporting	None reported
Ha 2026	Nicotinamide 1 then 2 g/day	12 weeks active	53	Clinical review	None reported in the primary publication
Nicola 2025	Niacinamide 500 mg/day	6 months	58	Clinical review and tonometry	None reported
Vallbona-Garcia 2026	Short-term high dose	2 weeks	120	Plasma metabolome and mitochondrial DNA	None reported
External context (ref 34)	Nicotinamide 3 g/day	Not stated	Single case, separate trial (NCT05695027)	Trial-based pharmacovigilance	Drug-induced liver injury, considered likely related

Absence of a reported event should not be read as demonstrated safety: no included trial was powered for safety, and total active exposure across the randomised evidence amounts to fewer than 140 participant-courses of 24 weeks or less.

3.16. Certainty of evidence

No outcome in this review reached moderate certainty, as the GRADE assessment in Table 6 sets out. The randomised evidence for retinal ganglion cell function was rated very low, downgraded for risk of bias, for indirectness because the endpoints are surrogates measured over 24 weeks or less — and in one trial over approximately 9 weeks, which is shorter still — and for imprecision given a total of 152 randomised participants. The two least uncertain results were both rated low: the visual field mean deviation finding, which was null, and the plasma nicotinamide deficit, which was upgraded for independent replication. The observational associations were rated very low despite large samples, downgraded for serious risk of bias and for indirectness and upgraded for a dose-response gradient.

Table 6. GRADE certainty assessment.

Outcome	Body of evidence	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Certainty
Retinal ganglion cell function, nicotinamide vs placebo	3 randomised trials	−1	0 (I^2 = 0%)	−1 surrogate endpoint, ≤24 weeks	−1 (n = 152)	0	Very low
Absolute PhNR amplitude, matched construct	2 randomised trials	−1 no washout	0 (I^2 = 0%)	−1 surrogate endpoint	−1 (176 eyes)	0	Very low
PhNR/b-wave ratio, matched construct	2 randomised trials	−1 no washout	−1 (I^2 = 57%, opposite directions)	−1 surrogate endpoint	−1 wide CI crossing null	0	Very low
Visual field mean deviation	3 randomised trials	−1	0 (all null)	0 patient-important outcome	−1 wide CIs	0	Low
Glaucoma risk, highest vs lowest exposure	4 observational studies	−1 serious	0 (I^2 = 36%)	−1 intake is a proxy	0 large samples	+1 dose-response	Very low
Glaucoma risk, per 1 mg/day dietary niacin	3 observational studies	−1 serious	0 (I^2 = 0%)	−1 intake is a proxy	0 large samples	+1 dose-response	Very low
Plasma nicotinamide in glaucoma vs controls	2 case-control cohorts	0	0 (I^2 = 0%)	0	−1 (n = 99)	+1 replication	Low
Dietary niacin intake in glaucoma vs controls	2 cross-sectional studies	−1 serious	−2 (I^2 = 94%, opposite directions)	0	0 large samples	0	Very low

PhNR, photopic negative response.

4. Discussion

4.1. The replication test and what it changes

The most consequential finding of this review is not any single pooled estimate but a comparison that no individual trial could make. When the two independent crossover trials were placed side by side on identical outcome constructs, as Figure 4 shows, absolute photopic negative response amplitude replicated cleanly, whereas the b-wave-normalised ratio did not

and the two trials disagreed in direction. Because the b-wave arises from bipolar cells rather than from retinal ganglion cells, a proportional rise in both components is at least as consistent with a general improvement in retinal metabolic capacity as with selective ganglion cell rescue.

This reading is not hostile to the nicotinamide hypothesis. A systemic agent that raises tissue NAD would be expected to benefit any energetically stressed retinal neuron, and the preclinical work shows exactly that pattern of mitochondrial rescue across retinal cell populations.[3,4,6] It does, however, mean that selective retinal ganglion cell neuroprotection in humans is at present a hypothesis supported by animal models and by absolute amplitudes, and not a demonstrated effect. The practical consequence is a recommendation to trialists: the b-wave-normalised photopic negative response should be a pre-specified outcome in every future trial, because it is the only routinely available measure that distinguishes the two possibilities, and it is currently reported inconsistently. A second recommendation follows from the risk-of-bias assessment: crossover designs in this field should incorporate a washout period, since the agent under test raises a tissue metabolite whose normalisation is not instantaneous.

4.2. Deficiency is metabolic, not dietary — with a caveat

The second dissociation concerns vitamin B_3 status. Plasma nicotinamide was approximately 30% lower in glaucoma in two independent cohorts, while pooled dietary intake did not differ and the two available dietary comparisons pointed in opposite directions. Among the possible explanations, the most parsimonious is a defect of metabolic handling, utilisation or salvage rather than a shortfall of supply. That reading aligns with the systemic bioenergetic deficit measured in peripheral blood mononuclear cells[1] and with the salvage-pathway biology that motivates NAD repletion in the first place. Two recent metabolomic studies point the same way. Unsupervised clustering of plasma metabolites in a longitudinal open-angle glaucoma cohort resolved five distinct endotypes, of which the highest-risk one progressed fastest in the central visual field while carrying a low polygenic risk score — a metabolic rather than a genetic phenotype.[35] In the UK Biobank, elevated glycolytic metabolites, pyruvate among them, marked resilience in individuals in the top decile of glaucoma polygenic risk, with an odds ratio of 0.71 for the highest versus the lowest quartile of those metabolites.[36] Both findings favour a metabolic-handling account, and the second gives an independent reason to think the pyruvate component of the combination trial was not inert.

It should be offered as the most parsimonious explanation rather than as the explanation. The plasma evidence comes from two small cohorts recruited at a single centre, and is compared against population surveys measuring an entirely different quantity by an entirely different method in different countries. Reverse causation cannot be excluded: glaucoma itself, its topical or systemic treatment, or the metabolic characteristics of people who develop it could plausibly lower circulating nicotinamide without any primary defect in handling. What can be said with more confidence is the negative half of the claim — that people with glaucoma have not been shown to eat less niacin — because that rests on two large national surveys pooling to a null.

Either way, the dose argument stands independently. The trials used 1 to 3 g daily, some fifty to one hundred and fifty times the difference between the highest and lowest dietary quartiles. Dietary intake and pharmacological repletion are different interventions, no trial has tested dietary modification, and the observational literature should not be read as though it supported dietary advice.

4.3. Case definition and the fragility of the observational signal

A finding that deserves more attention than it has received in this literature emerged within a single dataset. The United States survey analysis reported that higher niacin intake was associated with lower odds of glaucoma when the outcome was defined by fundus imaging, but found no significant association in the same participants when the outcome was defined by the international epidemiological criteria. A second analysis of the same survey cycles using regraded disc images found a significant association per milligram. The exposure, the sample and the analytic approach were essentially constant across these comparisons; only the case definition changed, and the conclusion changed with it.

This matters for how the observational strand should be read. A signal that survives one definition of glaucoma and not another within the same participants is not necessarily spurious — case definitions differ in sensitivity, and a stricter definition with fewer cases has less power — but it does indicate that the association is not robust to reasonable analytic choices. It also cautions against reading the pooled extreme-contrast estimate of 0.44 as a stable quantity. The one design feature that argues against pure artefact is that the two incident-disease cohorts produced a stronger association than the two prevalent-disease surveys, which is the opposite of what cross-sectional reverse causation would predict.

4.4. The electronic-record cohort: how a hazard ratio of 0.34 could arise

The electronic-record cohort contributes a hazard ratio larger than any signal randomisation has produced in this field, and its removal halves the harmonised descriptive average. A protective effect that exceeds what trials can demonstrate — compare the hazard ratio in Figure 5 with the randomised estimate in Figure 3 — is a warning rather than a triumph, and it is worth reasoning through the specific mechanisms rather than invoking healthy-user bias as a general label.

Individuals with a documented supplement exposure in an electronic record are individuals who attend, who are asked, and whose answers are coded. If supplement users attended more frequently than non-users, they would be expected to receive a glaucoma diagnosis sooner rather than later, which pushes against the observed direction and cannot explain the finding. The more plausible mechanisms run the other way. First, the comparison group is defined by the absence of any coded nicotinamide or niacin exposure, which includes patients whose care is fragmented across systems; such patients are also those most likely to have a glaucoma diagnosis recorded elsewhere and then captured on re-presentation, inflating apparent incidence in the unexposed group. Second, patients who take supplements on a physician's advice for ocular hypertension are, by definition, under active ophthalmic management with more attentive pressure control, and pressure control is the one intervention of proven efficacy; the estimate may therefore partly measure quality of conventional care. Third, exposure was inferred without dose, adherence or duration, so any true effect is averaged over an unknown mixture of actual exposures, which normally biases towards the null and makes the observed magnitude harder still to explain. A commentary published alongside that report raised comparable reservations; the present analysis quantifies their consequence by showing that the pooled magnitude, though not the direction, depends on that single study.

4.5. Comparison with previous syntheses

Two prior syntheses exist and the present results are consistent with both while going beyond them. The 2024 meta-analysis pooled five cross-sectional and case-control studies of dietary niacin and concluded that intake was lower in glaucoma.[12] The present review reproduces the direction of that association in the risk analyses but reaches a different conclusion about intake itself: with the addition of a Korean survey reporting higher niacin intake among older adults with glaucoma,[32] the pooled dietary status comparison became null with extreme heterogeneity. The earlier conclusion appears to have been driven by the composition of the available evidence at the time rather than by a robust effect, and it illustrates why a status comparison and a risk comparison should not be conflated.

The 2026 systematic review identified the same three randomised trials and judged meta-analysis infeasible because of heterogeneity in design, intervention, follow-up and reporting.[13] The present analysis shows that pooling was feasible once each trial's primary retinal-function endpoint was expressed on a standardised scale, and no heterogeneity was detectable. That review also restricted itself to visual field mean deviation and concluded that no benefit had been shown for that outcome; the present review agrees entirely, and Section 3.7 sets out the three null results in detail. A source-discrepancy check found that the earlier review transposed two electroretinographic values from one trial and quoted between-arm rather than within-arm p values from another; primary sources were used throughout here, and the discrepancy is recorded rather than silently resolved.

4.6. Heterogeneity

Heterogeneity behaved in an interpretable way. Within the randomised strand none was detectable, and within the per-milligram observational pool it was exactly zero. The extreme-contrast pool carried modest, non-significant heterogeneity. The high value of 87% appeared only in the harmonised display, and the moderator analysis in Table 3 identified its source precisely: exposure contrast, which is a difference of units rather than of biology. A per-milligram increment and a top-versus-bottom quartile comparison describe the same underlying relationship at different doses, so their standardised equivalents necessarily differ in magnitude while agreeing in sign. This is why the harmonised quantity was defined as descriptive before it was computed rather than after it proved inconvenient. The one substantively troubling heterogeneity is the 94% between the two dietary status comparisons, which reflects genuine disagreement in direction between two national surveys using different cycles, age ranges and case definitions.

4.7. Mechanistic engagement and its limits

The Swedish two-week study offers the only direct evidence that the intervention engages its intended target in patients. Nicotinamide raised blood mitochondrial DNA content by approximately 12% in healthy controls and 17% in high-tension glaucoma, with no significant increase in normal-tension or pseudoexfoliative glaucoma, while the plasma metabolome showed the expected rise in nicotinamide and its methylated metabolites in every group. The subtype specificity is intriguing and unexplained. If mitochondrial biogenesis responds to NAD repletion only where the initial deficit or the driving stressor takes a particular form, then subtype could be a genuine effect modifier, and it is notable that the one randomised trial restricted to normal-tension glaucoma nevertheless produced the largest single effect size. With one small mechanistic study and one trial per subtype, this can be no more than a hypothesis, but it is a testable one and future trials should stratify by glaucoma subtype. The companion analysis from the same trial found no change in circulating extracellular nicotinamide phosphoribosyltransferase, though with an inter-assay coefficient of variation of 37.9% a true effect could have been missed.

A further caution comes from outside ophthalmology. In a randomised comparison of the three principal NAD precursors in 65 healthy adults, nicotinamide riboside and nicotinamide mononucleotide each raised circulating NAD over 14 days whereas nicotinamide itself did not, its effect on the whole-blood NAD metabolome being acute and transient rather than sustained.[37] If oral nicotinamide is a weaker systemic booster than its alternatives, the modest and subtype-restricted mitochondrial response seen here is close to

what one would predict, and the choice of precursor becomes a design decision for future glaucoma trials rather than a detail. It also sharpens the question the replication analysis raised: an agent that does not reliably raise systemic NAD may still raise retinal amplitudes, but the mechanism would then need explaining.

4.8. Limitations

First, the entire randomised evidence base comprises 152 randomised participants across three trials with follow-up of no more than 24 weeks, and every randomised endpoint except mean deviation is a surrogate, as the certainty assessment in Table 6 records. No trial has shown that nicotinamide preserves the visual field over a clinically meaningful horizon, and the pooled mean deviation result was null. Any claim of neuroprotection in the sense that matters to a patient — slower progression towards blindness — remains unproven.

Second, the number of poolable studies did not reach ten in any single pool. This ceiling appears structural rather than a failure of searching: the earlier meta-analysis, which searched four databases, identified exactly five eligible observational studies, and the later review, which searched four sources including trial registries, identified exactly three randomised trials.[12,13] The present search recovered those same studies and added three more, but the literature does not contain ten poolable studies on this question. Consequently the pre-specified small-study analyses are underpowered and publication bias cannot be assessed.

Third, two of the three randomised effect sizes rest on quantities derived rather than reported: a standard deviation recovered from within-arm confidence intervals on a percentage-change scale, and a mean and standard deviation derived from medians and interquartile ranges of a skewed count outcome. Both derivations are standard, both are documented in Section 2.3, and a convergent check supports the first, but the resulting pooled estimate is more fragile than its confidence interval implies. Related to this, one trial contributed an eye-level analysis set that was treated as independent, which will have understated its standard error to an unquantifiable degree.

Fourth, the observational strand cannot support a causal claim. Dietary niacin travels with overall diet quality and specifically with meat, fish and legume intake, and a single 24-hour recall misclassifies habitual intake badly. Several source populations overlap, and the handling of that overlap is a defensible choice rather than the only possible one. The magnitude of the pooled association is not robust, halving when one electronic-record cohort is removed, and it is sensitive to case definition within a single dataset as set out in Section 4.3.

Fifth, screening was performed by a single reviewer using a single database, with hand-checking of two existing reviews. This is a real methodological weakness relative to a dual-reviewer, multi-database standard, and it is labelled as such within Figure 1 rather than glossed. The review was also not prospectively registered.

Sixth, the nicotinamide-specific effect cannot be isolated in the United States phase 2 trial, which administered nicotinamide together with pyruvate. Two of the five interventional studies were single-arm and contributed no controlled estimate. One large, well-conducted cross-sectional study reporting no association between dietary niacin and retinal nerve fibre layer thickness across three cohorts and 4,937 healthy eyes[29] could not be pooled because its outcome construct differed; that null is worth stating plainly, because if habitual dietary variation had a meaningful effect on the anatomical layer that thins in glaucoma, a study of that size using optical coherence tomography would have been well placed to detect it, and it did not. Finally, the harmonised display targets no causal estimand and is offered only as a description of directional concordance; readers should take the strand estimates, reported in their native scales, as the results of this review.

4.9. Clinical and neurological implications

For the practising neurologist and neuro-ophthalmologist, four implications follow. The first is conceptual. Glaucoma is behaving like other axonopathies in which NAD depletion and programmed axon death drive degeneration,[5] and the same class of intervention is under investigation in optic nerve injury with nicotinamide riboside and sirtuin-dependent signalling,[38,39] in inherited murine glaucoma,[40] and now through locally delivered mitochondrial-targeted devices.[41] Evidence generated in glaucoma is therefore informative beyond the eye, and the traffic runs in both directions.

The second concerns why this disease is a useful model system. Of the central neurodegenerations, glaucoma is the only one in which the dying projection neuron can be counted structurally and interrogated functionally in a living patient at the bedside, non-invasively, in minutes. A metabolic intervention can therefore be assessed for target engagement in weeks. That is why three randomised trials of a candidate neuroprotectant exist in glaucoma and essentially none of comparable design exist for the equivalent question in cerebral white matter, and it is the strongest reason for a neurological readership to follow this literature.

The third is practical and cautionary. No professional body recommends nicotinamide outside research settings, and nothing in this analysis argues for changing that. Gram quantities are not innocuous, as Table 5 and Section 3.15 set out. Patients who ask about over-the-counter nicotinamide should be told that the randomised evidence supports an electrophysiological signal of very low certainty, that the visual field evidence is null, that dietary niacin and gram-level supplementation are not the same intervention, and that supplementation must never displace pressure-lowering therapy, which every trial in this review continued unchanged alongside the study drug.

The fourth is about what would change the answer. The phase 3 trial of nicotinamide 3 g/day with calcium pyruvate 1 g/day against placebo, randomised 1:1 across two academic centres over 21 months with continued standard pressure-lowering care, completed recruitment in August 2025. Its primary outcome is a composite of functional change on central 10-degree automated perimetry and structural change on spectral-domain optical coherence tomography, with tolerability and safety among the secondary outcomes and serial blood sampling for metabolomic and proteomic analysis; the planned sample size was not stated in the published design paper.[16] That trial, and not any further synthesis of the present evidence, will determine whether metabolic neuroprotection has a place in glaucoma care.

5. Conclusion

This systematic review and meta-analysis brought together 15 independent human studies of vitamin B_3 and glaucomatous neurodegeneration, of which 11 contributed to pooled estimates. Across every randomised trial conducted to date, nicotinamide supplementation produced a moderate improvement in inner retinal function, with a pooled Hedges' g of 0.41 (95% CI 0.14 to 0.69) and no detectable heterogeneity, and the effect on absolute photopic negative response amplitude replicated across the two independent crossover trials. Higher vitamin B_3 exposure was associated with a pooled odds or hazard ratio for glaucoma of 0.44 (95% CI 0.33 to 0.59) across four non-overlapping populations, and each additional milligram per day of dietary niacin with an odds ratio of 0.94 (95% CI 0.92 to 0.97), an estimate that reproduced itself identically in three separate datasets. Plasma nicotinamide was measurably lower in primary open-angle glaucoma.

Four qualifications are equally firm. Selective retinal ganglion cell rescue was not demonstrated: the b-wave-normalised photopic negative response, the measure designed to isolate ganglion cell signal, failed to replicate between the two crossover trials. No trial has shown preservation of the visual field, the outcome that matters to patients, over follow-up of 24 weeks or less. The deficiency motivating the hypothesis is a plasma finding and not a dietary one, and the trial doses exceed dietary quartile differences fifty-fold or more, so the observational and interventional literatures describe different interventions and neither supports dietary advice. Every outcome was of low or very low certainty by GRADE, and the magnitude of the observational association halved when a single electronic-record cohort was removed.

The appropriate conclusion is therefore neither dismissal nor endorsement. Nicotinamide is the most promising metabolic neuroprotectant yet tested in glaucoma, and the consistency of its effect on inner retinal amplitude across three continents is encouraging. It is not, on present evidence, a treatment that can be recommended outside research settings, and the ongoing phase 3 trial with combined perimetric and structural endpoints over 21 months is the study that will settle the question. Until then, nicotinamide should be regarded as an investigational adjunct to pressure-lowering therapy rather than a substitute for it, and future trials should pre-specify the b-wave-normalised photopic negative response, incorporate a washout period in crossover designs, and stratify by glaucoma subtype.

6. Declarations

6.1. Ethics approval and consent to participate

Not required, as this review analysed previously published aggregate data and involved no new human participants or identifiable material.

6.2. Consent for publication

Not applicable; no identifiable individual patient data or images are presented.

6.3. Availability of data and materials

The extracted dataset, the analysis script and all figure outputs are available from the corresponding author on reasonable request.

6.4. Competing interests

The authors declare that they have no competing interests.

6.5. Funding

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6.6. Author contributions

IAPY conceived the review, designed the search and analysis, screened and extracted the data, performed the statistical synthesis and drafted the manuscript. IMAK contributed to study selection, data interpretation and critical revision of the manuscript. IGARS contributed to risk-of-bias assessment, data interpretation and critical revision. CIWP contributed to the interpretation of the clinical findings and critical revision for important intellectual content. All authors reviewed and approved the final version and agree to be accountable for all aspects of the work.

6.7. Use of generative artificial intelligence

All analytical and interpretive work was performed by the authors, who take full responsibility for the integrity and accuracy of the manuscript.

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