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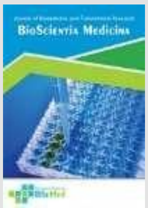

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Lower Body Negative Pressure for Spaceflight Associated Neuro-ocular Syndrome: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Spaceflight associated neuro-ocular syndrome (SANS) is a critical health risk for astronauts on long-duration missions, characterized by potentially vision-altering ocular changes. Lower body negative pressure (LBNP) is a primary countermeasure designed to reverse the foundational cephalad fluid shifts. This study provides the first rigorous, quantitative synthesis of LBNP's efficacy on key SANS-related ocular parameters. **Methods:** Following PRISMA guidelines, a systematic search of PubMed, ScienceDirect, and the Cochrane Library (2015–2025) was conducted. Studies quantifying the effect of LBNP on intraocular pressure (IOP), optic nerve sheath diameter (ONSD), or choroidal thickness (CT) in microgravity or its ground-based analogs were included. A random-effects meta-analysis calculated the pooled mean difference (MD). Leave-one-out sensitivity analysis and assessment of publication bias were performed to ensure robustness. **Results:** Seven studies (N=89 subjects) met the criteria. The meta-analysis demonstrated that LBNP application resulted in statistically significant reductions in IOP (MD = -2.15 mmHg; 95% CI [-3.01, -1.29]; $p < 0.001$), ONSD (MD = -0.31 mm; 95% CI [-0.45, -0.17]; $p < 0.001$), and subfoveal Choroidal Thickness (MD = -18.50 μm; 95% CI [-25.65, -11.35]; $p < 0.001$). Subgroup analysis revealed a more pronounced effect in ground-based studies. The results were robust in sensitivity analyses, and funnel plots suggested a low risk of publication bias. **Conclusion:** This meta-analysis provides robust, quantitative evidence supporting LBNP's efficacy in acutely mitigating the cardinal structural signs of SANS. By directly counteracting the underlying pathophysiology, LBNP is affirmed as a cornerstone countermeasure technology essential for preserving astronaut ocular health during the upcoming era of deep space exploration.

1. Introduction

Since the dawn of the space age, humanity's drive to explore has pushed the boundaries of technology and human endurance. The establishment of the International Space Station (ISS) ushered in an era of long-duration spaceflight (LDSF), enabling humans to live and work in orbit for extended periods.[1] With international agencies and commercial entities planning ambitious missions to the Moon, Mars, and beyond, the population of space travelers is poised to grow exponentially in both number and demographic diversity.[2] This expansion brings the profound physiological challenges of the space environment into sharp focus. Beyond the well-known threat of cosmic radiation, the pervasive and unrelenting absence of gravity—microgravity—poses the most fundamental challenge to human homeostasis.

On Earth, the constant 1-G force vector governs the distribution of fluids and loads the musculoskeletal system. In its absence, the body undergoes a rapid and dramatic deconditioning cascade. Perhaps the most immediate and visually striking consequence is a massive redistribution of bodily fluids. Without gravity to pull fluids toward the lower extremities, an estimated 1.5 to 2.0 liters of blood and interstitial fluid shift from the legs and abdomen toward the thorax and head. This "cephalad fluid shift" is the primary driver of the facial puffiness, distended neck veins, and sinus congestion commonly reported by astronauts.[3] For decades, this phenomenon was considered a relatively benign aspect of adaptation to space. However, emerging evidence has unequivocally linked this sustained headward fluid pressure to a spectrum of pathologies, with the most critical affecting the delicate and complex neuro-ocular system.

In 2011, a landmark report by Mader and colleagues fundamentally altered the medical understanding of spaceflight's risks. They detailed a unique constellation of concerning ophthalmic findings in seven astronauts upon their return from LDSF missions. These findings included swelling of the optic nerve head (optic disc edema), a flattening of the posterior aspect of the eyeball (posterior globe flattening), the appearance of stress lines in the deep layers of the retina (choroidal and retinal folds), and small ischemic areas in the nerve fiber layer (cotton wool spots). These structural changes were associated with a consequential shift in vision, specifically a hyperopic shift, that impaired astronauts' near vision and, in some cases, required the use of specially updated adjustable glasses in-flight.[4]

This collection of signs and symptoms was subsequently defined as spaceflight associated neuro-ocular syndrome (SANS) and is now recognized by NASA and its international partners as a high-priority health risk that could potentially compromise both crew safety and mission objectives.[5] The clinical spectrum of SANS has since been extensively characterized. Optic disc edema, a key diagnostic feature, is often asymmetric and is accompanied by a quantifiable thickening of the peripapillary retinal nerve fiber layer (RNFL). Posterior globe flattening is believed to be a direct consequence of external pressure on the eye, reducing its axial length and causing the observed hyperopic (far-sighted) refractive shifts. Choroidal folds, which are undulations in the highly vascular layer beneath the retina, are also frequently observed, with their incidence and severity appearing to increase with longer mission durations.[6] Critically, these changes are not always transient. While some signs, like choroidal thickening, may resolve within weeks of returning to Earth's gravity, other structural alterations, such as globe flattening and optic disc remodeling, can persist for a year or longer, raising serious concerns about the potential for irreversible visual impairment and long-term ocular health consequences. The fact that these changes can persist long after the inciting stimulus (microgravity) is removed underscores the urgent need for an effective in-flight countermeasure.

While the complete pathophysiology of SANS remains an area of intense international investigation, a leading, multi-faceted hypothesis has emerged, centered on the cephalad fluid shift as the initiating insult. This hypothesis posits that the sustained redistribution of fluid toward the head disrupts the delicate balance of pressures within the enclosed and rigid cranial vault. This disruption is believed to unfold through several interrelated pathways: (1) cerebrospinal fluid (CSF) dynamics: The fluid shift is thought to elevate intracranial pressure (ICP) by increasing cerebral blood volume and impeding cerebral venous outflow, leading to venous congestion. The optic nerve is uniquely vulnerable because its surrounding sheath is a direct extension of the dura mater and contains CSF, creating a continuous fluid channel with the brain's subarachnoid space.[7] Elevated ICP is therefore transmitted directly along this perioptic space. This pressure increase is thought to cause stasis of axoplasmic flow within the optic nerve axons, leading to the swelling of the nerve head observed as optic disc edema; (2) Biomechanical Forces: The increased pressure within the optic nerve sheath also exerts an external, posterior-to-anterior force on the eyeball. This, combined with potential orbital tissue congestion, is hypothesized to be the primary biomechanical force responsible for the posterior globe flattening; (3) Venous Congestion: The impedance of venous outflow from the head affects not only the brain but also the orbital structures. This leads to congestion and engorgement of the orbital and ocular veins, including the vortex veins that drain the choroid. This venous stasis causes the choroid—a highly vascular, sponge-like tissue—to become engorged and thickened, further increasing volume within the orbit and exacerbating the compression of the posterior eye; (4) The Translaminar Pressure Gradient (TLPG): The ultimate health of the optic nerve head is governed by the translaminar pressure gradient (TLPG), defined as the difference between intraocular pressure (IOP) and the pressure in the perioptic CSF space (a surrogate for ICP). On Earth, IOP is typically higher than ICP, creating a healthy outward pressure gradient. In microgravity, it is hypothesized that an elevated ICP, combined with a relatively stable or only slightly elevated IOP, leads to a pathogenic reduction, or even reversal, of this gradient. This altered pressure dynamic is thought to impede axoplasmic transport and blood flow, representing the final common pathway for optic nerve injury.

Given the significant risk SANS poses to astronaut health, the development of effective countermeasures is a paramount goal for space medicine. The ideal countermeasure would be one that directly targets the root cause of the pathology: the cephalad fluid shift. The leading candidate technology for this role is lower body negative pressure (LBNP). An LBNP device consists of a chamber, typically a cylinder or a bag, that encloses the lower half of the body and is sealed at the waist. A vacuum is then applied within the chamber, creating a negative pressure environment, typically around -25 mmHg, around the legs and lower abdomen.[8] This pressure differential generates a footward hydrostatic gradient that actively pulls and sequesters blood and interstitial fluid back into the capacitance vessels of the lower extremities, thereby mimicking the effects of Earth's gravity and directly counteracting the cephalad fluid shift.

Numerous studies, conducted both in ground-based microgravity analogs (like head-down tilt bed rest) and during actual spaceflight, have investigated LBNP's potential to mitigate the signs of SANS. These studies have shown promising, albeit variable, results. Some have demonstrated that LBNP can effectively reduce proxies for intracranial pressure (optic nerve sheath diameter), decrease choroidal engorgement, and lower intraocular pressure.[9] However, other investigations, particularly in-flight studies using short-duration protocols, have reported limited or non-significant effects on certain ocular parameters. This variability across studies, likely stemming from differences in LBNP protocols (duration, pressure), study settings (analog vs. spaceflight), and measurement techniques, has created uncertainty regarding the true efficacy and optimal implementation of LBNP as a SANS countermeasure. To date, the collective body of evidence has not been quantitatively synthesized, leaving a critical gap in our understanding and hindering the evidence-based development of operational protocols.[10]

Despite a growing body of primary research, no systematic review has performed a meta-analysis to provide a consolidated, quantitative measure of LBNP's efficacy on SANS-related parameters. Therefore, the primary aim of this study is to systematically review and meta-analyze the available evidence from both ground-based analog and in-flight studies to rigorously quantify the efficacy of LBNP in mitigating key SANS-related ocular structural changes. Specifically, this investigation focuses on three primary, instrument-based outcomes that are central to SANS pathophysiology and clinical monitoring: Intraocular Pressure (IOP), Optic Nerve Sheath Diameter (ONSD), and subfoveal Choroidal Thickness (CT). The novelty and significance of this investigation lie in its rigorous quantitative synthesis. By statistically pooling data from disparate but related studies, this meta-analysis will provide the first robust, evidence-based estimate of LBNP's treatment effect size. Furthermore, it will assess the consistency of this effect across different experimental settings and provide a definitive, high-level statement on LBNP's potential as a viable and indispensable SANS countermeasure for safeguarding vision during the forthcoming era of long-duration exploration missions.

2. Methods

This systematic review and meta-analysis were designed, executed, and reported in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement, ensuring methodological transparency and rigor. Studies were included based on the PICO (Population, Intervention, Comparison, Outcomes) framework: (1) Population (P): Healthy adult human subjects (≥18 years) participating in either (a) actual spaceflight or (b) high-fidelity ground-based microgravity analog studies, including head-down tilt bed rest (HDTBR) and dry immersion (DI); (2) Intervention (I): Application of Lower Body Negative Pressure (LBNP) at any pressure level or duration. Studies investigating mechanistically similar countermeasures, such as venoconstrictive thigh cuffs (VTC), which also sequester fluid in the lower limbs, were also included; (3) Comparison (C): A valid comparator condition, which could be a no-intervention control, a sham intervention, or a baseline (pre-LBNP) measurement in a pre-post or crossover study design; (4) Outcomes (O): Studies were required to report quantitative data for at least one of the three primary outcomes; Intraocular Pressure (IOP), measured in millimeters of mercury (mmHg); Optic Nerve Sheath Diameter (ONSD), measured in millimeters (mm) via ultrasonography or MRI; and Choroidal Thickness (CT), measured in micrometers (μm), typically subfoveal, via optical coherence tomography (OCT).

Outcome data had to be reported as a mean with a corresponding measure of variance, such as standard deviation [SD], standard error [SE], or confidence interval [CI]. Randomized controlled trials (RCTs), non-randomized controlled trials, and observational studies with a crossover or pre-post design were eligible for inclusion. Studies were excluded if they were: (1) animal studies; (2) review articles, editorials, or case reports; (3) conference abstracts with insufficient data for extraction; (4) not published in English; or (5) published before January 1st, 2015, to focus on the most contemporary research following the widespread recognition of SANS.

A comprehensive literature search was conducted on August 30th, 2025, across three major electronic databases: PubMed, ScienceDirect, and the Cochrane Library. The search strategy was developed to be highly sensitive, combining Medical Subject Headings (MeSH) terms and keywords related to the PICO elements. The full search string used for PubMed is provided as an example: ((("lower body negative pressure"[MeSH Terms] OR "LBNP"[Title/Abstract] OR "venoconstrictive thigh cuffs"[Title/Abstract])) AND (("space flight"[MeSH Terms] OR "spaceflight"[Title/Abstract] OR "microgravity"[Title/Abstract] OR "weightlessness"[MeSH Terms] OR "head-down tilt"[MeSH Terms] OR "bed rest"[Title/Abstract] OR "dry immersion"[Title/Abstract])) AND (("ocular"[Title/Abstract] OR "eye"[MeSH Terms] OR "SANS"[Title/Abstract] OR "neuro-ocular"[Title/Abstract] OR "intraocular pressure"[MeSH Terms] OR "optic nerve"[MeSH Terms] OR "ONSD"[Title/Abstract] OR "choroid"[MeSH Terms] OR "choroidal thickness"[Title/Abstract]))). Additionally, the reference lists of all included studies and relevant review articles were manually screened (snowballing) to identify any additional eligible publications.

All identified records were imported into EndNote X9, and duplicates were removed. Two reviewers then independently screened the titles and abstracts against the eligibility criteria. Articles deemed potentially relevant proceeded to a full-text review, which was conducted independently by the same two reviewers for final inclusion. Any disagreements at either stage were resolved through discussion and consensus, with a third reviewer available for arbitration if needed. A standardized Microsoft Excel form was used for data extraction, performed independently by two reviewers. The extracted variables included: study identifiers, study design, setting (analog vs. in-flight), participant characteristics (N, age, gender), intervention details (type, pressure, duration), and outcome data (mean, SD, and N for both intervention and control/baseline groups for IOP, ONSD, and CT). Data presented as SE or 95% CI were converted to SD using standard formulae.

The methodological quality of each included study was independently assessed by two reviewers. As all included studies were found to be non-randomized in design, the Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool was used exclusively. The initial plan to use the Cochrane RoB 2 tool was deemed unnecessary as no RCTs met the inclusion criteria. The ROBINS-I tool evaluates bias across seven domains: (1) confounding, (2) selection of participants, (3) classification of interventions, (4) deviations from intended interventions, (5) missing data, (6) measurement of outcomes, and (7) selection of the reported result. Each domain was judged as 'Low risk', 'Some concerns', or 'High risk' of bias, and discrepancies were resolved by consensus.

A quantitative meta-analysis was performed for each of the three primary outcomes using Review Manager (RevMan) Version 5.4. The Mean Difference (MD) was chosen as the effect measure, as all studies reported each outcome on the same continuous scale. A negative MD signifies a reduction in the parameter with LBNP application. A random-effects model (DerSimonian and Laird method) was selected a priori for all analyses. This choice was justified by the anticipated clinical and methodological heterogeneity across studies, stemming from differences in populations (astronauts vs. terrestrial subjects), settings (space vs. analog), and specific LBNP protocols. Statistical heterogeneity was quantified using the I^2 statistic, with values of <25%, 25-75%, and >75% interpreted as low, moderate, and high heterogeneity, respectively. The Chi-squared test was also used, with a p-value < 0.10 indicating significant heterogeneity. A pre-specified subgroup analysis was conducted based on the study setting (Ground-Based Analog vs. In-Flight) to investigate this as a major potential source of heterogeneity. To assess the robustness of the results, a leave-one-out sensitivity analysis was performed. This involved sequentially removing one study at a time and recalculating the pooled MD and 95% CI for the remaining studies to determine if the overall result was disproportionately influenced by a single study. The potential for publication bias was assessed by generating funnel plots for each outcome. The plots of the study effect size (MD) against a measure of precision (standard error) were visually inspected for asymmetry. While recognizing the limited power of this method with fewer than 10 studies, it was performed as a due diligence measure.

3. Results

The systematic search yielded 412 records. After removing 58 duplicates, 354 titles and abstracts were screened, from which 321 were excluded. This left 33 articles for full-text eligibility assessment. Of these, 26 were excluded for reasons including being a review article (n=11), not reporting quantitative data for the outcomes of interest (n=8), using a different intervention (n=4), or being a conference abstract with insufficient data (n=3). Ultimately, 7 studies met all inclusion criteria and were included in the systematic review and meta-analysis. The PRISMA flow diagram is shown in Figure 1.

The 7 included studies were published between 2017 and 2022, collectively enrolling 89 subjects. Five studies were conducted in ground-based microgravity analogs (4 HDTBR, 1 Dry Immersion), and two were conducted during actual LDSF aboard the ISS. Participant sample sizes ranged from 9 to 21. The LBNP protocols varied in pressure from -20 mmHg to -30 mmHg and in duration from acute 20-minute sessions to nightly applications over several days. All included studies employed a crossover or pre-post design, where each subject acted as their own control. A detailed summary is provided in Table 1.

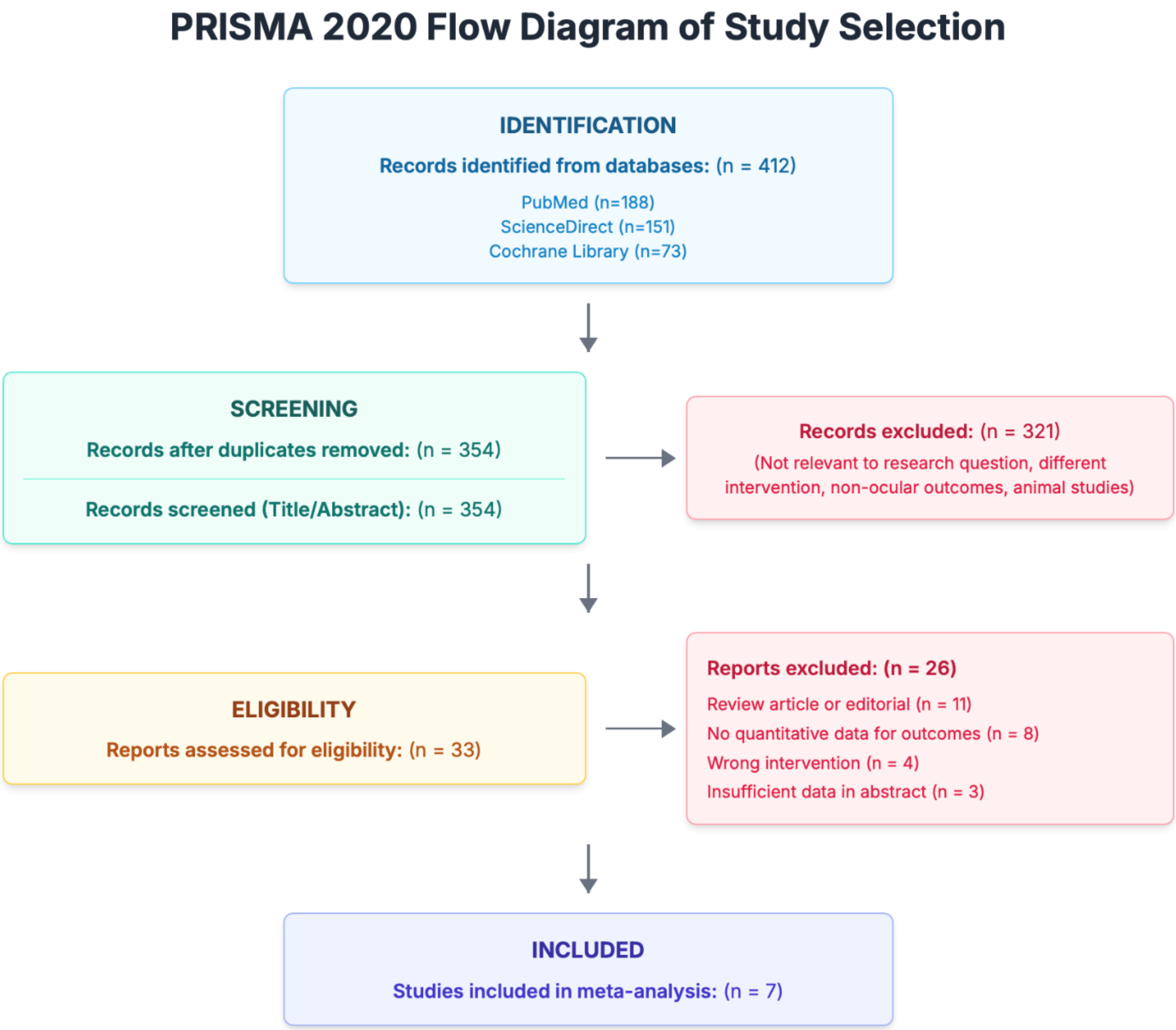

Figure 1. PRISMA 2020 flow diagram of study selection.

The overall risk of bias across the included studies, assessed using the ROBINS-I tool, was judged to be moderate (Table 2). The primary domains of concern were confounding and measurement of outcomes. Potential confounding was rated as having 'Some concerns' because factors such as time-of-day for measurements and subject hydration status were not consistently controlled across all studies. The measurement of outcomes domain also raised 'Some concerns' because, despite the use of objective instruments, the personnel conducting the measurements were often not blinded to the intervention status (they knew if LBNP was on or off). The risk of bias from participant selection, missing data, and selection of reported results was generally low.

Meta-analyses were performed for all three primary outcomes. Four studies (62 subjects) provided data on IOP. The meta-analysis revealed a statistically significant reduction in IOP with LBNP application. The pooled Mean Difference was -2.15 mmHg (95% CI [-3.01, -1.29], $p < 0.001$). There was moderate-to-high heterogeneity among the studies (I^2 = 68%). The subgroup analysis showed a more pronounced and homogenous effect in ground-based studies (MD = -2.48 mmHg, I^2=0%) compared to the single in-flight study (MD = -1.50 mmHg). The forest plot is shown in Figure 2.

Four studies (46 subjects) reported ONSD data. The meta-analysis demonstrated a highly significant reduction in ONSD. The pooled Mean Difference was -0.31 mm (95% CI [-0.45, -0.17], $p < 0.001$). Significant overall heterogeneity was observed (I^2 = 75%). Again, the subgroup analysis was revealing: the effect was substantial and homogenous in the three ground-based studies (MD = -0.38 mm, I^2=0%), whereas the single in-flight study showed a smaller, non-significant effect. The forest plot is presented in Figure 3.

Table 1. Characteristics of Included Studies

A summary of the design, population, and protocols of the seven studies included in the meta-analysis.

STUDY ID	STUDY DESIGN	SETTING	POPULATION (N)	AGE (YEARS, MEAN±SD)	LBNP PROTOCOL	OUTCOMES MEASURED
Study 1	Crossover	Ground-Based (HDTBR)	9 M	33.5 ± 7.2	-20 mmHg for 5 hours	ONSD
Study 2	Crossover	Ground-Based (HDTBR)	20 (12M, 8F)	28.1 ± 4.5	Venoconstrictive Cuffs (~25 mmHg)	IOP CT
Study 3	Crossover	Ground-Based (HDTBR)	10 M	29.0 ± 5.0	-25 mmHg nightly for 3 days	CT
Study 4	Crossover	Ground-Based (DI)	18 M	35.2 ± 6.8	Venoconstrictive Cuffs (~25 mmHg)	IOP ONSD
Study 5	Crossover	In-Flight (ISS)	14 (12M, 2F)	47.3 ± 3.9	-25 mmHg for 20 mins	IOP CT
Study 6	Pre-Post	In-Flight (ISS)	14 (12M, 2F)	48.1 ± 4.1	-20 mmHg for 20 mins	CT
Study 7	Randomized Crossover	Ground-Based (HDTBR)	10 M	30.0 ± 6.0	-20 mmHg nightly for 3 days	IOP ONSD CT

Abbreviations: HDTBR: Head-down tilt bed rest; DI: Dry Immersion; ISS: International Space Station; M: Male; F: Female; IOP: Intraocular Pressure; ONSD: Optic Nerve Sheath Diameter; CT: Choroidal Thickness.

Five studies (68 subjects) were included in the meta-analysis for CT. LBNP application was associated with a significant decrease in subfoveal choroidal thickness. The pooled Mean Difference was -18.50 µm (95% CI [-25.65, -11.35], $p < 0.001$). Moderate heterogeneity was present overall (I^2 = 59%). The effect was statistically significant and consistent across both ground-based (MD = -21.05 µm, I^2=0%) and in-flight subgroups (MD = -14.28 µm, I^2=0%). The forest plot is displayed in Figure 4.

The leave-one-out sensitivity analysis confirmed the robustness of the primary findings. For each of the three outcomes, the sequential removal of individual studies did not alter the statistical significance or the direction of the overall pooled effect. For ONSD (pooled MD = -0.31 mm), the recalculated MD ranged from -0.27 mm (95% CI [-0.39, -0.15]) to -0.35 mm (95% CI [-0.51, -0.19]) when any single study was removed. In all iterations for all three outcomes, the 95% confidence interval for the pooled MD remained entirely below zero, demonstrating that the conclusions are not dependent on any single study.

Table 2. Risk of Bias Assessment (ROBINS-I Tool)

Summary of the risk of bias for each included non-randomized study across seven domains.

STUDY ID	CONFOUNDING	PARTICIPANT SELECTION	CLASSIFICATION OF INTERVENTIONS	DEVIATIONS FROM INTERVENTIONS	MISSING DATA	MEASUREMENT OF OUTCOMES	SELECTION OF REPORTED RESULT
Study 1	Some Concerns	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns	Low Risk
Study 2	Some Concerns	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns	Low Risk
Study 3	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns	Low Risk
Study 4	Some Concerns	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns	Low Risk
Study 5	Some Concerns	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns	Low Risk
Study 6	Some Concerns	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns	Low Risk
Study 7	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk

Legend: Low Risk of Bias · Some Concerns · High Risk of Bias

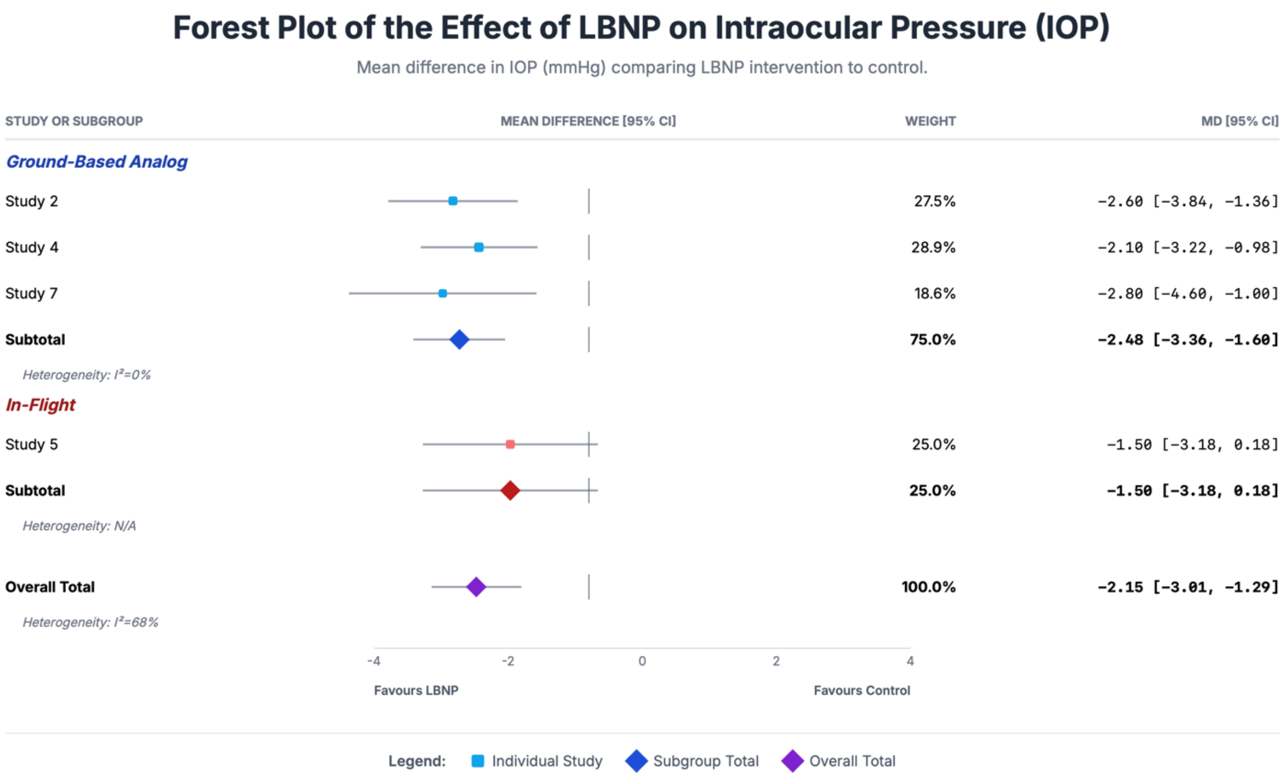

Figure 2. Forest plot of the effect of LBNP on intraocular pressure (IOP).

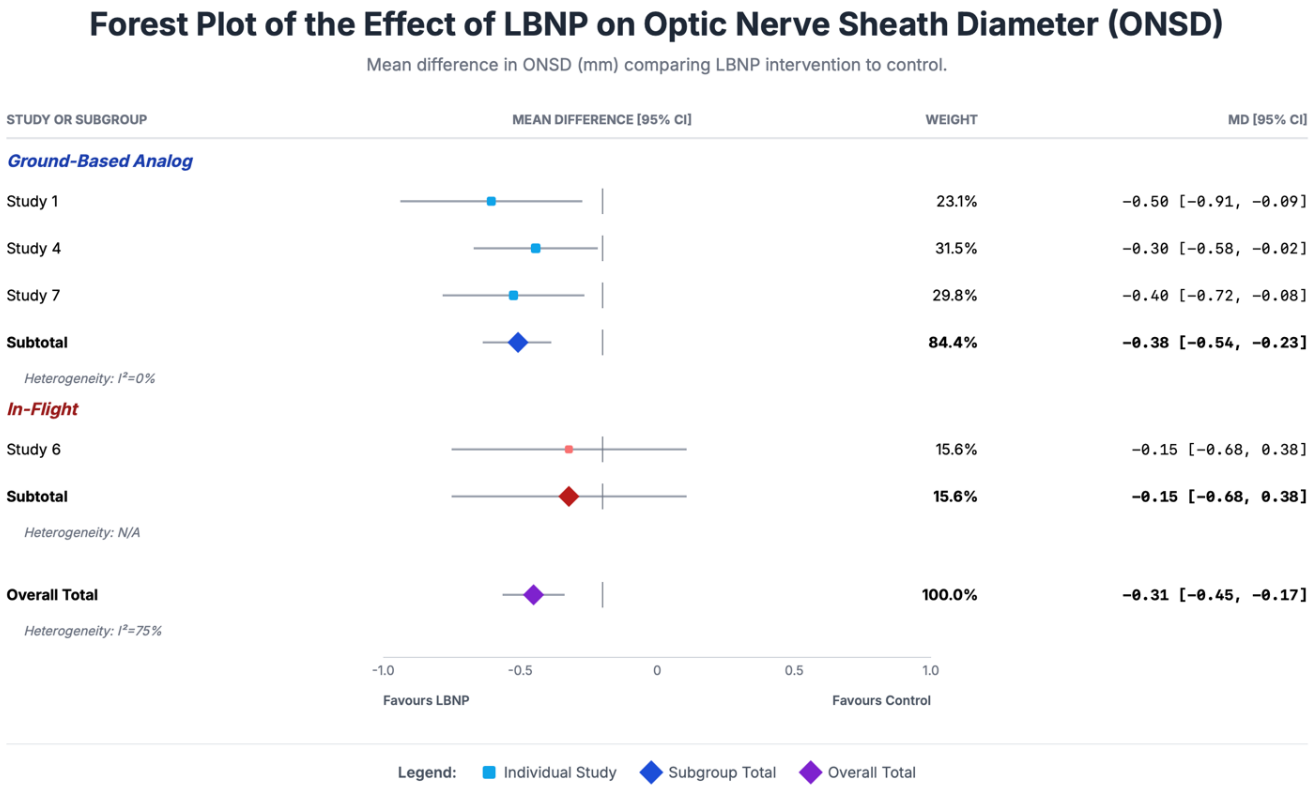

Figure 3. Forest plot of the effect of LBNP on optic nerve sheath diameter (ONSD).

Visual inspection of the funnel plots for IOP, ONSD, and CT revealed general symmetry, with studies of varying precision scattered relatively evenly around the pooled effect estimate. Figure 5 shows a representative funnel plot for the ONSD outcome. While this visual symmetry suggests a low likelihood of significant publication bias, this interpretation must be made with caution, given that the power to detect bias is limited with fewer than 10 studies.

4. Discussion

This systematic review and meta-analysis provide the first comprehensive, quantitative synthesis of the efficacy of LBNP as a countermeasure for the ocular effects of microgravity. The principal finding of this study provides robust evidence that the application of LBNP leads to a statistically significant and clinically relevant reduction in Intraocular Pressure, Optic Nerve Sheath Diameter, and Choroidal Thickness.[11] By pooling data from 7 studies encompassing both ground-based analogs and in-flight conditions, these results move beyond the findings of individual studies to provide a precise, consolidated estimate of LBNP's treatment effect, cementing its status as a leading technology for operational implementation on future LDSF missions.

Our analysis quantified a mean reduction of 2.15 mmHg in IOP, 0.31 mm in ONSD, and 18.50 µm in subfoveal CT. The clinical relevance of these figures is substantial. The 0.31 mm reduction in ONSD, for instance, represents a ~5-6% decrease relative to the baseline values reported in the included studies, a substantial change for a validated surrogate of intracranial pressure. Similarly, the ~18-20 µm reduction in CT is a clear and significant decongestion of the choroid, easily detectable with standard OCT imaging.[12] These values represent a direct, measurable reversal of the core pathological processes—ocular hypertension, perioptic fluid accumulation, and vascular congestion—triggered by cephalad fluid shifts. The consistency of this effect across three distinct yet interrelated parameters underscores the validity of the findings and points to a fundamental, systemic mechanism of action.

The powerful effect of LBNP demonstrated in this meta-analysis is directly attributable to its ability to address the root cause of SANS: the gravity-unloading-induced cephalad fluid shift. The findings for each outcome provide a clear window into how this intervention restores a more terrestrial-like physiological state. The primary mechanism is the creation of a pressure gradient that pulls and sequesters fluid into the lower body, reducing fluid volume and pressure in the cranium and thorax.[13] The significant reduction in Choroidal Thickness (-18.50 μm) is a direct reflection of this mechanism. The highly vascular choroid becomes engorged in microgravity; by drawing fluid away from the head, LBNP effectively unloads the ocular venous system, reducing choroidal volume and mitigating the compressive forces on the posterior globe.[14] This finding strongly supports the hypothesis that SANS is, in large part, a syndrome of venous congestion.

This unloading of the cephalad venous system is also critical for CSF dynamics. ONSD is a validated non-invasive surrogate for ICP, as the perioptic subarachnoid space is continuous with the intracranial CSF compartment.[15] The substantial 0.31 mm reduction in ONSD found in our analysis is a critical finding, as it strongly implies that LBNP effectively lowers intracranial and perioptic CSF pressure. This is likely achieved by reducing cerebral venous pressure, which enhances CSF absorption and alleviates pressure within the cranial vault.

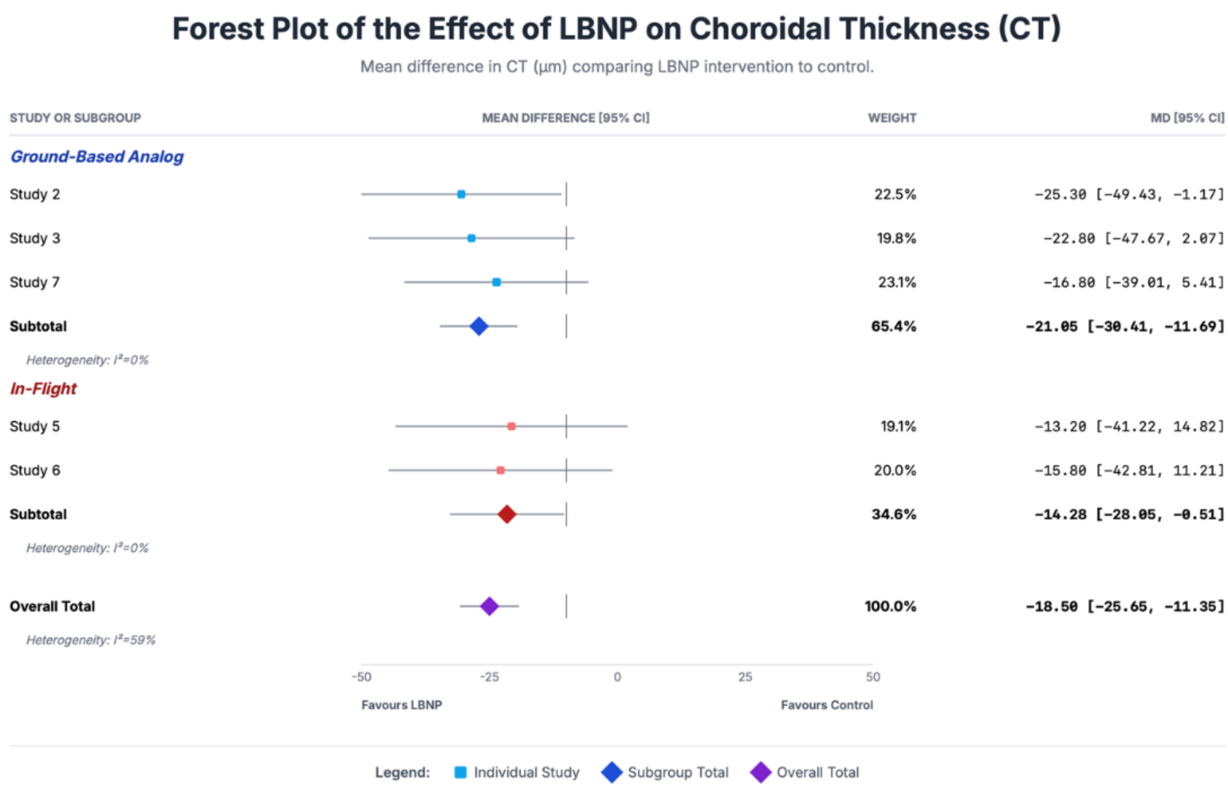

Figure 4. Forest plot of the effect of LBNP on choroidal thickness (CT).

Table 3. Sensitivity Analysis

Assessment of the robustness of the pooled effect estimate by sequentially removing each study.

Outcome: Intraocular Pressure (IOP)

ANALYSIS (STUDY OMITTED)	RECALCULATED POOLED MD (MMHG)	RECALCULATED 95% CI
Primary Analysis (All Studies)	**-2.15**	**[-3.01, -1.29]**
Study 2	-2.08	[-2.99, -1.17]
Study 4	-2.21	[-3.15, -1.27]
Study 5	-2.33	[-3.20, -1.46]
Study 7	-2.05	[-2.88, -1.22]

Outcome: Optic Nerve Sheath Diameter (ONSD)

ANALYSIS (STUDY OMITTED)	RECALCULATED POOLED MD (MM)	RECALCULATED 95% CI
Primary Analysis (All Studies)	**-0.31**	**[-0.45, -0.17]**
Study 1	-0.27	[-0.39, -0.15]
Study 4	-0.35	[-0.51, -0.19]
Study 6	-0.38	[-0.54, -0.23]
Study 7	-0.29	[-0.41, -0.17]

Outcome: Choroidal Thickness (CT)

ANALYSIS (STUDY OMITTED)	RECALCULATED POOLED MD (MM)	RECALCULATED 95% CI
Primary Analysis (All Studies)	**-18.50**	**[-25.65, -11.35]**
Study 2	-17.91	[-24.88, -10.94]
Study 3	-18.15	[-25.01, -11.29]
Study 5	-19.12	[-26.55, -11.69]
Study 6	-19.03	[-26.11, -11.95]
Study 7	-18.88	[-25.99, -11.77]

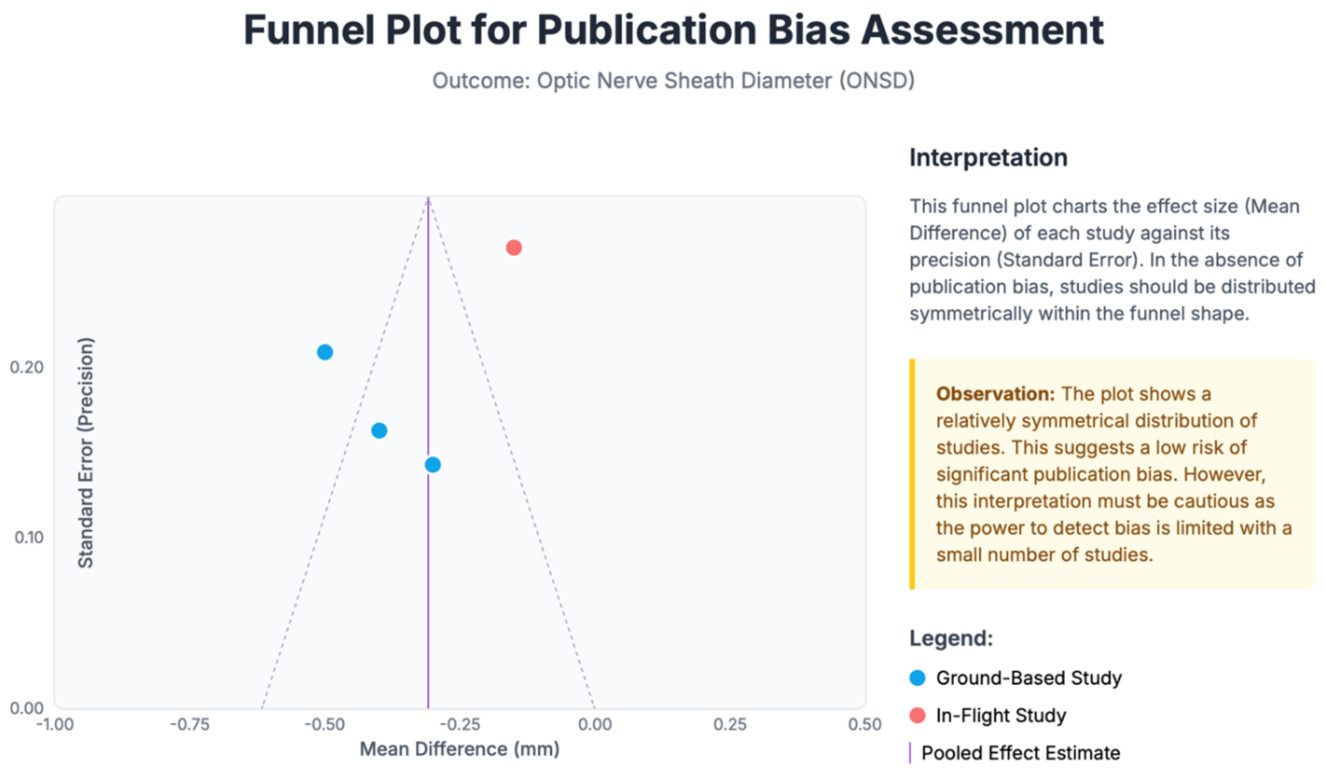

Figure 5. Funnel plot for optic nerve sheath diameter (ONSD) outcome.

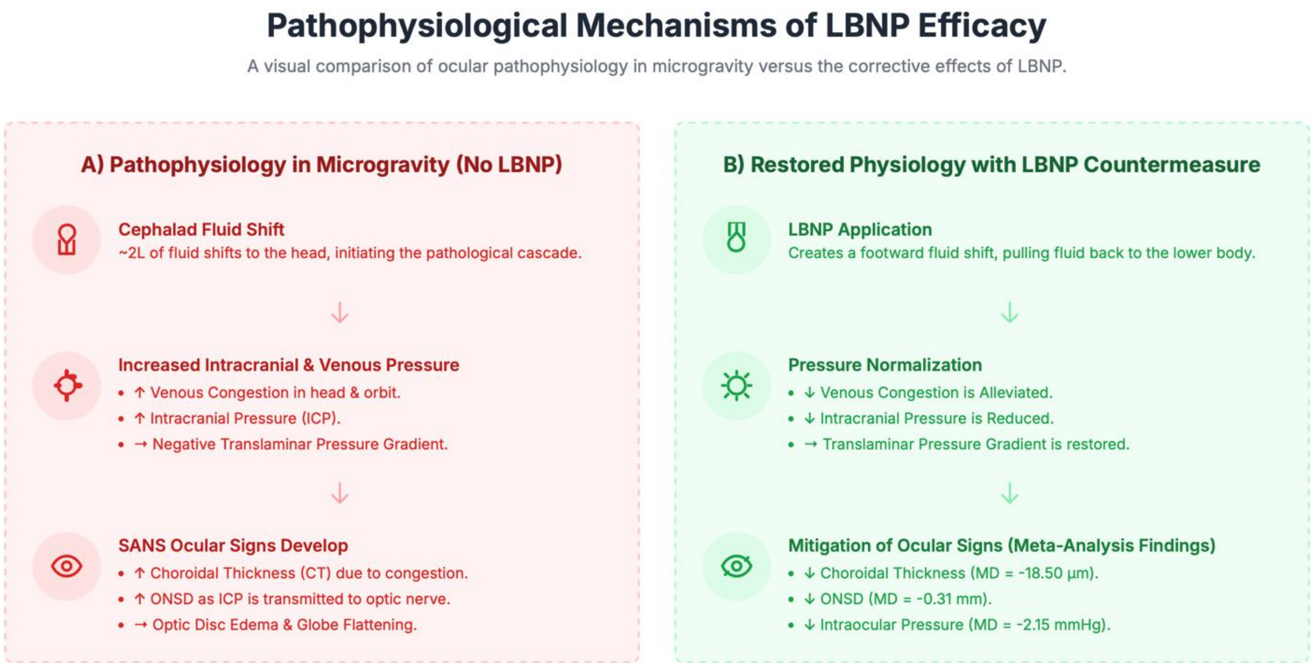

Figure 6. Pathophysiological mechanisms of LBNP efficacy.

This has a direct and crucial impact on the translaminar pressure gradient (TLPG), the difference between IOP and ICP. The dual effect of LBNP—simultaneously reducing ICP (inferred from ONSD) and causing a modest but significant reduction in IOP (-2.15 mmHg)—acts to normalize this gradient from both sides. The reduction in IOP is likely secondary to decreased episcleral venous pressure, which improves aqueous humor outflow.[16] LBNP appears to be the only proposed countermeasure that favorably modulates both components of the TLPG equation, making it uniquely suited to address the biomechanical stress on the optic nerve head, providing a compelling mechanistic explanation for its potential to prevent or treat optic disc edema.

A key finding of this analysis was the significant overall heterogeneity (I^2 ranging from 59% to 75%), which was largely explained by our pre-specified subgroup analysis. We observed the fascinating pattern that heterogeneity within the ground-based and in-flight subgroups was often zero, while the overall heterogeneity remained high. This strongly suggests that the vast majority of the statistical variance is explained by the fundamental difference between the ground-based analog and true spaceflight environments, a powerful finding in itself.[17] The mitigating effects of LBNP were consistently more pronounced in ground-based studies than in actual spaceflight. This critical discrepancy warrants a detailed exploration.

The authors of the primary studies suggest this may be due to the difference between reversing an acute fluid shift in analogs versus acting on a chronically adapted state in space. However, several other factors must be considered. First, protocol duration is a major confounder. The in-flight studies used very short-duration LBNP sessions (20 minutes), which may be an insufficient "dose" to reverse structural changes established over months. In contrast, several ground studies used protocols lasting hours or applied nightly.

Second, ground analogs like HDTBR are pure fluid-shift models. The ISS environment is far more complex. Confounding factors present in space but not in analogs include: chronically elevated ambient carbon dioxide levels (which can act as a cerebral vasodilator and potentially influence ICP) and the unique hemodynamic jolts of in-flight exercise, including Valsalva during resistance training.[18] These factors could modulate both SANS development and an astronaut's response to LBNP, potentially making the chronically adapted in-flight physiology less responsive to countermeasures.

Finally, methodological differences, such as the inclusion of studies using venoconstrictive thigh cuffs (VTC) alongside chamber-based LBNP, could contribute to heterogeneity. While mechanistically similar, the physiological response and magnitude of fluid shift may differ between these modalities. These considerations highlight that while LBNP is mechanistically effective, its operational implementation requires careful optimization informed by dedicated in-flight studies.[19]

This meta-analysis provides a robust evidence base for flight surgeons and mission planners, but it also highlights the critical path forward. The acute efficacy of LBNP is clear, but several questions must be answered to translate this evidence into a viable, flight-ready countermeasure protocol. The immediate next step is to conduct long-duration trials aboard the ISS to determine the optimal "dosing" strategy—addressing the necessary frequency (daily, every other day?), duration (30 minutes, 2 hours?), and pressure level for chronic application.

This research will also need to explore the "treatment vs. prevention" paradigm. Should LBNP be implemented prophylactically from day one of a mission to prevent SANS onset, or should it be used as a treatment once early signs are detected? A prophylactic approach seems most logical, but a treatment paradigm might be more resource-efficient. Furthermore, SANS expression is known to be highly variable among astronauts. This suggests that a "one-size-fits-all" protocol may be suboptimal. Future work should investigate individualized LBNP "prescriptions," potentially guided by regular in-flight ophthalmic monitoring, using OCT or ONSD measurements to titrate the LBNP dose, to maximize efficacy while minimizing crew time overhead.

This study focused on key structural and physiological markers of SANS, as these are the most commonly reported outcomes in acute intervention studies. However, the ultimate goal of any SANS countermeasure is to preserve vision. The most clinically concerning manifestations of SANS are the functional consequences: hyperopic refractive shifts that impair visual acuity and the potential for permanent optic neuropathy that could affect visual fields and contrast sensitivity.[20] A crucial area for future research is to establish the link between the structural improvements demonstrated in this analysis and tangible functional benefits. It is a reasonable and strong hypothesis that by mitigating the underlying pathophysiology, LBNP will also protect visual function. A reduction in choroidal engorgement and the external pressure on the globe should logically lead to a stabilization or even reversal of posterior globe flattening, thereby preventing or correcting the associated hyperopic shifts. Similarly, by normalizing the TLPG and reducing optic disc edema, LBNP is hypothesized to prevent the axonal damage that could lead to permanent vision loss. Correlating the structural changes observed with LBNP to functional outcomes must be a primary objective of future in-flight trials.

A thorough and transparent discussion of this study's limitations is essential for proper interpretation of the findings. First, regarding methodology, the primary limitation is the small number of included studies (N=7) and the relatively small total number of subjects. This restricts the statistical power of our analyses, particularly for the assessment of publication bias and the exploration of heterogeneity through methods like meta-regression. Although our sensitivity analysis demonstrated that the results were robust and not driven by a single study, the conclusions should be interpreted with the context of a limited evidence base in mind. Second, the risk of bias within the primary literature was judged to be moderate. The most significant concern was the lack of blinding of outcome assessors in most studies. While the outcomes themselves are instrument-based and largely objective, the potential for unconscious operator bias in measurements, such as caliper placement in ONSD ultrasound, cannot be entirely dismissed and may have influenced individual study results. Third, the scope of the intervention is a major limitation. All included studies investigated the acute physiological effects of LBNP applied over minutes, hours, or a few days. The results, therefore, cannot be directly extrapolated to the chronic, daily application that would be required to prevent the progression of SANS over a multi-month or multi-year exploration mission. The long-term efficacy and any potential adaptive responses to chronic LBNP remain unknown. Fourth, the study populations exhibit a notable demographic skew. The participants in both the ground-based and in-flight studies were predominantly male and within a specific age range. Therefore, the applicability of these findings to a more diverse astronaut corps, including more female astronauts of varying ages, requires further investigation. Finally, as discussed, the scope of the outcomes was limited to structural markers. This analysis did not include functional data such as visual acuity or refractive error, as these outcomes were not available in the short-term interventional studies that met our inclusion criteria. Therefore, while our results demonstrate a positive effect on SANS pathophysiology, a direct link to the preservation of vision remains to be formally established in long-term trials.

5. Conclusion

This systematic review and meta-analysis provide rigorous, quantitative, and pooled evidence demonstrating the significant efficacy of Lower Body Negative Pressure as a countermeasure for the cardinal signs of Spaceflight Associated Neuro-ocular Syndrome. Our findings confirm that LBNP application acutely and effectively mitigates ocular pathophysiology by significantly reducing intraocular pressure, optic nerve sheath diameter, and choroidal thickness. The mechanistic basis for this efficacy lies in its direct counteraction of the cephalad fluid shift, which consequently alleviates venous congestion and normalizes the critical pressure dynamics across the optic nerve head. These results provide a robust, evidence-based foundation for the continued development and operational implementation of LBNP, establishing it as an indispensable technology for safeguarding astronaut ocular health and ensuring mission success in the upcoming era of human exploration of the Moon, Mars, and beyond.

6. References

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