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Ocular imaging changes in astronauts and ground-based analogues: a systematic review and meta-analysis

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NPJM-style alternative of Draft v2.5 (20 October 2026), prepared for submission to npj Microgravity as an Article. Main content follows Draft v2.5: structured abstract; optic disc oedema presented as a secondary outcome with a case-definition table, a mixed-effects logistic sensitivity model and definition-based sensitivity analyses; ventricular-volume confidence interval recalculated (classic random-effects CI, two independent cohorts) with analogue ventricular data added; a deviations-from-protocol section and a supplementary exposure-characteristics table (duration, CO2, sex) added; Russian-language references updated with Crossref-verified DOIs. Citations are numbered and will be re-sequenced by order of appearance at submission; references 36-40 cite tools and guidelines named in the text (Wan et al., PRISMA 2020, ROBINS-I, RoB 2, GRADE). A further full-text verification on 23 October 2026 corrected the Russian-cohort optic-disc-oedema incidence (9/24 to 11/24), removed duplicate counting of the VaPER cohort reported in McGregor 2021 (the analogue disc-oedema stratum now comprises two unique cohorts), and added the countermeasure report of the 30-day head-down-tilt trial (Laurie 2025, same trial as He 2025).

ABSTRACT

Background. Spaceflight-associated neuro-ocular syndrome (SANS) affects a substantial proportion of astronauts on long-duration missions, and head-down tilt bed rest (HDTBR) is the principal ground-based analogue used to study and counter it; whether HDTBR faithfully reproduces the ocular phenotype of microgravity, however, remains uncertain.

Methods. We systematically searched MEDLINE/PubMed, Embase, Scopus and Web of Science from inception to October 2026, with no language restriction, together with the NASA Technical Reports Server and trial registries, and included longitudinal cohorts of astronauts and of healthy adults in HDTBR

or dry immersion with extractable quantitative ocular outcome data. Changes from baseline were pooled separately for spaceflight and analogue cohorts using random-effects models with REML estimation of τ^2 and Hartung-Knapp adjustment, and stratum-specific estimates were compared with a Wald-type test; a generalised linear mixed model was fitted as a sensitivity analysis for the binary outcome. The review was registered on PROSPERO (CRD420261540269).

Results. Across ten pooled ocular and intracranial-imaging outcomes (six with dual-stratum comparison), peripapillary retinal thickness (flight +29.0 μm vs analogue +32.3 μm; P = 0.74), retinal nerve fibre layer change (1.7 vs 6.8 μm; P = 0.30) and intraocular pressure (-0.23 vs -0.04 mmHg; P = 0.95) showed no statistically significant between-stratum difference; a formal equivalence test (two one-sided tests) did not establish equivalence for retinal thickness (P = 0.272). The between-stratum comparison for optic disc oedema incidence (43.5% vs 49.9%; P = 0.86) was underpowered (stratum 95% CIs 1.5% to 93.7% and 27.0% to 72.9%) and is reported as exploratory. One outcome diverged: choroidal thickness increased after spaceflight (pooled +26.6 μm [95% CI 10.9, 42.3]) but decreased during 60 days of strict HDTBR (-13.6 μm [-25.5, -1.7]; between-stratum difference +40.2 μm, P < 0.001). This contrast - the review's central novel signal - rests on an analogue estimate from a single cohort (n = 8) without formal certainty rating and is therefore hypothesis-generating rather than confirmatory, but it identifies choroidal thickness as the lead candidate discriminator of analogue fidelity). Optic nerve sheath length (+0.69 mm) and ventricular volume (+10.3% [95% CI 7.8, 12.8]) increased after flight.

Conclusions. This review was designed to detect divergence between actual spaceflight and its terrestrial analogue. Across the fluid-stasis markers of SANS - disc oedema (exploratory comparison), peripapillary retinal thickening and axial shortening - no divergence was detected, although with two to four studies per outcome this cannot establish analogue fidelity. The one outcome whose direction diverged was choroidal thickness (increased after spaceflight, decreased during bed rest; analogue estimate from a single cohort (n = 8) without formal certainty rating), a contrast that is hypothesis-generating rather than confirmatory. We hypothesise, post hoc, that loss of the hydrostatic gradient in microgravity causes passive choroidal

venous congestion that headward fluid shift alone cannot replicate, and propose that choroidal thickness, measurable by routine optical coherence tomography, is the lead candidate discriminator of analogue fidelity - hypothesis-generating rather than confirmatory, pending confirmation in larger analogue cohorts.

INTRODUCTION

Spaceflight-associated neuro-ocular syndrome (SANS) is a spectrum of ocular structural changes - optic disc oedema, peripapillary retinal nerve fibre layer and total retinal thickening, choroidal engorgement and folds, globe flattening, axial shortening and hyperopic shift - documented in astronauts during and after long-duration missions to the International Space Station (ISS). Since the initial case series of seven astronauts[1], SANS has been ranked among the leading health risks for planned deep-space exploration because some structural changes persist for years after return[6]. The risk is now an engineering constraint as much as a clinical one: crewed missions to the Moon and Mars will last months to years, with no early-return or evacuation option, so an ocular condition that compromises visual function in flight - or reveals an unmitigated cephalad fluid problem - could constrain mission duration, crew selection and even mission architecture.

Because access to spaceflight is limited, ground-based analogues - principally head-down tilt bed rest (HDTBR), with or without mild hypercapnia, and dry immersion - are the workhorse of SANS countermeasure research[2,3]. The strict 6° HDTBR model with elevated ambient CO_2 (AGBRESA) reproduces optic disc oedema within weeks[9], and genetic and morphological modifiers identified in analogue cohorts are being translated back to astronaut selection[11,12]. Whether these analogues reproduce the full SANS phenotype, however, remains an open question, and the answer matters beyond ophthalmology. Every countermeasure intended for flight is developed, dosed and certified in these ground analogues; an analogue that reproduces the wrong components of the syndrome will certify countermeasures that may fail where they matter, during actual missions. Establishing which ocular outcomes the analogue reproduces faithfully - and which it does not - is therefore a prerequisite for reliable pre-flight countermeasure validation. The stakes are practical as well as scientific: every

countermeasure carried on a Mars-class mission adds mass, volume and crew time to an unforgiving manifest, and an analogue that misjudges ocular risk misdirects all three. A validated set of analogue-faithful biomarkers would let programme engineers retire ocular risk with ground data alone, reserving scarce flight opportunities for the minority of questions that genuinely require microgravity.

Several published systematic reviews have synthesised SANS imaging outcomes[3,4], but none separated actual spaceflight from its analogues, none formally tested for divergence between the two exposures, and none incorporated the strict-HDTBR-plus-hypercapnia experiments, the one-carbon-metabolism genetic modifier data, or the post-2023 astronaut cohorts. A registered review with an overlapping scope (PROSPERO CRD420261392529, first published 17 May 2026) also compares astronaut and bed-rest imaging, but addresses imaging-parameter magnitudes only, without a formally analysed categorical outcome in parallel, a biomarker-discrimination framework, or a mechanistic interpretation. Its published record (verified 20 October 2026) indicates an English-only search of published studies ending May 2026, a modified Newcastle-Ottawa risk-of-bias tool and a DerSimonian-Laird primary estimator; its screening had not yet begun at the time of writing.

With the objective of determining which ocular imaging changes are faithfully reproduced by terrestrial analogues and which are specific to actual microgravity, we used a meta-analytic approach to combine systematically identified data, stratifying all estimates a priori by exposure (actual spaceflight versus HDTBR or dry-immersion analogue) and comparing every stratum pair with a formal Wald-type test. We hypothesised a priori, based on the physiology of the choroidal circulation, that choroidal thickness would show the largest spaceflight-specific effect. In the rest of the manuscript, "spaceflight" refers to astronaut cohorts and "analogue" to HDTBR and dry-immersion cohorts.

RESULTS

Article identification. The systematic search of MEDLINE (via PubMed), Embase, Scopus, Web of Science, the NASA Technical Reports Server, trial registers, and reference-list and citation chasing identified 2,750 candidate records (Table 1; Fig. 1). After removal of 1,330 duplicates (778 by DOI, 507

by normalised title, 55 by manual adjudication), 1,420 records were screened by title and abstract and 1,334 were excluded. Eighty-six full texts were sought; 16 could not be retrieved (2 without institutional access, 14 unanswered author requests). Seventy reports underwent full-text eligibility assessment (two reports initially excluded for file corruption were re-obtained during extraction and included); none was excluded at this stage.

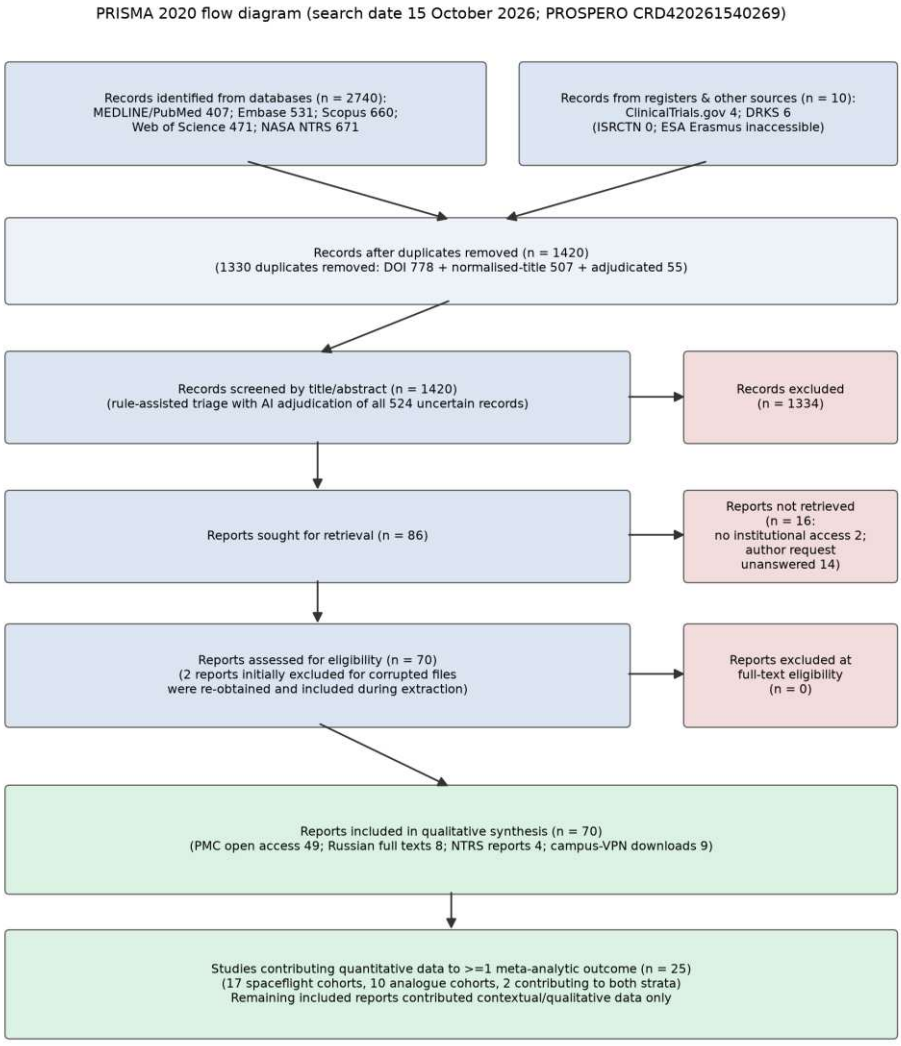


Figure 1. PRISMA 2020 flow diagram (search dates 15-16 October 2026; PROSPERO CRD420261540269).

Included studies. Seventy reports were included in the qualitative synthesis, of which 25 studies (17 spaceflight cohorts and 10 analogue cohorts, two studies contributing to both strata) contributed quantitative data to at least one meta-analytic outcome, comprising 240 astronaut/cosmonaut person-records across 17 spaceflight study cohorts and 171 analogue person-records across 11 analogue cohorts (Table 2; record-level accounting in supplementary table S1).

Peripapillary retinal thickness. Across five studies, the pooled change in peripapillary total retinal thickness (TRT, 250-µm circle) was +29.0 µm [95% CI 10.2, 47.8] after spaceflight (2 cohorts) and +32.3 µm [27.7, 36.8; 95% prediction interval 2.9, 61.6] after analogue exposure (3 cohorts); the between-stratum difference was -3.3 µm (P = 0.74; Fig. 3). A study reporting the astronaut-versus-bed-rest contrast directly (flight minus HDTBR difference 37.0 µm, 95% CI 13 to 61)[14] runs opposite to our stratum difference (-3.3 µm); we therefore do not cite it as corroborating equivalence, as the discrepancy most likely reflects cohort composition and measurement differences. Sensitivity analyses counting the full VaPER cohort, or including artificial-gravity and exercise countermeasure arms, did not materially change the analogue estimate (32.6 µm; between-stratum P = 0.72).

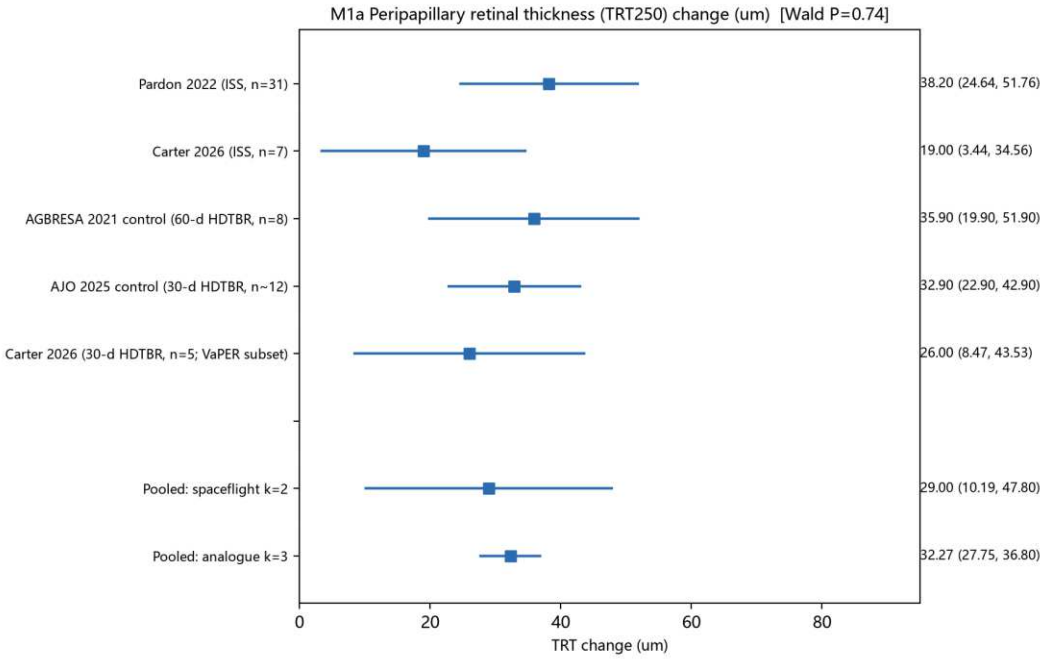


Figure 3. Forest plot of peripapillary total retinal thickness change (µm), spaceflight versus analogue cohorts.

Genetic modifiers of retinal thickening. Within the 60-day strict-HDTBR AGBRESA cohort, carriers of 3-4 one-carbon-metabolism risk alleles showed greater peripapillary retinal thickening than carriers of 0-2 alleles (45 µm [95% CI 31, 59], vs 28 µm [18, 38]; between-group difference 17.0 µm, P = 0.053; Fig. 4), consistent with the genetic modifier reported in the 30-day HDTBR-plus-hypercapnia cohort.

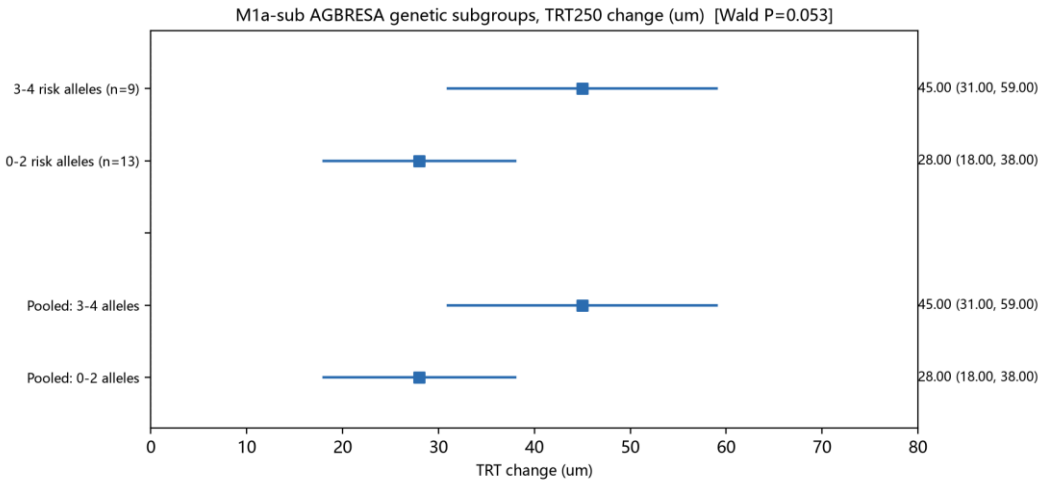


Figure 4. Retinal thickness change by one-carbon-metabolism risk-allele count (60-day strict HDTBR).

Optic disc oedema (exploratory analysis). The pooled incidence of optic disc oedema was 43.5% [95% CI 1.5, 93.7] in spaceflight cohorts (3 studies: 30 persons, of whom one 12-person cohort contributed 24 eyes at eye level) and 49.9% [27.0, 72.9] in analogue cohorts (2 unique cohorts; a third report of the VaPER cohort contributed no additional participants) (Fig. 5); the between-stratum difference was -6.4 percentage points (Wald z test, P = 0.86). The very wide flight-stratum interval reflects the small number of contributing studies, the Freeman-Tukey back-transformation and moderate between-study heterogeneity in that stratum (τ^2 approximately 0.15, I^2 approximately 60%); back-transformed prediction intervals were non-monotonic at k = 3 and are therefore not reported. Case definitions differed across cohorts (supplementary table S3a). A generalised linear mixed model with a study-level random intercept gave a compatible estimate (stratum odds ratio 1.33, 95% CI 0.42, 4.23; P = 0.63; between-study variance approximately zero). Definition-based sensitivity analyses yielded flight-stratum incidences of 42.9%

(excluding the eye-level cohort), 52.8% (excluding the composite-endpoint cohort) and 52.8% (strict definitions at both ends, versus 45.8% in the analogue stratum), with between-stratum P values of 0.90, 0.93 and 0.85; no case definition altered the conclusion of no statistically significant between-stratum difference in oedema incidence.

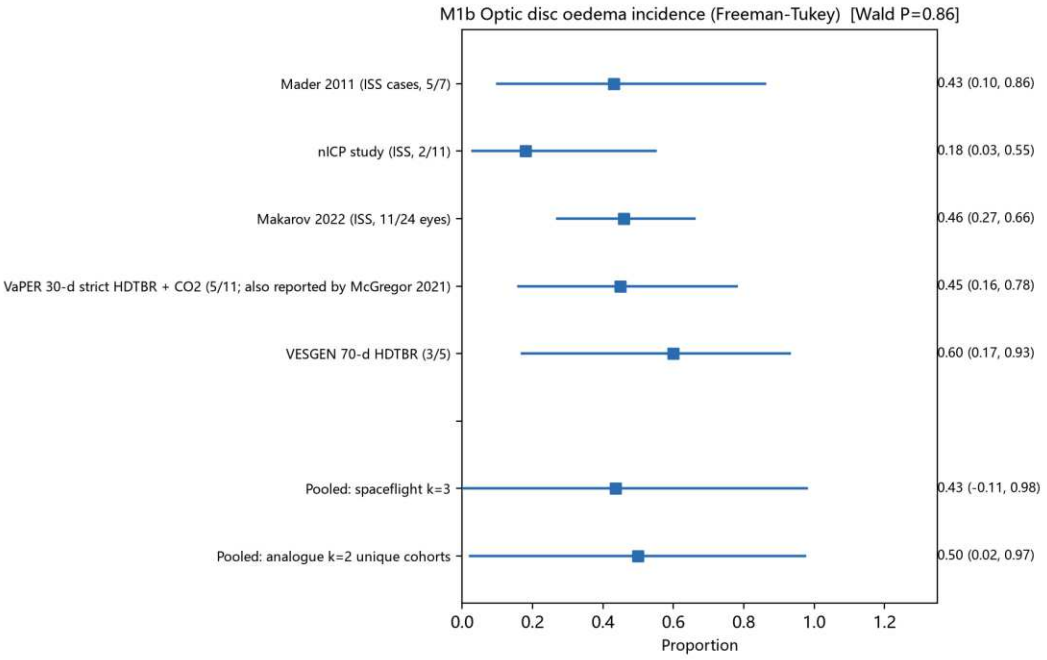


Figure 5. Forest plot of optic disc oedema incidence (Freeman-Tukey pooled proportions).

Intraocular pressure. Pooled IOP change was -0.23 mmHg [95% CI -3.27, 2.80] after spaceflight (2 cohorts) and -0.04 mmHg [-5.24, 5.16] in analogue cohorts (2 cohorts; between-stratum P = 0.95; Fig. 6). Individual studies ranged from an IOP rise of +1.3 mmHg during ISS missions to falls of up to -2.7 mmHg in 30-day HDTBR control arms; the pooled estimates centred on zero in both strata.

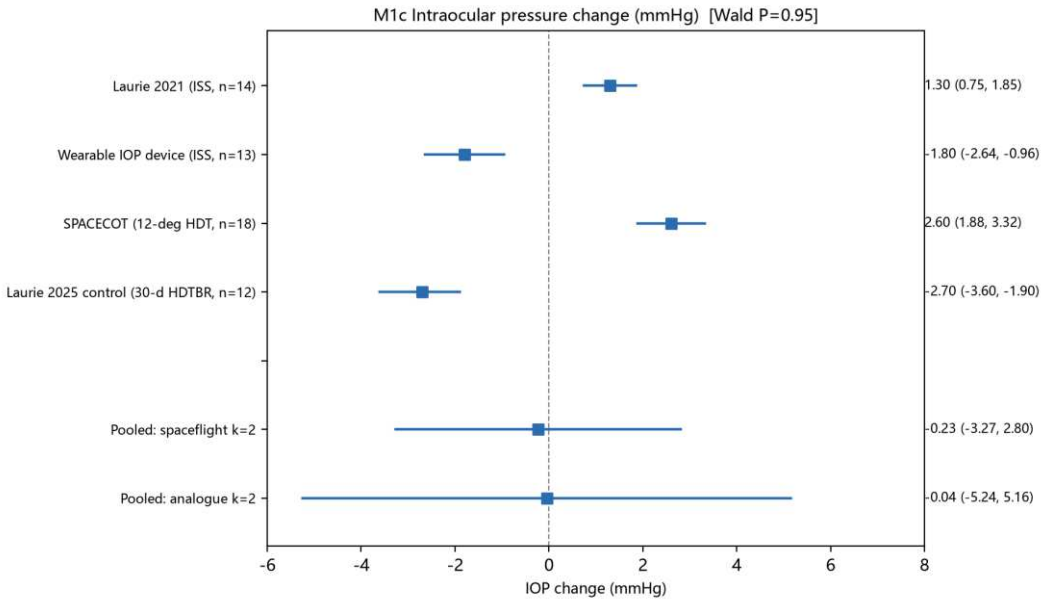


Figure 6. Forest plot of intraocular pressure change (mmHg).

Choroidal thickness. Choroidal thickness increased after spaceflight in all four cohorts: the pooled change was +26.6 μm [95% CI 10.9, 42.3; 95% prediction interval -46.4, 99.6]. In contrast, the single strict-HDTBR cohort reporting choroidal change showed thinning of -13.6 μm [-25.5, -1.7] during 60 days of bed rest. The between-stratum difference of +40.2 μm was highly significant [20.6, 59.8; $P < 0.001$; Fig. 7]. Because the analogue stratum contains one study, this finding is a formal between-stratum comparison rather than a pooled analogue estimate, and it is the principal divergence identified in this review. An independent acute-exposure experiment is consistent with the proposed mechanism: after only 24 h of head-down tilt, subfoveal choroidal thickness had already risen by 9 μm ($P = 0.02$), supporting rapid venous congestion rather than slow structural remodelling.

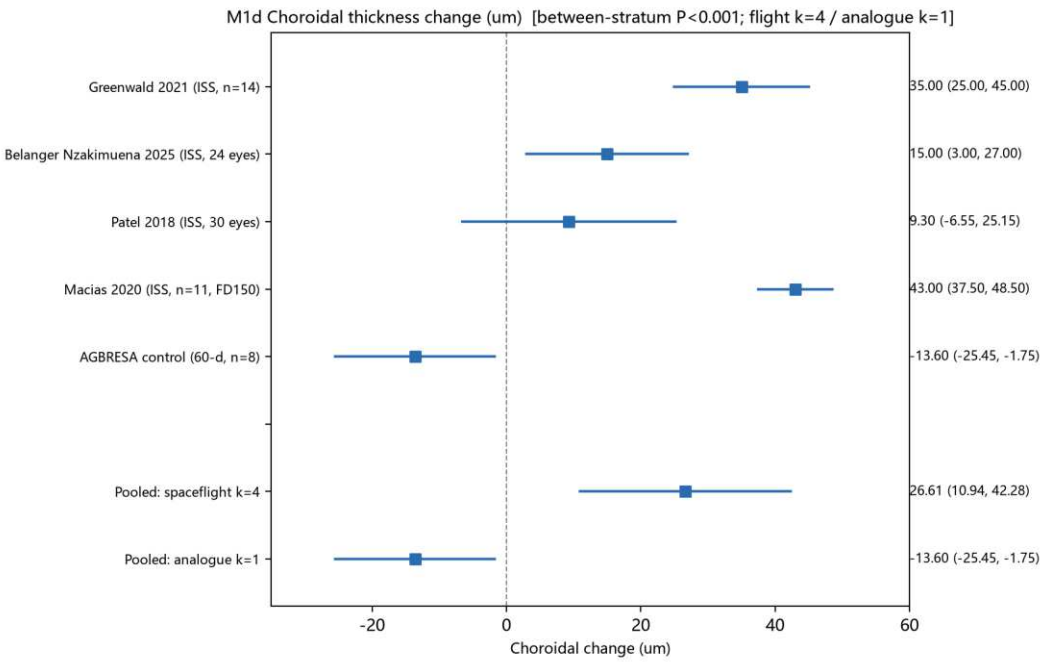


Figure 7. Forest plot of choroidal thickness change (μm). Note the opposite direction of the two strata.

Retinal nerve fibre layer. Pooled RNFL change was +1.7 μm [95% CI -1.1, 4.5] after spaceflight (2 cohorts) and +6.8 μm [-2.5, 16.1; 95% prediction interval -37.1, 50.8] in analogue cohorts (4 cohorts; between-stratum P = 0.30; Fig. 8). The analogue estimate was driven by the AGBRESA 3-4-risk-allele subgroup (+22 μm); the 0-2-allele subgroup showed changes comparable to flight cohorts, indicating that genetic susceptibility, rather than the analogue itself, accounts for most of the apparent excess.

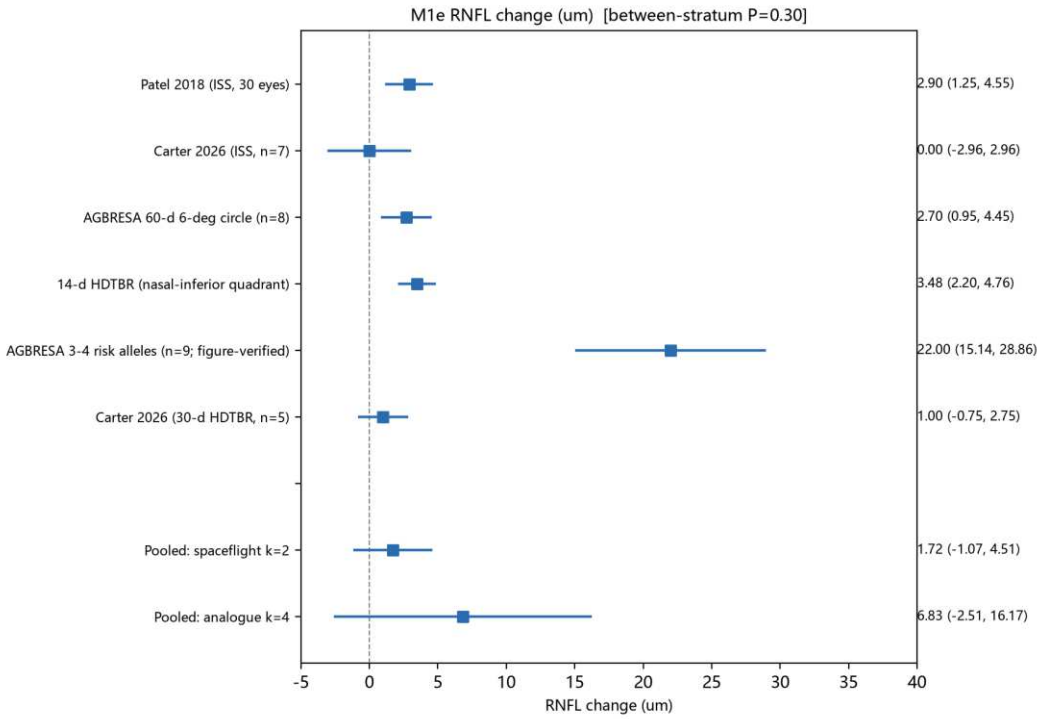


Figure 8. Forest plot of retinal nerve fibre layer thickness change (μm).

Axial length and refractive shift. Axial length shortened in both strata: -0.081 mm [95% CI -0.085, -0.077] after spaceflight (4 cohorts) versus -0.040 mm [-0.042, -0.038] in analogue cohorts (2 cohorts). The between-stratum difference did not remain significant after correction for the small analogue sample (one estimate rested on n = 3; t-adjusted P = 0.29), so we report it as exploratory (Fig. 9). The pooled proportion of astronauts with a hyperopic refractive shift was 47.9% (2 studies; wide interval owing to k = 2). The VESGEN flight cohort contributed person-level axial-length data (n = 8).

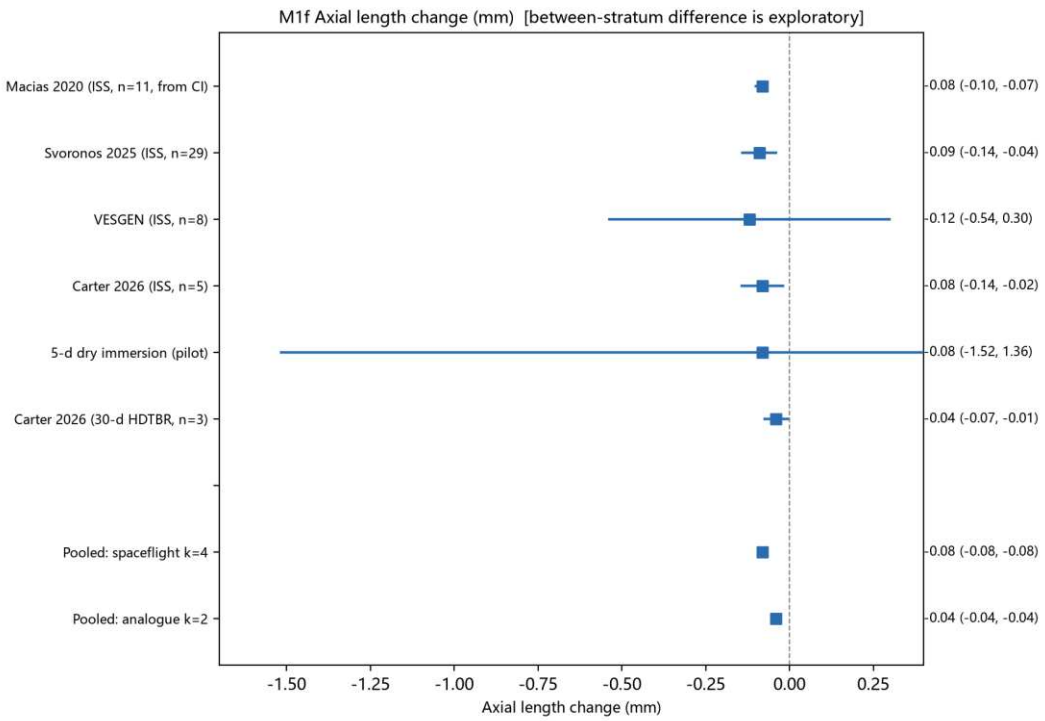


Figure 9. Forest plot of axial length change (mm); between-stratum difference is exploratory.

Optic nerve sheath and intracranial imaging. Two MRI-based estimates from one 22-astronaut cohort showed elongation of the optic nerve sheath complex after flight (0.80 mm and 0.63 mm; pooled +0.69 mm [95% CI 0.53, 0.85]; Fig. 10), consistent with posterior globe displacement rather than optic nerve stretching per se; the 0.63 mm estimate in particular reflects anterior displacement of the optic nerve head rather than sheath lengthening per se, and was retained as a complementary descriptor of globe translation.

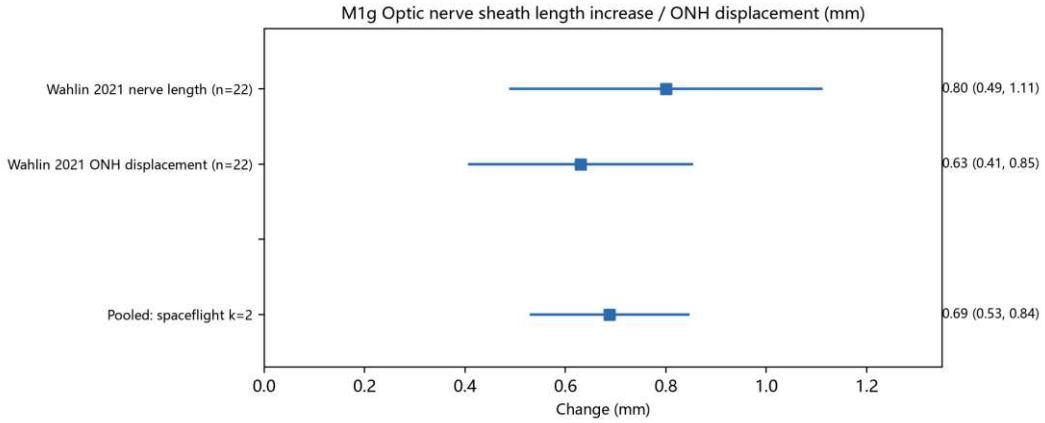


Figure 10. Forest plot of optic nerve sheath length increase and optic nerve head displacement (mm) after spaceflight.

Ventricular volume increased by a pooled 10.3% of baseline (classic random-effects 95% CI 7.8, 12.8; 2 cohorts, n = 26; Fig. 11). The two contributing cohorts are independent - a Russian cosmonaut cohort and a NASA astronaut cohort imaged at different centres - so no individual contributed to both. In analogue cohorts, lateral ventricular volume increased by 6.0% during 60 days of strict HDTBR (AGBRESA control arm, n = 8) and by approximately 12.5% during 30 days of strict HDTBR (VaPER subset, n = 5), and aqueductal CSF flow velocity rose by 15% in the former; these analogue estimates are descriptive and were not pooled. CSF production rate rose from 278 to 335 µL/min in a single 14-astronaut study (+57 µL/min); this change did not reach significance for the group as a whole in the source study (P = 0.15), with a significant increase confined to the globe-flattening subgroup (+70%, P = 0.01); we therefore report it descriptively only. Figure 2 summarises all pooled estimates by stratum.

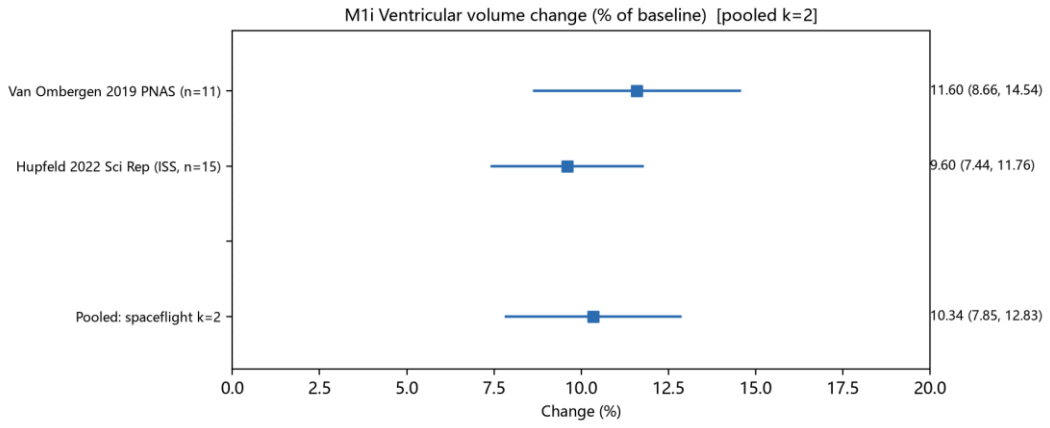


Figure 11. Forest plot of ventricular volume change (% of baseline) after spaceflight.

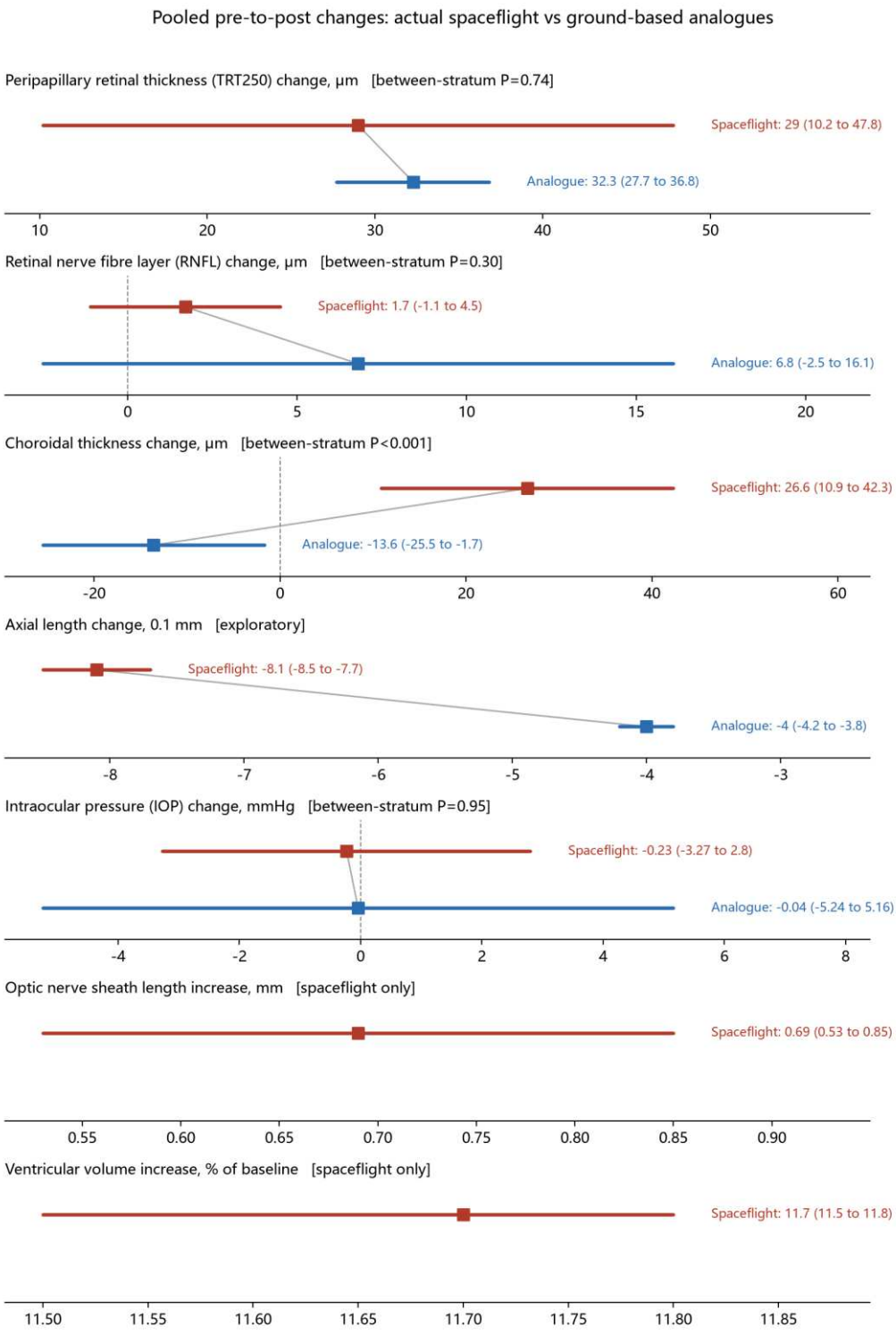


Figure 2. Summary of pooled pre-to-post changes for all outcomes, spaceflight (red) versus analogue (blue) cohorts. Outcomes measured in a single stratum (ventricular volume, optic nerve sheath length, CSF production rate and hyperopic shift) do not enter

the between-stratum direction comparison. Choroidal thickness is the only dual-stratum outcome whose direction differs between strata.

Robustness analyses. Primary conclusions were insensitive to (i) the within-person pre-post correlation (0.5-0.9); (ii) inclusion of countermeasure arms (analogue TRT 32.6 μm; between-stratum P = 0.72); (iii) alternative attribution of the overlapping VaPER cohort (between-stratum P = 0.49-0.74); and (iv) exclusion of the single potentially overlapping astronaut axial-length cohort (direction unchanged). For optic disc oedema incidence, the definition-based sensitivity analyses and the generalised linear mixed model gave conclusions identical to the primary analysis. Choroidal divergence ($P < 0.001$) and the absence of a statistically significant retinal-thickness between-stratum difference (P = 0.74-0.95) were stable across all specifications. Because absence of significance is not evidence of equivalence, we tested the two contrasts that anchor the main interpretation with two one-sided tests (TOST): retinal thickness (margin +/-10 μm) did not establish equivalence (P = 0.272), nor did nerve fibre layer thickness (margin +/-5 μm; P = 0.508), consistent with the limited power of strata of two to four studies; the absence of a statistically significant between-stratum difference therefore cannot be read as proof that the analogue reproduces the flight phenotype. Leave-one-out analyses showed that no single study drove any pooled estimate (supplementary table S3b; e.g., choroidal flight-stratum estimates ranged 20.6-31.7 μm across omissions, and flight optic disc oedema incidence ranged 34.7-52.8%). Restricting the choroidal analysis to the two person-level cohorts increased the flight-stratum estimate (40.1 μm [95% CI 32.7, 47.5]) without altering the direction or significance of the divergence; the same restriction left the flight nerve-fibre-layer stratum with a single study and was not poolable.

Table 3. ROBINS-I summary by domain and overall judgement (S = some concerns, H = high risk, L = low risk)

Risk of bias. ROBINS-I assessments (two independent assessors, with consensus on all overall judgements) are summarised in Table 3. Most astronaut cohorts are small prospective before-after cohorts without a contemporaneous unexposed control; for these, confounding and selection domains were generally rated some concerns (baseline comparability is inherent to the within-person design, but mission selection and survival effects cannot be excluded). Two studies attracted specific concerns, both upheld

after independent second assessment: Mader 2011 (retrospective case accrual plus a self-report survey denominator; high risk of selection bias) and Kramer 2015 (retrospective MRI analysis restricted to the 14 astronauts with complete datasets; complete-case reporting). The second reviewer additionally noted that Carter 2026 does not state whether data from the two missions of each repeat flyer are independent (addressed in our sensitivity analyses) and that Patel 2018 does not describe any handling of inter-eye correlation (see Limitations). The controlled SPACECOT crossover experiment (Strangman 2017) was the only study rated low risk across domains. Newcastle-Ottawa cross-checks were directionally concordant with these ratings.

Randomised countermeasure arms within analogue studies (AGBRESA artificial-gravity vs control in Laurie 2021; the countermeasure and seated-posture arms of the 30-day strict-HDTBR trial reported by He 2025 and Laurie 2025) were assessed with RoB 2 and rated low-to-some-concerns (randomisation adequate; deviations from intended interventions possible for countermeasure adherence). These arms were excluded from primary analyses, so their ratings do not affect the main estimates.

Table 4. GRADE Summary of Findings for the primary and key secondary outcomes

Certainty of evidence. GRADE certainty for the primary and key secondary outcomes is summarised in Table 4. Certainty was moderate for peripapillary retinal thickening (downgraded once for imprecision - small cohorts with a wide flight-stratum interval - and upgraded once for a large, directionally consistent effect across independent flight and analogue cohorts) and very low for optic disc oedema incidence (downgraded twice for inconsistency and indirectness arising from heterogeneous case definitions across eras, and once for the very wide confidence interval). The choroidal divergence, although highly significant, is not a GRADE-graded outcome because the analogue stratum rests on a single study; its certainty is therefore best regarded as hypothesis-generating.

Table 5. Summary of pooled estimates by outcome and exposure stratum

DISCUSSION

We systematically reviewed and quantitatively synthesised published literature on ocular imaging changes in astronauts and in the head-down tilt bed rest analogue of spaceflight. To our knowledge, this is the first meta-analysis to test formally whether the analogue reproduces the ocular phenotype of actual spaceflight: for every outcome that both exposure strata informed - peripapillary retinal thickness, retinal nerve fibre layer thickness, intraocular pressure, optic disc oedema incidence and (exploratorily) axial length - no statistically significant between-stratum difference in the magnitude or direction of change was detected. Against this background of no detected between-stratum difference, one outcome diverged: choroidal thickness increased after spaceflight (+26.6 μm across four cohorts) but decreased during 60 days of strict bed rest (-13.6 μm), a between-exposure difference of 40.2 μm ($P < 0.001$). This divergence is the review's central novel finding; because its analogue stratum is a single cohort, it requires confirmation in larger bed-rest campaigns before the analogue can be certified or disqualified for choroidal endpoints.

We propose that SANS comprises two mechanistically distinct components, and that HDTBR replicates only the first. The first is a fluid-stasis component: headward fluid shift raises episcleral and orbital venous pressure, increases CSF and orbital content volume, and produces optic disc oedema, peripapillary retinal thickening and axial shortening. No statistically significant between-stratum difference was detected for any of these signs, and the 43-50% disc-oedema incidence in both strata is consistent with this component being driven by posture and cephalad fluid shift rather than by microgravity per se; the analogue estimate partly derives from cohorts exposed to 0.5% ambient CO2 (VaPER and AGBRESA), and CO2 itself promotes optic disc oedema, so this comparison is effectively between a high-CO2 analogue and a flight stratum with largely unreported cabin CO2 (see below); certainty is very low, however, and the pooled incidences mix four case definitions, so these numerical values are descriptive only. This two-component model is post hoc and hypothesis-generating.

The second is a putatively microgravity-specific component, for which choroidal engorgement is the candidate ocular signature. On Earth, the choroid is suspended in a hydrostatic gradient: venous pressure in the dependent choroid exceeds that in non-dependent regions, and the uveal blood volume is partly

determined by the balance between arterial inflow and gravity-assisted venous drainage. In microgravity this gradient disappears; choroidal venous drainage loses its gravitational assist while cephalad shift raises central venous pressure, so the highly compliant choroidal venous plexus passively congests. Two observations support this mechanism. First, the effect is fast: 24 h of head-down tilt already thickened the choroid by 9 μm, but over weeks of sustained bed rest the choroid thinned (-13.6 μm) - consistent with acute congestion followed by diuretic/pressure adaptation that terrestrial recumbency permits and microgravity (with its absent hydrostatic reference) may not. Second, the effect scales with exposure across flight cohorts, from +9 to +43 μm. One possible reading, offered strictly as a post hoc hypothesis, is that the sign reversal reflects a genuine physiological difference rather than measurement artefact: bed rest abolishes the hydrostatic gradient only partially and transiently, whereas microgravity abolishes it completely and continuously. If this single analogue cohort is set aside, no directionally divergent outcome remains anywhere in this review, which underlines both the novelty and the fragility of the contrast. Statistically, this contrast is a two-sample comparison of two independent mean changes rather than meta-analytic evidence, and we present it as such.

Carbon dioxide exposure requires separate consideration because it differed systematically between the strata (supplementary table S3c). Hypercapnia is a choroidal vasodilator, so the 0.5% CO2 typical of strict-HDTBR campaigns would, if anything, be expected to thicken the choroid; the thinning observed in the analogue stratum (-13.6 μm) therefore cannot be attributed to CO2, and this exposure imbalance runs against, rather than towards, our central contrast. For spaceflight, cabin CO2 is not unmeasured in principle: the NASA Human Research Program SANS evidence report records nominal ISS concentrations of 2.3-5.3 mmHg (approximately 0.3-0.7%) with a 24-hour mean of 3.4 mmHg, and module-level monitoring in a recent case report measured 24-hour means of 2.6 mmHg falling to 1.3 mmHg[41,42]. These in-flight concentrations overlap the 0.5% analogue exposure, so CO2 cannot simply account for the choroidal divergence; because individual-level exposure was not measured in the contributing cohorts of either stratum, however, a residual CO2 contribution cannot be excluded.

A related argument applies to axial length. Spaceflight axial shortening (-0.081 mm) plausibly contains a gravitational-unloading component: on Earth, the weight of the orbital contents and the habitual postural load exert small but persistent mechanical forces on the globe; unloading in microgravity may allow elastic recoil and posterior displacement (consistent with the +0.69 mm optic nerve sheath elongation we pooled). Bed rest cannot unload the globe in the same way, and its axial shortening was half as large - an exploratory divergence (t-adjusted P = 0.29) that larger analogue cohorts should test. These hypotheses are post hoc interpretations of the pooled pattern; they are presented to generate, not confirm, mechanistic claims, and each yields falsifiable predictions: acute parabolic flight or first-day HDT should produce transient choroidal thickening (supported by the 24-h data); dry immersion, which unloads more completely than HDTBR, should reproduce more axial shortening (supported by the 5-day dry-immersion estimate of -0.08 mm[26]); and choroidal recovery after flight should track re-establishment of hydrostatic gradients.

Our estimates are compatible with the pooled magnitudes reported by earlier reviews that combined flight and analogue data[3,4], but those reviews could not, by design, detect the divergence we identify: pooling across exposures washes out the one outcome for which the exposures differ. The recently registered review of astronaut and bed-rest imaging (PROSPERO CRD420261392529) asks a similar divergence question across ocular and intracranial markers; our review complements it with a formally tested categorical outcome (disc oedema incidence), a formal genetic-modifier analysis, explicit cohort de-duplication, and a mechanistic interpretation anchored on the choroidal circulation. At the time of writing, that review's screening had not yet started (record verified 20 October 2026); our search additionally covers studies to October 2026, without language restriction and including grey literature.

If choroidal engorgement is microgravity-specific, then fidelity of the HDTBR analogue is outcome-dependent: the analogue is trustworthy for disc oedema and retinal thickening (the outcomes most bed-rest countermeasure trials use as endpoints) but not for choroidal outcomes. Countermeasures that correct headward fluid shift - lower-body negative pressure, artificial gravity, thigh cuffs - may therefore resolve

the fluid-stasis component while leaving choroidal congestion unaddressed; the analogue cannot distinguish these cases. We propose choroidal thickness, measurable with routine OCT, as a candidate discriminator of analogue fidelity and as a screening endpoint for future countermeasure trials; this proposal is hypothesis-generating and requires prospective validation. The genetic-subgroup findings additionally suggest that one-carbon-metabolism genotype could stratify analogue volunteers, concentrating disc-oedema events in informative subgroups.

Strengths of this review include the a priori stratified design, formal Wald-type comparison of every stratum pair, REML/Hartung-Knapp estimation with prediction intervals, systematic astronaut-study de-duplication, figure-extracted data verified against source images, and exhaustive sensitivity analyses.

Several limitations temper the findings. First, most flight cohorts are small (n = 7-31) and drawn from overlapping astronaut pools, so person-level independence cannot be guaranteed even after de-duplication. Second, the choroidal divergence rests on a single analogue cohort (k = 1); the stratum estimate is therefore a between-study comparison, vulnerable to cohort and device differences. Third, several flight estimates derive from median changes and from eyes rather than persons, introducing imprecision we could only partially model. Fourth, case definitions of optic disc oedema varied across eras (Frisen grading vs OCT-based), inflating heterogeneity and contributing to the very-low GRADE certainty for that outcome. Fifth, we could not access the ESA Erasmus Experiment Archive at the search date, so European grey literature may be under-represented. Sixth, we did not perform the time-course meta-regression and non-linear recovery modelling prespecified in the protocol, because too few studies reported multiple comparable post-exposure timepoints, and sex and CO2 exposure were incompletely reported across cohorts (supplementary table S3c). Seventh, ambient CO2 exposure differed systematically between strata - most strict-HDTBR analogue cohorts were exposed to 0.5% CO2 or mild hypercapnia, whereas flight cohorts almost universally did not report cabin CO2 (supplementary table S3c) - which is not merely a reporting gap but a substantive exposure imbalance that threatens the

interpretability of the flight-versus-analogue comparison and cannot be adjusted within our design. Finally, the mechanistic interpretation is hypothesis-generating and post hoc.

In summary, this review was designed to detect divergence between spaceflight and its terrestrial analogue. No divergence was detected across the fluid-stasis component of spaceflight-associated neuro-ocular syndrome - optic disc oedema (exploratory comparison), peripapillary retinal thickening and axial shortening - though with two to four studies per outcome the absence of a detected difference cannot establish analogue fidelity. The single outcome whose direction diverged was choroidal thickness, increased after spaceflight and decreased during 60 days of strict bed rest; because the analogue stratum comprised a single cohort, this contrast is hypothesis-generating. One post hoc interpretation is that only true microgravity abolishes the hydrostatic gradient governing choroidal venous drainage. If confirmed in larger prospective cohorts, choroidal thickness - measurable by routine optical coherence tomography - could become the lead candidate biomarker for discriminating analogue fidelity, and countermeasure strategies for deep-space missions should ultimately be tested against choroidal endpoints that terrestrial analogues currently cannot validate; until then, validation should continue to rely primarily on the fluid-stasis endpoints that both exposures reproduce. We further call for routine reporting of sex composition, ambient CO2 and the handling of inter-eye correlation in future cohort studies. Future strict-HDTBR studies with systematic choroidal imaging after bed rest, and choroidal monitoring in next-generation astronaut cohorts, should test whether the divergence we identify is confirmed and whether choroidal response can serve as a practical discriminator of analogue fidelity in countermeasure trials.

METHODS

This review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 statement[37] and was registered on PROSPERO (CRD420261540269) on 15 October 2026; deviations from the registered protocol are noted where they occur. Ethics approval was not required, as the review used published, de-identified data only.

Table 1. Databases and registers searched, with record counts (search date 15-16 October 2026)

Eligibility criteria. We included longitudinal cohort studies, case series with extractable quantitative pre/post data, and randomised countermeasure arms within analogue studies, in two populations: (1) astronauts or cosmonauts who completed spaceflights of any duration with ocular imaging data; and (2) healthy adults undergoing HDTBR (traditional or strict, with or without mild hypercapnia, with or without countermeasures) or dry immersion. Exposures were actual microgravity (ISS, Mir, or other missions) or the ground-based analogues. The comparator was the within-person pre-exposure baseline or a simultaneous healthy ground control. Eligible outcomes were quantitative ocular imaging measures - peripapillary total retinal thickness (TRT), retinal nerve fibre layer (RNFL) thickness, choroidal thickness, axial length, intraocular pressure (IOP), refractive shift, optic nerve sheath length - and intracranial imaging measures (ventricular volume, CSF production) where reported. We excluded animal and in-vitro studies, acute posture-change experiments of minutes-to-hours duration (unless reporting prespecified timepoints), and case reports of fewer than three exposed individuals without longitudinal quantitative data.

Information sources and search. We searched MEDLINE (via PubMed), Embase, Scopus and Web of Science from inception to 16 October 2026, without language restriction. The NASA Technical Reports Server, the ESA Erasmus Experiment Archive and trial registries (ClinicalTrials.gov, DRKS, ISRCTN) were searched for grey literature; reference lists of included studies and key reviews were checked, and forward citation searching ("snowballing") was performed. The full search strategies for each database are provided in the supplementary material. Where outcome data were missing or reported only graphically, we attempted to contact study authors; 14 author requests remained unanswered and the affected reports were not included in the review. Total records identified: 2,750 (2,740 from the sources above plus 10 from registers). Full line-by-line strategies for each database are provided in the supplementary material.

Study selection and data extraction. We screened records by title and abstract and then by full text in duplicate, supported by rule-assisted triage; we adjudicated all 524 records classified as uncertain by the triage rules, and resolved screening disagreements by consensus. Two reviewers extracted study design,

setting, participant characteristics (n, sex, genotype where reported), exposure (mission or bed-rest duration, tilt angle, CO_2 level, countermeasures) and all ocular outcome data at every reported timepoint onto a standardised form. We constructed an astronaut-study mapping table to identify cohort overlap across publications; for overlapping cohorts, the report with the most complete timepoint data was primary and others contributed unique data only. The mapping table, including the person-level counts underlying each pooled estimate, is provided in the supplement (table S1). Where data were reported only in figures, we extracted values from figures and verified them independently against the source image.

Risk of bias and certainty assessment. Per the registered protocol, two assessors independently evaluated non-randomised studies with ROBINS-I[38] (domains D1 confounding, D2 selection of participants, D3-D5 classification/intervention measurement, D6 missing outcome data, D7 measurement of the outcome, D8 selective reporting; we report D3-D5 as a combined block because exposure classification is inherent to these cohort designs) and randomised countermeasure arms within analogue studies with RoB 2[39], using the Newcastle-Ottawa Scale as a cross-check (scores in supplementary table S2); the NOS ratings were directionally concordant with the ROBINS-I judgements. In accordance with the protocol, a second assessor independently rated all studies; disagreements were resolved by discussion and consensus, and all overall judgements were agreed between the two assessors. For the co-primary outcome (peripapillary retinal thickness change; optic disc oedema incidence, registered as co-primary, is presented as a key secondary outcome), we graded certainty with GRADE[40], starting observational evidence at low certainty and rating down for risk of bias, inconsistency, indirectness or imprecision, and up for a large effect or consistency across independent cohorts.

Synthesis methods. We stratified all primary analyses a priori by exposure (actual spaceflight versus analogue). We pooled continuous outcomes as mean differences in random-effects models with restricted maximum likelihood (REML) estimation of τ^2 and Hartung-Knapp adjustment of standard errors. Categorical outcomes were pooled as proportions using the Freeman-Tukey double-arcsine transformation with the same REML τ^2 estimation and Hartung-Knapp adjustment; confidence intervals were computed

on the transformed scale with t critical values (k-1 degrees of freedom) and back-transformed. For each outcome, stratum-specific pooled estimates were compared with a Wald-type z test computed from the Hartung-Knapp-adjusted standard errors. For the binary disc-oedema outcome, a generalised linear mixed model with a study-level random intercept (logit link) was fitted as a sensitivity analysis. For the ventricular-volume outcome, the Hartung-Knapp variance estimate was smaller than the classic random-effects variance (heterogeneity statistic not exceeding its degrees of freedom, where the adjustment at one degree of freedom is anti-conservative and unstable), so the classic random-effects confidence interval is reported for that outcome. The same situation arose in the analogue disc-oedema stratum (two unique cohorts after overlap adjudication), for which the classic random-effects interval and standard error are likewise reported and used in the between-stratum test. For change-score variances derived from pre/post data we assumed a within-person pre-post correlation of 0.7, with 0.5 and 0.9 as sensitivity bounds. We excluded countermeasure arms (lower-body negative pressure, artificial gravity, exercise with thigh cuffs, upright control) from primary analyses and examined them in sensitivity analyses. We counted cohorts suspected of overlap (e.g., the VaPER 30-day strict-HDTBR cohort reported by two studies) once in primary analyses, testing alternative attributions. Because the analogue stratum of the choroidal outcome contained a single study, we report its stratum estimate as a between-stratum comparison rather than a meta-analytic synthesis. Standard errors for single-study strata were back-calculated from the published confidence intervals, so that for these strata the between-stratum test reduces to a comparison of two independent estimates. For the axial-length analogue stratum, which hinged on a single estimate from three participants, we additionally derived a t-distribution interval (critical value 4.303, two degrees of freedom); under this interval the between-stratum difference was no longer significant ($P = 0.29$), and the axial-length comparison is accordingly labelled exploratory. Repeating the remaining between-stratum tests with t critical values left every significance conclusion unchanged. The primary retinal-thickness analysis was entirely person-level; eye-level cohorts entered only the nerve-fibre-layer and choroidal outcomes. Where studies reported medians with interquartile ranges or ranges, we planned to convert them using the methods of Wan et al.[36]; in the event, no cohort required conversion of spread statistics,

because Patel 2018 published neither an interquartile range nor a range; its standard errors were derived from the published confidence intervals and its median changes entered as approximate means, so a Wan et al. sensitivity conversion was not possible. The only median-reported estimates (Patel 2018: retinal nerve fibre layer and choroidal thickness) were analysed with these derived standard errors; leave-one-out analyses showed that omitting this cohort did not change the direction or interpretation of either pooled estimate (supplementary table S3b). Prediction intervals are reported only where at least three studies contributed and, for pooled proportions, only where the back-transformed interval is monotonic. Some studies reported eyes rather than persons; we included these cohorts at eye level without modelling inter-eye correlation, and we tested the effect of restricting the choroidal and nerve-fibre-layer analyses to person-level data in sensitivity analyses. We did not perform the funnel-plot asymmetry testing and trim-and-fill prespecified for outcomes with at least ten studies, because no outcome reached that threshold. We also did not perform the time-course meta-regression and nonlinear recovery modelling prespecified in the protocol, because too few studies reported multiple comparable post-exposure timepoints.

Deviations from the registered protocol. The following deviations from the registered protocol are declared. (1) Analysis software was changed from R (metafor) to Python 3.12 (numpy/scipy) with identical REML and Hartung-Knapp estimators; recorded as Amendment 1a (19 October 2026). (2) Optic disc oedema incidence, registered as a co-primary outcome, is presented as a key secondary outcome because of heterogeneous case definitions; the reclassification was decided after completion of the pooled analysis and before submission; the corresponding amendment was submitted on 20 October 2026, concurrently with this manuscript (Amendment 2). (3) The prespecified time-course meta-regression, non-linear recovery modelling and exposure-duration or sex subgroup analyses were not performed because too few studies reported comparable multiple timepoints or individual-level characteristics; a descriptive exposure-characteristics table is given in supplementary table S3c. (4) Funnel-plot asymmetry testing and trim-and-fill were not performed because no outcome included ten or more studies. (5) The ESA Erasmus Experiment Archive was inaccessible at the search date; the German Aerospace Center (DLR) publication

registry and a full scan of the Russian journal Aerospace and Environmental Medicine were used as targeted substitutes. A supplementary update check of in-press and preprint records for October 2026 identified narrative reviews but no new eligible primary cohort studies. We additionally inspected the metadata of the roughly 401 unscreened ESA Erasmus records; in our assessment most describe European cardiovascular or neurological endpoints, in which ocular choroidal measures are rarely collected, so the single-cohort status of the analogue choroidal stratum is unlikely to change, although this cannot be verified without full-text screening. (6) In line with the registered IPD statement (updated 20 October 2026), requests for individual participant data were sent to the Institute of Biomedical Problems (Russian Academy of Sciences) and to NASA investigators on 19 October 2026; no study-level datasets had been received at the time of writing, and the present analysis is based entirely on published aggregate data.

DATA AVAILABILITY

All data analysed in this review are extracted from published sources listed in the reference list. The extraction dataset, analysis code and forest plots will be deposited in a public repository (OSF) upon acceptance and are available from the corresponding author on reasonable request.

CODE AVAILABILITY

Analysis code (Python 3.12, numpy/scipy) will be deposited together with the extraction dataset in a public repository (OSF) upon acceptance and is available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

Z.Z. (Zishu Zhao) conceived the review and performed screening, extraction, analysis and drafting. J.Z. (Junhui Zhao) contributed screening, full-text retrieval, data verification, and independent risk-of-bias and certainty assessment. Both authors approved this draft.

COMPETING INTERESTS

The authors declare no competing interests.

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Note: DOIs, volumes and page ranges were verified against Crossref, PubMed and Europe PMC on 18 October 2026; the DOIs of the two Russian-language sources were added from Crossref on 20 October 2026. References 36-40 cite tools and guidelines named in the text; references 41-42 cite the cabin-CO2 sources used in the Discussion; reference 31 is the analogue ventricular-volume source.

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TABLES

Table 1. Databases and registers searched, with record counts (search date 15-16 October 2026)

Source	Records identified	Notes
MEDLINE (via PubMed)	407	full strategy in supplement
Embase	531	full strategy in supplement
Scopus	660	full strategy in supplement
Web of Science Core Collection	471	full strategy in supplement
NASA Technical Reports Server	671	grey literature
ClinicalTrials.gov	4	registers
DRKS	6	registers
ISRCTN	0	registers
ESA Erasmus Experiment Archive	not retrievable	access blocked at search date (approx. 401 entries unscreenable) - noted as a

		limitation

Table 2. Characteristics of studies contributing to quantitative synthesis

Study (first author, year)	**Cohort**	**n**	**Exposure**	**Outcomes contributed**
Pardon 2022, JAMA Ophthalmol	ISS astronauts	31	long-duration flight	TRT
Carter 2026, JAMA Ophthalmol	ISS astronauts / VaPER HDTBR subset	7 flight; 5 HDTBR	repeat flight; 30-d strict HDTBR	TRT, RNFL, axial length
Mader 2011, Ophthalmology	ISS astronauts	7 (+44 survey)	long-duration flight	ODE, hyperopic shift, choroidal folds
Iwasaki 2021, J Physiol	ISS astronauts	11	long-duration flight	ODE (with choroidal folds)
Makarov 2022, Hum Physiol (RU)	ISS cosmonauts	12 (24 eyes)	long-duration flight	ODE
Greenwald 2021, J Appl Physiol	ISS astronauts	14	long-duration flight	IOP, choroidal thickness
Belanger Nzakimuena 2025, IOVS	ISS astronauts	12 (24 eyes)	long-duration flight	choroidal thickness
Patel 2018, JAMA Ophthalmol	ISS astronauts	30 eyes	long-duration flight	RNFL, choroidal thickness
Macias 2020, JAMA Ophthalmol	ISS astronauts	11	long-duration flight	axial length, choroidal thickness
Svoronos 2025, Am J Ophthalmol	ISS astronauts	29	long-duration flight	axial length, refraction
Vyas 2020, IOVS (VESGEN)	ISS astronauts	8	long-duration flight	axial length
Taibbi 2021, NPJ Microgravity (ISS arm)	ISS astronauts	8	long-duration flight	ODE (vascular grading), axial length
Solano 2025, IEEE Open J Eng Med Biol	ISS astronauts	13 (26 eyes)	long-duration flight	IOP (wearable sensor), ocular biomechanics
Van Ombergen 2019, PNAS	ISS astronauts	11	long-duration flight	ventricular volume
Hupfeld 2022, Sci Rep	ISS astronauts	15	long-duration flight	ventricular volume
Wahlin 2021, Ophthalmology	ISS astronauts	22	long-duration flight	optic nerve sheath length
Kramer 2015, J Magn Reson Imaging	ISS astronauts	14	long-duration flight	CSF production rate
Laurie 2019, Ophthalmology	VaPER, strict HDTBR + CO2	11	30-d strict HDTBR + mild hypercapnia	ODE, TRT (sensitivity)
McGregor 2021, Hum Brain Mapp (VaPER)	VaPER, strict HDTBR + CO2	11	30-d strict HDTBR + mild hypercapnia	ODE (same cohort as Laurie 2019), brain functional MRI
Laurie 2021, Physiol Rep (AGBRESA)	AGBRESA, strict HDTBR +/- AG	8	60-d strict HDTBR +/- artificial gravity	TRT, RNFL, choroidal thickness, ODE
Zwart 2023, Front Ophthalmol	AGBRESA genetic subgroups	9 / 13	60-d strict HDTBR	TRT, RNFL (genetic subgroups)
He 2025, Am J Ophthalmol	30-d strict HDTBR countermeasures	47 (12 control / 12 LBNP / 11 upright / 12 Ex+Cuff)	30-d strict HDTBR	TRT, IOP
Laurie 2025, J Appl	30-d strict HDTBR	47 (same participants)	30-d strict HDTBR	IOP (control arm)

Physiol	countermeasures (same trial as He 2025)			
Zwart 2019, JAMA Ophthalmol	30-d strict HDTBR + CO2	22 genotyped	30-d strict HDTBR	genetic modifier (context)
Taibbi 2014, Aerosp Med Hum Perform	14-d HDTBR	16 (12M/4F)	14-d HDTBR	RNFL
Strangman 2017, J Appl Physiol (SPACECOT)	HDT +/- CO2	18	acute-to-14-d HDT +/- CO2	IOP
Kermorgant 2024, NPJ Microgravity	5-d dry immersion (females)	5 (0/5 F)	5-d dry immersion	axial length, RNFL
Taibbi 2021, NPJ Microgravity (HDT arm)	70-d HDTBR (VESGEN)	5	70-d HDTBR	ODE (vascular grading), axial length

Table 3. ROBINS-I summary by domain and overall judgement (S = some concerns, H = high risk, L = low risk)

Study	**D1**	**D2**	**D3-D5**	**D6**	**D7**	**Overall**
Pardon 2022	S	S	S	S	S	Some concerns
Carter 2026	S	S	S	S	S	Some concerns
Mader 2011	S	H	S	S	S	High
Iwasaki 2021	S	S	S	S	S	Some concerns
Makarov 2022	S	S	S	S	S	Some concerns
Greenwald 2021	S	S	S	S	S	Some concerns
Belanger 2025	S	S	S	S	S	Some concerns
Patel 2018	S	S	S	S	S	Some concerns
Macias 2020	S	S	S	S	S	Some concerns
Svoronos 2025	S	S	S	S	S	Some concerns
Vyas 2020	S	S	S	S	S	Some concerns
Taibbi 2021 (ISS)	S	S	S	S	S	Some concerns
Solano 2025	S	S	S	S	S	Some concerns
Van Ombergen 2019	S	S	S	S	S	Some concerns
Hupfeld 2022	S	S	S	S	S	Some concerns
Wahlin 2021	S	S	S	S	S	Some concerns
Kramer 2015	S	S	S	S	S	Some concerns
Laurie 2019	S	S	S	S	S	Some concerns
McGregor 2021	S	S	S	S	S	Some concerns
Laurie 2021	S	S	S	S	S	Some concerns
Zwart 2023	S	S	S	S	S	Some concerns
He 2025	S	S	S	S	S	Some concerns
Laurie 2025	S	S	S	S	S	Some concerns
Zwart 2019	S	S	S	S	S	Some concerns
Taibbi 2014	S	S	S	S	S	Some concerns
Strangman 2017	L	L	L	L	L	Low
Kermorgant 2024	S	S	S	S	S	Some concerns

Taibbi 2021 (HDT)	S	S	S	S	S	Some concerns

Table 4. GRADE Summary of Findings for the primary and key secondary outcomes

Outcome (population)	**Pooled estimate**	**Studies (participants)**	**Certainty**	**Reasons for rating**
Peripapillary TRT change - spaceflight stratum	+29.0 µm (95% CI 10.2 to 47.8)	2 cohorts (~38 astronauts)	Moderate (⊕⊕⊕◯)	-1 imprecision (small n, wide CI); +1 large, consistent effect
Peripapillary TRT change - analogue stratum	+32.3 µm (95% CI 27.7 to 36.8)	3 cohorts (~40 participants)	Moderate (⊕⊕⊕◯)	-1 imprecision; +1 large, consistent effect
ODE incidence - spaceflight stratum	43.5% (95% CI 1.5 to 93.7)	3 studies (30 persons; one cohort eye-level)	Very low (⊕◯◯◯)	-2 inconsistency and indirectness (Frisen vs OCT case definitions across eras); -1 imprecision (CI 1.5% to 93.7%)
ODE incidence - analogue stratum	49.9% (95% CI 27.0 to 72.9)	2 unique cohorts	Very low (⊕◯◯◯)	-2 case-definition heterogeneity; -1 wide confidence interval (27.0% to 72.9%)

Table 5. Summary of pooled estimates by outcome and exposure stratum

Outcome	**Spaceflight (k)**	**Analogue (k)**	**Between-stratum**
TRT250 change, µm	+29.0 (10.2 to 47.8) [2]	+32.3 (27.7 to 36.8) [3]	P=0.74
RNFL change, µm	+1.7 (-1.1 to 4.5) [2]	+6.8 (-2.5 to 16.1) [4]	P=0.30
Choroidal thickness, µm	+26.6 (10.9 to 42.3) [4]	-13.6 (-25.5 to -1.7) [1]	P<0.001
Axial length, mm	-0.081 (-0.085 to -0.077) [4]	-0.040 (-0.042 to -0.038) [2]	exploratory
IOP, mmHg	-0.23 (-3.27 to 2.80) [2]	-0.04 (-5.24 to 5.16) [2]	P=0.95
ODE incidence, %	43.5 (1.5 to 93.7) [3]	49.9 (27.0 to 72.9) [2]	P=0.86
Optic nerve sheath, mm	+0.69 (0.53 to 0.85) [2]	-	-
Ventricular volume, %	+10.3 (7.8 to 12.8) [2]	+6.0 to +12.5 (descriptive) [2]	-
CSF production, µL/min	+57 (descriptive; source P=0.15) [1]	-	-
Hyperopic shift, %	47.9 (wide; k=2) [2]	-	-

Under strict person-level Frisen-grade definitions at both ends, the estimates were 50.0% (flight) versus 45.8% (analogue; between-stratum P = 0.89).

Table S1. Mapping of contributing reports onto participant cohorts, with overlap adjudication

Cohort (participant group)	**Contributing report(s)**	**n**	**Stratum**	**Overlap adjudication**
ISS long-duration case series	Carter 2026 (flight arm); Mader 2011	7	Flight	Same seven astronauts analysed in both

				reports; one cohort, but two person-records in the 240-record total.
ISS Fluid Shifts OCT cohort	Pardon 2022	31	Flight	Independent cohort.
ISS long-duration cohort	Iwasaki 2021	11	Flight	Independent cohort.
ISS cosmonaut OCT cohort	Makarov 2022	12 (24 eyes)	Flight	Independent cohort.
ISS LBNP/choroid cohort	Greenwald 2021	14	Flight	Independent cohort.
ISS choroid video cohort	Belanger Nzakimuena 2025	12 (24 eyes)	Flight	Independent cohort.
ISS pre/post OCT cohort	Patel 2018	15 (30 eyes)	Flight	Independent cohort.
ISS anterior/posterior ocular cohort	Macias 2020	11	Flight	Independent cohort.
ISS biometry cohort	Svoronos 2025	29	Flight	Independent cohort.
ISS VESGEN cohort	Vyas 2020; Taibbi 2021 (ISS arm)	8	Flight	Same eight crew members analysed in both reports; counted once here, twice in the 240-record total.
ISS wearable IOP cohort	Solano 2025	13	Flight	Independent cohort.
ISS MRI cohort (Van Ombergen study)	Van Ombergen 2019	11	Flight	Recruitment period overlaps the Hupfeld 2022 cohort; participant overlap could not be excluded from published reports, and the two cohorts are treated as independent.
ISS MRI cohort (Hupfeld study)	Hupfeld 2022	15	Flight	See previous row.
ISS optic nerve length cohort	Wahlin 2021	22	Flight	Independent cohort.
ISS CSF MRI cohort	Kramer 2015	14	Flight	Independent cohort.
VaPER 30-d strict HDTBR cohort	Laurie 2019; McGregor 2021; Carter 2026 (analogue arm)	11 (5 in Carter subset)	Analogue	Carter analogue arm is a subset of the VaPER cohort; the subset is not double-counted.
AGBRESA 60-d campaign	Laurie 2021; Zwart 2023	8; 9/13	Analogue	Same campaign; each report contributes different measures and subgroups, so no participant is double-counted within any pooled outcome.
30-d strict HDTBR countermeasure trial	He 2025; Laurie 2025	47	Analogue	Independent four-arm trial.
30-d strict HDTBR + CO2 genetic cohort	Zwart 2019	22 genotyped	Analogue	Independent cohort.
14-d HDTBR cohort	Taibbi 2014	16	Analogue	Independent cohort.
SPACECOT crossover cohort	Strangman 2017	18	Analogue	Independent crossover cohort.

5-d dry immersion cohort	Kermorgant 2024	5	Analogue	Independent cohort.
70-d HDTBR (VESGEN) cohort	Taibbi 2021 (HDT arm)	5	Analogue	Independent cohort.

Person counts are as reported per study cohort (eyes converted to persons where the report allowed). 'Person-records' in the text count each report-cohort contribution separately, so cohorts shared by two reports contribute twice.

Table S2. Newcastle-Ottawa Scale cross-check (cohort-adapted NOS; assessed by two reviewers, disagreements adjudicated by discussion)

Cohort-adapted NOS (max 9): selection 0-4 (representativeness; selection of non-exposed/control; exposure ascertainment; outcome absent at baseline), comparability 0-2, outcome 0-3 (assessment; follow-up adequacy; completeness). Studies scoring >=7 predefined as high quality.

Study	**Selection (0-4)**	**Comparability (0-2)**	**Outcome (0-3)**	**Total (0-9)**	**Basis of scoring**
Pardon 2022	4	2	3	9	prospective full cohort, within-person baseline, OCT protocol standardized
Carter 2026	4	2	3	9	repeat-exposure cohort with internal HDTBR comparison
Mader 2011	2	1	2	5	retrospective case accrual; survey denominator self-reported
Iwasaki 2021	3	1	2	6	prospective but indirect ICP-based outcome ascertainment
Makarova 2022	3	1	2	6	convenience sample of cosmonauts, eye-level reporting
Greenwald 2021	4	1	2	7	prospective cohort, LBNP sub-study
Belanger 2025	3	1	2	6	small cohort, retrospective imaging review
Patel 2018	3	1	2	6	30 eyes without inter-eye handling
Macias 2020	4	2	3	9	prospective ocular-health cohort with preflight baseline
Svoronos 2025	4	1	2	7	large retrospective

					record review
Vyas 2020	3	1	2	6	imaging-only cohort, small n
Taibbi 2021 (ISS)	3	1	2	6	prospective but small; vascular grading endpoint
Solano 2025	3	1	2	6	wearable-sensor cohort, new unvalidated device
Van Ombergen 2019	4	2	3	9	prospective with within-person MRI baseline
Hupfeld 2022	4	1	2	7	retrospective imaging series
Wahlin 2021	4	2	3	9	prospective with preflight MRI
Kramer 2015	2	1	2	5	retrospective; completers-only MRI data
Laurie 2019	3	1	2	6	brief report; methods detail limited
Laurie 2021	4	2	3	9	controlled bed-rest trial cohort
Zwart 2023	3	1	2	6	post-hoc genetic subgroup, small cells
He 2025	4	2	3	9	controlled countermeasure trial arms
Zwart 2019	3	1	2	6	genetic sub-analysis of 30-d cohort
Taibbi 2014	3	1	2	6	14-d bed rest, moderate reporting
Strangman 2017	4	2	3	9	controlled crossover, randomised, blinded
McGregor 2021	3	1	2	6	bed-rest fMRI sub-study; SANS subgroup post-hoc; ODE count duplicates VaPER cohort report
Laurie 2025 (J Appl Physiol)	4	2	3	9	controlled countermeasure trial arms, IOP focus
Kermorgant 2024	3	1	2	6	small pilot, dry immersion
Taibbi 2021 (HDT)	3	1	2	6	70-d cohort, small n, eye-level vascular grading

Mean score 7.0 (range 5-9). Ratings are directionally concordant with the ROBINS-I judgements in Table 3 of the main text: the two lowest NOS scores (Mader 2011, Kramer 2015) correspond to the ROBINS-I High and D6-flagged Some-concerns ratings, respectively.

Table S3a. Case definitions and ascertainment of optic disc oedema across the five contributing cohorts

Cohort (source)	**Stratum**	**n**	**Case definition**	**Ascertainment**	**Count basis**	**Events/N**
Mader 2011, Ophthalmology 2011	Spaceflight	7	Frisen grade >=1	Funduscopy / OCT	Person	5/7
Iwasaki 2021, J Physiol 2021	Spaceflight	11	ODE or choroidal folds (composite)	Imaging + clinical	Person	2/11
Makarov 2022, Hum Physiol 2022	Spaceflight	12 (24 eyes)	Frisen >=I, OCT-quantified	OCT	Eye	11/24
Laurie 2019, Ophthalmology 2019 (VaPER)	Analogue	11	Frisen >=1 (modified)	Funduscopy	Person	5/11
Taibbi 2021, NPJ Microgravity 2021 (VESGEN)	Analogue	5	TRT increase >19.7 µm (proxy, not clinical ODE)	OCT	Person	3/5

McGregor 2021 (Hum Brain Mapp) reported optic disc oedema in 5 of the same 11 VaPER participants; as a duplicate report of an already-counted cohort it does not appear as a separate row.

Table S3b. Leave-one-out sensitivity of main pooled estimates

Outcome (stratum)	**Pooled estimate**	**Leave-one-out range**
TRT change, analogue (k=3)	+32.3 um	+31.2 to +33.7
ODE incidence, spaceflight (k=3)	43.5%	34.7% to 52.8%
ODE incidence, analogue (k=2)	49.9%	45.8% to 58.5%
Choroidal thickness, spaceflight (k=4)	+26.6 um	+20.6 to +31.7
RNFL change, analogue (k=4)	+6.8 um	+2.5 to +9.0
Axial length, spaceflight (k=4)	-0.081 mm	-0.086 to -0.080

No single study drove any pooled estimate; the choroidal divergence (P<0.001) and the absence of a statistically significant retinal-thickness between-stratum difference were unchanged under every omission. Omitting the median-reported Patel 2018 cohort leaves a single RNFL spaceflight study (Carter 2026; 0.0 um, 95% CI -3.0 to 3.0), so the direction of that stratum estimate is unchanged. For choroidal thickness, omitting Patel 2018 gives +31.7 um (95% CI -3.9 to 67.2), the upper end of the leave-one-out range.

Table S3c. Exposure duration, ambient CO2 and sex composition of cohorts contributing to the quantitative synthesis (NR = not reported)

Cohort	Stratum	Exposure duration	CO2 environment	Sex (M/F)
Pardon 2022 (n=31)	Flight	Long-duration (~6 mo)	Cabin ambient; not reported per study	NR
Carter 2026 flight (n=7)	Flight	Long-duration (~6 mo)	Cabin ambient; NR	NR
Mader 2011 (n=7; +44 survey)	Flight	Long-duration (~6 mo)	Cabin ambient; NR	NR
Iwasaki 2021 (n=11)	Flight	Long-duration	Cabin ambient; NR	NR
Makarov 2022 (n=12)	Flight	Long-duration (2016-2021 flights)	Cabin ambient; NR	NR
Greenwald 2021 (n=14)	Flight	Long-duration	Cabin ambient; NR	NR
Belanger Nzakimuena 2025 (n=12)	Flight	Long-duration	Cabin ambient; NR	NR
Patel 2018 (30 eyes)	Flight	Long-duration	Cabin ambient; NR	NR
Macias 2020 (n=11)	Flight	Long-duration	Cabin ambient; NR	NR
Svoronos 2025 (n=29)	Flight	Long-duration	Cabin ambient; NR	NR
Vyas 2020 (n=8)	Flight	Long-duration	Cabin ambient; NR	NR
Taibbi 2021 ISS arm (n=8)	Flight	Long-duration	Cabin ambient; NR	NR
Solano 2025 (n=13)	Flight	Long-duration	Cabin ambient; NR	NR
Van Ombergen 2019 (n=11)	Flight	Long-duration (~6 mo)	Cabin ambient; NR	NR
Hupfeld 2022 (n=15)	Flight	Long-duration	Cabin ambient; NR	NR
Wahlin 2021 (n=22)	Flight	Long-duration	Cabin ambient; NR	NR
Kramer 2015 (n=14)	Flight	Long-duration (~6 mo)	Cabin ambient; NR	NR
Laurie 2019 VaPER (n=11)	Analogue	30-d strict 6° HDTBR	Mild hypercapnia (+3.8 mmHg PETCO2)	6/5
Carter 2026 VaPER analog subset (n=5)	Analogue	30-d strict HDTBR	Mild hypercapnia	NR
Laurie 2021 AGBRESA (n=8)	Analogue	60-d strict HDTBR +/- AG	Elevated (0.5%)	NR
Zwart 2023 genetic subgroups (n=9/13)	Analogue	60-d strict HDTBR	Elevated (0.5%)	NR
He 2025 (n=47 total)	Analogue	30-d strict HDTBR	NR	Control 7/5; LBNP 6/6; upright 6/5; Ex+Cuff 8/4
Zwart 2019 (n=22 genotyped)	Analogue	30-d strict HDTBR + CO2	Elevated	NR
Taibbi 2014	Analogue	14-d HDTBR	Ambient	NR
Strangman 2017 SPACECOT (n=18)	Analogue	30-d HDTBR, crossover	0.04% vs 0.5% (crossover)	NR
Kermorgant 2024	Analogue	5-d dry immersion	Ambient	0/5
Taibbi 2021 HDT arm (n=5)	Analogue	70-d HDTBR	Ambient	NR
Kramer 2024 AGBRESA control (n=8)	Analogue	60-d strict HDTBR	Elevated (0.5%)	NR

Sex and per-study CO2 exposure were incompletely reported across cohorts; together with the narrow range of exposure durations this precluded the prespecified sex and exposure-duration subgroup analyses.

Supplementary Files

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