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Understanding the relationship between intracranial pressure and spaceflight associated neuro-ocular syndrome (SANS): a systematic review

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Neuro-ocular changes, such as globe flattening, optic disc edema or chorioretinal folds, are a major worry when considering astronaut health. These findings are now known as Spaceflight Associated Neuro-Ocular Syndrome. This systematic review aims to discuss the possible mechanisms involved in the pathogenesis of this syndrome. Contemplating the different reports regarding the impact of intracranial pressure (ICP), cardiovascular system, hypercapnia or glymphatic system, we hypothesize that a relationship exists between variations in ICP and SANS development. A literature search of five databases was conducted using the PICO model. Twenty studies were subsequently included, and two main theories discussed. The first suggests that cerebrospinal fluid (CSF) shifts can lead to a rise in ICP, while the second supports the importance of CSF compartmentalization, independently of ICP variation. These hypotheses are not mutually exclusive and environmental factors may also be essential for the development of this syndrome.

Long-duration spaceflight (LDSF) has a strong impact on the human body, exposing astronauts for extended periods of time to unique conditions, such as microgravity, radiation, and hypercapnia. This extreme environment leads to various health and physiologic alterations in astronauts during space missions. Following decades of human space exploration, it has been possible to identify and study several neuro-ocular findings in astronauts submitted to LDSF¹. These ophthalmic changes are called Spaceflight Associated Neuro-Ocular Syndrome (SANS), a syndrome characterized by the development of different neuro-ocular alterations, such as hyperopic refractive error shifts, optic disc edema, choroidal and retinal folds and globe flattening after LDSF².

SANS was first described in 2011, by Mader et al.², with the study and presentation of different clinical and imaging findings in seven astronauts after LDSF, and soon became one of the most important astronaut health risks identified. Five of the seven participants presented with optic disc edema, which led to the presumption that elevated intracranial pressure (ICP) could be the cause of this syndrome. Moreover, the similarities with Idiopathic Intracranial Hypertension (IIH) symptoms, such as optic nerve sheath (ONS) expansion, stasis of axoplasmic flow and globe flattening, also contributed to this theory². Consequently, this syndrome was initially termed Visual Impairment and Intracranial Pressure (VIIP) syndrome³.

However, it was noted over time that astronauts did not develop the typical symptoms of IIH, such as severe headaches, structural changes in the olfactory nerve, transient visual obscurations, or diplopia, and it remained unclear whether the optic disc edema could be considered papilledema⁴. In addition, measurement of post-LDSF ICP in astronauts has shown values considered to be only borderline high. In other words, the impact of ICP has not been significant enough to solely explain the symptoms described above⁴. The realization that the rise of intracranial pressure was not the only possible pathophysiology mechanism and with new theories strengthening the hypothesis of a multifactorial etiology, the syndrome was redefined as SANS⁵.

Although the SANS pathophysiology remains uncertain, several studies in the last decade have contributed to two main and non-mutually exclusive theories that try to explain the mechanism responsible for SANS⁴. The first considers the neuro-ocular findings to result from a rise in ICP from cerebrospinal fluid (CSF) shifts⁶. In normal terrestrial environment conditions, ICP depends on three main factors: CSF production volume, system resistance to CSF and venous pressure in the intracranial space, or equivalently, pressure in the superior longitudinal sinus⁷. Meanwhile, the second theory states that SANS can be explained by a compartmentalization of CSF in the optic

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nerve sheath^{2,8}. On the one hand, this hypothesis suggests a fragile flow equilibrium may lead to locally elevated sheath pressures, regardless of a rise, or not, of ICP, or the optic nerve and globe being retracted posteriorly due to the brain shifting upward during LDSF, and may cause localized pressure elevation and optic nerve sheath expansion⁶. On the other hand, this optic nerve compartment syndrome could be explained by the existence of a glymphatic system, responsible for the exchange of CSF with the interstitial fluid⁴.

During LDSF, astronauts are exposed to completely different and extreme conditions that can strongly impact on ICP, brain structure and CSF hemodynamics, such as changes in cerebral blood flow and glymphatic drainage, hypercapnia, intense resistive exercises, and imbalances in daily circadian cycles and genetics, among other variables. Therefore, these theories of potential pathophysiological mechanisms prove that SANS may have a multifactorial pathogenesis, strongly affected by changes in ICP and CSF shifts.

The main objective of the present study was to systematically review the scientific literature addressing the mechanisms responsible for SANS, focusing on knowledge related to the possible impact that variations in intracranial pressure can have in the development of this syndrome. Accordingly, the PI(C)O question we want to answer is **“Is the variation of ICP (I) in astronauts who undergo LDSF (P) related to the development of SANS (O)?”**

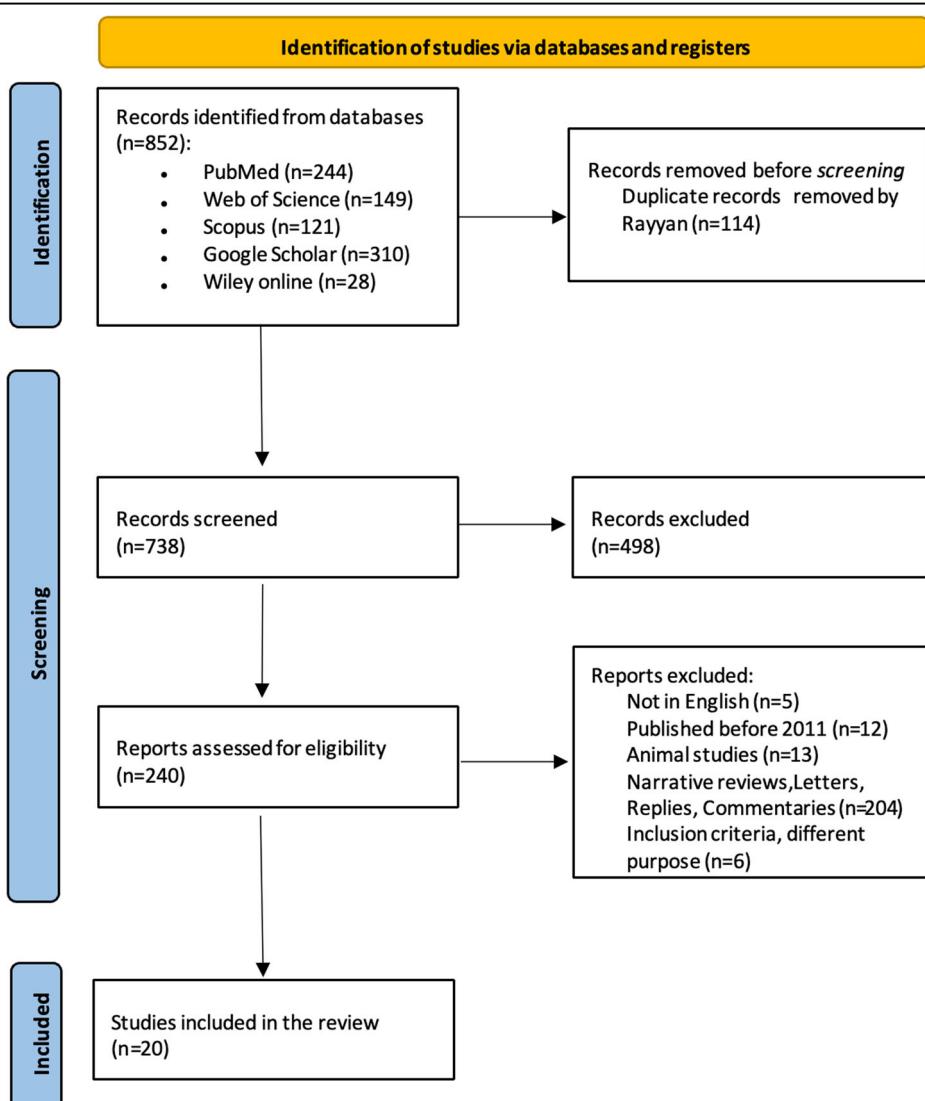
Results

Study selection

A total of 852 studies were identified after applying the keywords in several databases, of which 114 duplicates were removed before screening. The remaining 738 studies were screened independently by two reviewers, based on the title and abstract, and, following a subsequent discussion between reviewers, 240 results remained. After applying the eligibility criteria once again, a final discussion led to 20 studies being included in the review. Figure 1 summarizes this process.

Several studies met most of the inclusion criteria but were excluded for other reasons (referred to on the flow diagram as “inclusion criteria, but different purpose”). “Spaceflight-Associated Brain White Matter Micro-structural Changes and Intracranial Fluid Redistribution”⁶, “Effects of Spaceflight Stressors on Brain Volume, Microstructure, and Intracranial Fluid Distribution”⁸ and “Association of Structural Changes in the Brain and Retina After Long-Duration Spaceflight”⁹ were centered on describing how the brain structures change after spaceflight and not on SANS itself. The main focus of “Mechanical countermeasures to headward fluid shifts”¹⁰, “Effect of Nightly Lower Body Negative Pressure on Choroid Engorgement in a Model of Spaceflight-Associated Neuro-ocular Syndrome”¹¹ and “Daily generation of a footward fluid shift attenuates ocular changes associated with head-down tilt (HDT) bed rest”¹² focused more on the description of different countermeasures.

Fig. 1 | Overview of the research method, based on the PRISMA flow diagram. Summary of the different research steps followed to choose the final included studies.



Study Characteristics

Table 1 summarizes all of the study characteristics (title, doi, authors, month and year of publication, country, journal and type of study design), organized by date of publication.

Risk of bias in studies

Considering the non-randomized studies, six of the eleven were considered to have a “Moderate” risk of confounding bias due to insufficient information regarding the control for any post-intervention variables that could have been affected by the intervention. No apparent source of bias was identified in the selection of study participants, classification of interventions, deviations from the intended interventions, or due to missing data in all the included studies. When talking about bias in the measurement of the outcome, six studies were also considered to have a “Moderate” risk, as the assessors were aware of the intervention received by study participants, and it is believed that outcome measures could be minimally influenced by knowledge of the intervention received. In relation to any bias in the selection of the reported result, Ombergen et al.¹³ and Mader et al.¹⁴ presented a “Moderate” and “Serious” risk, respectively. The former was considered as “Moderate” risk due to the existence of different subgroups, while the latter was considered to have a “Serious” risk of bias due to multiple outcome measurements within the outcome domain and different subgroups. Finally, the overall risk of bias was “Low” for all, except Mader et al.¹⁴, which was considered “Moderate” due to the combination of a “Moderate” risk of confounding bias and in outcome measurement, together with a “Serious” risk of bias in the selection of the reported result. This information is displayed in Figs. 2 and 3.

In relation to the randomized studies, two^{15,16} of the three were considered to have “Some concerns” about the randomization process due to insufficient information for the allocation sequence. All three studies were evaluated as having “Some concerns” in relation to the bias risk due to deviations from the intended interventions, since in these studies, the participants, carers and people delivering the intervention were aware of the interventions assigned to participants. It was concluded that all had a “Low” risk of bias due to missing outcomes. The study by Scott et al.¹⁵ was considered to have “Some concerns” and “High” risk of bias in terms of the measurement of outcome, and in the selection of the reported result, respectively. These conclusions were drawn from this study as, not only were the assessors aware of the intervention, there was a higher probability that outcomes could have been influenced by having this knowledge of the intervention received. Moreover, the numerical results being assessed were likely selected, based on the results from multiple eligible analyses of the data. Accordingly, Scott et al.¹⁵ was considered to have “Some concerns” in the overall risk, while the other studies were considered to have a “Low” overall risk. This information is displayed in Figs. 4 and 5.

All three of the systematic reviews included were considered to have a “Low” risk of bias when contemplating the eligibility criteria and identification and selection of studies. In regards to the data collection and study appraisal domain, the review by Elwy et al.⁵ was concluded to have an “Uncertain” risk of bias due to insufficient information about the criteria to assess bias risk or methodological study and to minimize the errors associated with its assessment. Furthermore, both Galdamez et al.¹⁷ and Paez et al.⁴ were considered to have “High” risk for this parameter as the risk of bias was not formally assessed, and its criteria not defined. Considering the synthesis and findings domain, Galdamez et al.¹⁷ and Elwy et al.⁵ both lacked description regarding following analysis and biases in primary studies, indicating an “Uncertain” risk of bias, whereas, Paez et al.⁴ was considered “High” risk due to insufficient details in the analysis while addressing the synthesis and biases. Finally, the systematic reviews by Galdamez et al.¹⁷ and Elwy et al.⁵ have a “Low” risk of bias, while Paez et al.⁴ has a “High” risk of bias. This information is displayed in Fig. 6.

Of the two cohort studies included, Wählén et al.¹⁸ was considered of “Good quality”, fulfilling eight of the nine criteria, while Rosenberg et al.¹⁹ was noted as “Fair Quality”, fulfilling six of the criteria but having a lack of information for the selection parameter. The only case report, Mader et al.¹,

was “Included” through satisfying all the criteria that formed part of the respective evaluation scale.

Results of syntheses

The research synthesis for the present review was conducted based on analysis of each included article and subsequent creation of Table 2, in which a description, main findings and significance of each study were summarized by the reviewers.

Discussion

Summary of evidence and interpretation

Visual Impairment and Intracranial Pressure (VIIP) was the first denomination of this syndrome, since it was thought that the permanent elevation of Intracranial pressure during spaceflight was the pathophysiological mechanism responsible for SANS. Mader et al.², the first group to report this syndrome, in 2011, followed up seven astronauts who had experienced a LDSF. Several neuro-ocular changes, such as optic disc edema, choroidal folds and hyperopic shift, were described after 6 months of spaceflight, while a post-flight lumbar puncture also revealed five of the group to have increased ICP². Therefore, it was hypothesized that, during spaceflight, there was a mild, but chronic elevation in ICP. This raised ICP was then transmitted to the globe via the optic nerve sheath⁴, becoming responsible for the ocular changes also seen in pathologies associated with elevated ICP on Earth, such as Idiopathic Intracranial Hypertension²⁰. In this theory, it is believed that the microgravity environment leads to increased venous outflow resistance from the head, causing increased cerebral venous pressure and decreased CSF resorption, and, consequently, a rise of ICP⁴.

Iwasaki et al.²¹ sought to validate this hypothesis by noninvasively estimating ICP (nICP) in 11 astronauts, before and shortly after spaceflight, using transcranial doppler to measure blood flow. This study showed that supine nICP decreased or remained unchanged in 10 of the 11 participants after spaceflight and that it increased and decreased in the two astronauts who developed neuro-ocular changes. However, the investigators concluded that any change, such as structural ocular findings or elevation of mean cerebral blood velocity in the middle cerebral artery, occurred independently of the variations in nICP²¹.

In 2020, a longitudinal follow up conducted by the same Mader et al.² group, identified persistent globe flattening in three of the seven astronauts from the 2011 report. Aside from this alteration, no other symptoms, such as transient visual obscurations, headaches, diplopia, pulsatile tinnitus or vision changes with eye movement, were reported by the astronauts during their space missions, as well as no complaint of any symptoms associated with increased ICP¹⁴.

Another report also related neuro-ocular changes with ICP through studying a subset of LDSF astronauts. It observed that only one subject with significant retinal thickening, diagnosed with Frisen grade 1 optic disc edema, also displayed the largest bilateral increases in ONS area, compared to the other participants, however, the increase was considered relatively small in comparison to clinical populations with increased ICP²².

Opportunities to conduct research with astronauts are limited, therefore, several researchers over the years have tried other ways to corroborate the hypothesis described above. Lawley et al.²³ were the first to directly measure ICP in humans, during zero gravity (0 G) and prolonged simulated microgravity. These investigators placed a fluid-filled 25 g butterfly needle into the Ommaya reservoir inserted in 8 participants, following a single intravenous dose of cefazolin, and studied them in different conditions. During the 0 G phase of parabolic flight, ICP decreased, compared to the supine posture. A more significant variation in ICP was noted during a prolonged microgravity exposure countermeasure achieved through a -6° head-down tilt position, which mimics spaceflight only in terms of fluid pressure and flow dynamics⁵. In the first seconds, ICP suffered a slight increase in every participant. After 3 hours, the ICP returned to the supine value, reducing through the night and increasing again to baseline supine values by the end of 24 hours of HDT²³.

Table 1 | General characteristics of the included papers (title, DOI, authors, month and year, country, journal and study design)

a)						
Title	Optic Disc Edema, Globe Flattening, Choroidal Folds, and Hyperopic Shifts Observed in Astronauts after Long-duration Space Flight ¹	Optic Disc Edema in an Astronaut After Repeat Long-duration Space Flight ²³	Effect of gravity and microgravity on intracranial pressure ²³	Effects of short-term mild hypercapnia during head-down tilt on intracranial pressure and ocular structures in healthy human subjects ³¹		
DOI	https://doi.org/10.1016/j.jophtha.2011.06.021	https://doi.org/10.1097/MNO.0b0.13631829b41a6	https://doi.org/10.1111/JP273557	https://doi.org/10.1481/phy2.13.02		
Authors	Thomas H. Mader, C. Robert Gibson, Anastas F. Pass, Andrew G. Lee, Hanspeter E. Klier, Hans-Christian Hansen, Joseph P. Dervay, Douglas R. Hamilton, Ashot Sargsyan, John L. Phillips, Duc Tran, William Lipsky, Jung Choi, Claudia Stern, Raffi Kuyumjian, James D. Polk	Thomas H. Mader, C. Robert Gibson, Anastas F. Pass, Andrew G. Lee, Hanspeter E. Klier, Hans-Christian Hansen, Joseph P. Dervay, Michael R. Barratt, William J. Tarver, Ashot E. Sargsyan, John A. Kramer, Roy Riascos, Deepak G. Bedi, Donald R. Pettit	Justin S. Lawley, Lorraine G. Petersen, Erin J. Howden, Satyam Sarma, William K. Cornwell, 3, Rong Zhang, Louis A. Whitworth, Michael A. Williams, Benjamin D. Levine	Steven S. Laurie, Giannarco Vizzari, Giovanni Taibbi, Connor R. Ferguson, Xiao Hu, Stuart M. C. Lee, Robert Ploutz-Snyder, Scott M. Smith, Sara R. Zwart and Michael B. Stenger		
Month, Year	October, 2011	September, 2013	February, 2017	May, 2017		
Country	USA	USA	USA	USA		
Journal	American Academy of Ophthalmology	Journal of Neuro-Ophthalmology	The Journal of Physiology	Physiological Reports		
Study design	Retrospective, non-randomized study	Case study	Non-randomized study	Non-randomized study		
b)						
Title	Association of Exercise and Swimming Goggles With Modulation of Cerebro-ocular Hemodynamics and Pressures in a Model of SANS ¹⁵	Brain ventricular volume changes induced by long-duration spaceflight ¹³	Hypercapnia augments resistive exercise-induced elevations in intraocular pressure (IOP) in older individuals ¹⁶	Origins of Cerebral Edema: Implications for SANS ¹⁷		
DOI	https://doi.org/10.1001/jamaophth.halmol.2019.0459	https://doi.org/10.1073/pnas.1820354116	https://doi.org/10.1113/EP088236	https://doi.org/10.1097/MNO.00000000000000852		
Authors	Jessica M. Scott, Wesley J. Tucker, David Martin, James B. Crouse, Elizabeth Goettsch, Omar Ozgur, Scott Hamilton, Christian Otto, Rebecca Gonzales, Monica Ritter, Nathaniel Newby, John DeWitt, Michael B. Stenger, Robert Ploutz-Snyder, Lori Ploutz-Snyder, William H. Morgan, Mark J. Haykovsky	Angélique Van Ombergen, Steven Jilgins, Ben Jeurissen, Elena Tomilovskaya, Alena Rumshiskaya, Liudmila Litvinova, Inna Nosikova, Ekaterina Pechenkova, Ilya Rukavishnikov, Olga Manko, Sergey Danylichev, R. Maxine Ruhn, Inessa B. Kozlovskaya, Stefan Sundert, Paul M. Panzel, Valentin Sintsov, Steven Laureys, Jan Sijbers, Peter zu Eulenburg, and Floris L. Wuyts	Igor B. Mekjavić, Winfried Arnošački, Tinkara Mlinar, Polona Mekjavić	Laura A. Galadamez, MD, FAWM, Tyson J. Brunstetter, OD, PhD, Andrew G. Lee, MD, William J. Tarver, MD, MPH		
Month, Year	April, 2019	May, 2019	February, 2020	March 2020		
Country	USA	USA	UK, Slovenia	USA		
Journal	JAMA Ophthalmology	PNAS	Experimental Physiology	Neuro-Ophthalmology		
Study design	Randomized study	Non-randomized study	Randomized study	Systematic review		
c)						
Title	Spaceflight induces peripapillary edema ³⁸	Visual changes after space flight: is it really caused by increased intracranial tension? A systematic review ⁵	Optic Nerve Length before and after Spaceflight ¹⁸	Persistent Globe Flattening in Astronauts following Long-Duration Spaceflight ¹⁴		
DOI	https://doi.org/10.1001/jamaophth.halmol.2020.0673	https://doi.org/10.23736/S03905616.20.04927-9	https://doi.org/10.1016/j.joptha.2020.07.007	https://doi.org/10.1080/01658107.2020.1791189		
Authors	B.R. Macias, N. Patel, C. Gibson, B. Samuels, C. Otto, S.M.C. Lee, R. Ploutz-Snyder, A. Sargsyan, D. Alexander, L. Kramer, R. Riascos, S.S. Laurie, T.H. Mader, T. Brunstetter, and M.B. Stenger	Reem Ewly, Mohamed A. Soliman, Amr A. Hasnain, Ahmad A. Ezzat, Mohammad Elbaroudy, Mohamed F. Alisawy, Ehab El Retaee	Anders Wärnlin, Petter Holmlund, Abigail M. Fellows, Jan Malm, MD, Jay C. Buckley, Anders Eklund	Thomas H. Mader, C. Robert Gibson, Michael R. Barratt, Neil R. Miller, Prem S. Subramanian, Hanspeter E. Klier, William J. Tarver, Ashot E. Sargsyan, Kathleen Garcia, Stephen F. Hart, Larry A. Kramer, Roy Riascos, Tyson J. Brunstetter, William Lipsky, Peter Wostyn and Andrew G. Lee		

Table 1 (continued) | General characteristics of the included papers (title, DOI, authors, month and year, country, journal and study design)

c)	Title	Spaceflight induces peripapillary edema ²⁶	Visual changes after space flight: is it really caused by increased intracranial tension? A systematic review ⁵	Optic Nerve Length before and after Spaceflight ¹⁸	Persistent Globe Flattening in Astronauts following Long-Duration Spaceflight ¹⁴
Month, Year	April, 2020		April, 2020	July, 2020	September, 2020
Country	USA	Italy	Journal of Neurosurgical Sciences	USA	USA
Journal	Ophthalmology		Systematic review	Ophthalmology	Neuro-Ophthalmology
Study design	Non-randomized study			Cohort study	Non-randomized study
d)	Title	Quantitative magnetic resonance image (MRI) assessment of the optic nerve and surrounding sheath after spaceflight ²²	Spaceflight Associated NeuroOcular Syndrome (SANS): A Systematic Review and Future Directions ⁴	Altered cerebral perfusion in response to chronic mild hypcapnia and head-down tilt Bed rest as an analog for Spaceflight ³⁰	Long-duration spaceflight alters estimated intracranial pressure and cerebral blood velocity ²¹
DOI		https://doi.org/10.1038/s41526020-00119-3	https://doi.org/10.2147/EB.S234076	https://doi.org/10.1007/s00234021-02660-8	https://doi.org/10.1111/JP280318
Authors	Jesse J. Rohr, Stuart Sater, Austin M. Sass, Karina Marshall-Goebel, Robert J. Ploutz-Snyder, C. Ross Ethier, Michael B. Stenger, Bryn A. Martin and Brandon R. Macias	Yosbelkyvs Martin Paez, Lucy J Mudie, Prem S Subramanian	Donna R. Roberts, Heather R. Collins, Jessica K. Lee, James A. Taylor, Matthew Turner, Greg Zaharchuk, Max Wintermark, Michael U. Antonucci, Edwin R. Mulder, Darius A. Gehach, David Asemani, Heather R. McGregor, Rachael D. Seidler	Ken-ichi Iwasaki, Yojiro Ogawa, Takuwa Kurazumi, Syed M. Imaduddin, Chiaki Mukai, Satoshi Furukawa, Ryo Yanagida, Tomokazu Kato, Toru Konishi, Aki Shingjima, Benjamin D. Levine, Thomas Heldt	
Month, Year	October, 2020		October, 2020	January 2021	February, 2021
Country	USA	USA	USA	USA	USA, Japan
Journal	NPJ Microgravity		Eye and Brain	Neuroradiology	The Journal of Physiology
Study design	Non-randomized study		Systematic review	Non-randomized study	Non-randomized study
e)	Title	MRI-based quantification of ophthalmic changes in healthy volunteers during acute 15° headdown tilt as an analogue to Microgravity ²⁴	Longitudinal change in ventricular volume is accelerated in astronauts undergoing long-duration spaceflight ³⁸	Effects of Venoconstrictive Thigh Cuffs on Dry Immersion-Induced Ophthalmological Changes ²⁵	Comparison of Dural Venous Sinus Volumes Before and After Flight in Astronauts With and Without Spaceflight-Associated NeuroOcular Syndrome ¹⁹
DOI		https://doi.org/10.1098/rsif.2020.03920	https://doi.org/10.1016/j.nbs.2022.11.00017	https://doi.org/10.3389/fphys.2022.1.692361	https://doi.org/10.1001/janatnet.workopen.2021.31465
Authors	Stuart H. Sater, Austin M. Sass, Akari Seiner, Gabryel Conley, Natividad, Dev Shrestha, Audrey Q. Fu, John N. Oshinski, C. Ross Ethier and Bryn A. Martin	Donna R. Roberts, Dani C. Inglesby, Truman R. Brown, Heather R. Collins, Mark A. Eckert, David Asemani	Marc Kermorgant, Ayria Sadegh, Thomas Geeraerts, Fanny Varenne, Jérémie Liberto, François-Philippe Roubalat, Noémie Bataille, Marie-Pierre Barelle, Amaud Beck, Brigitte Godard, Adriano Golemis, Nathalie Nasr, Dina N. Arvanitis, Ophélie Hélissen, Jean-Michel Senard, Anne Payr-Le Traon, Vincent Soler	Mark J. Rosenberg, Michael A. Coker, James A. Taylor, Milad Jazdani, M. Gisele Matheus, Christopher K. Blouin, Sami Al Kasab, Heather R. Collins, Donna R. Roberts	
Month, Year	April, 2021		May, 2021	July, 2021	October, 2021
Country	USA	USA	USA	France	USA
Journal	Journal Royal Society - Interface		Aging brain	Frontiers in Physiology	JAMA Network Open
Study design	Non-randomized study		Non-randomized study	Randomized study	Retrospective cohort study

a)– General characteristics of the included papers (title, DOI, authors, month and year, country, journal and study design). b)– General characteristics of the included papers (title, DOI, authors, month and year, country, journal and study design). c)– General characteristics of the included papers (title, DOI, authors, month and year, country, journal and study design). d)– General characteristics of the included papers (title, DOI, authors, month and year, country, journal and study design). e)– General characteristics of the included papers (title, DOI, authors, month and year, country, journal and study design)

Fig. 2 | Risk of bias summary of the included non-randomized studies. Overview of the non-randomized studies risk of bias, illustrated by ROBINS-I traffic light plot bias assessment, obtained using the Robvis web-app studies.

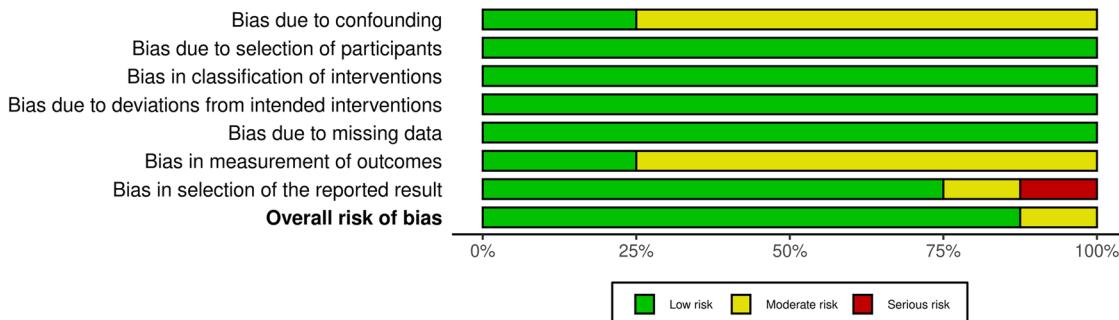
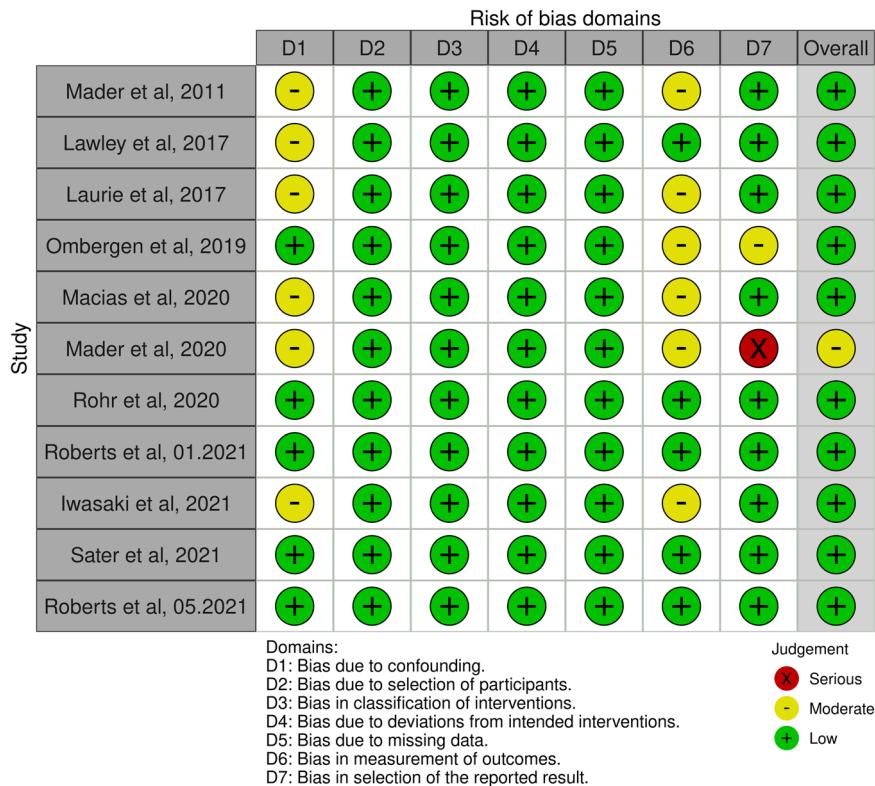
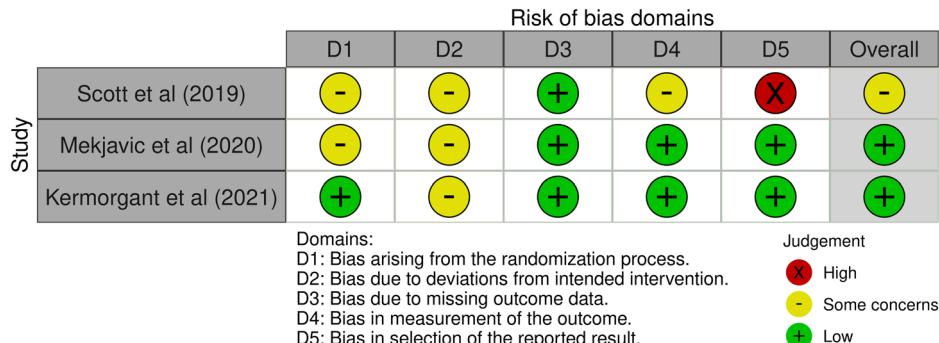


Fig. 3 | Risk of bias summary of the included non-randomized studies. Overview of the non-randomized studies risk of bias, illustrated by ROBINS-I weighted values according to sample size bias assessment, obtained using the Robvis web-app.

Fig. 4 | Risk of bias summary of the included randomized studies. Overview of the randomized studies risk of bias, illustrated by RoB 2 traffic light plot bias assessment, obtained using the Robvis web-app.



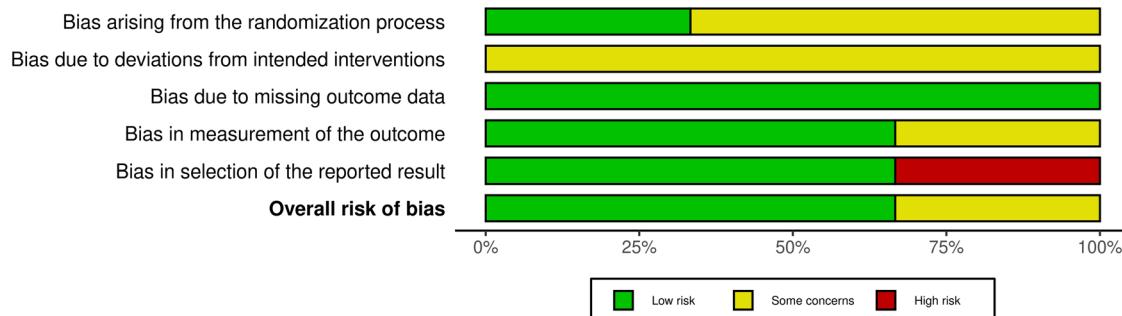
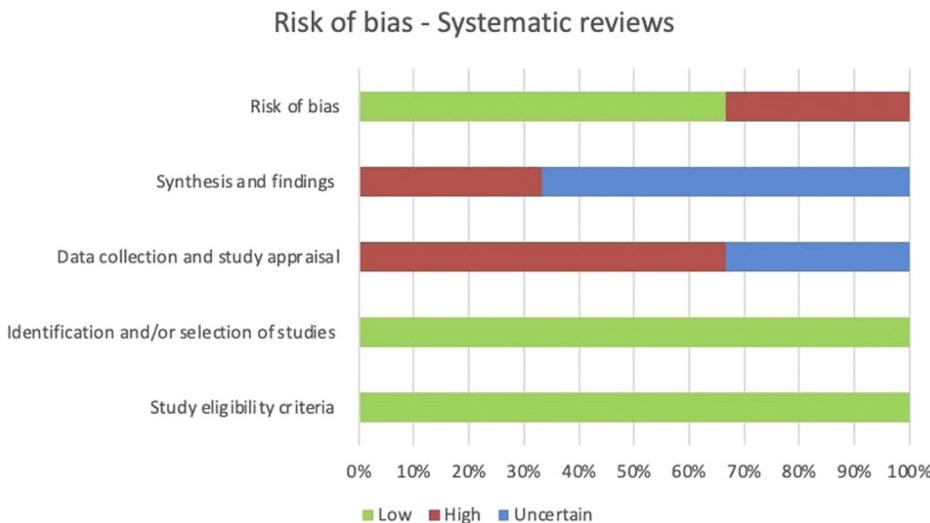


Fig. 5 | Risk of bias summary of the included randomized studies. Overview of the randomized studies risk of bias, illustrated by RoB 2 weighted values according to sample size, obtained using the Robvis web-app.

Fig. 6 | Risk of bias summary of the included systematic reviews. Overview of the systematic reviews risk of bias, illustrated by ROBIS weighted values according to sample size.



Using -15° HDT, a report showed a mismatch between arterial inflow and venous outflow, with a phenotype consistent with venous congestion, suggesting that venous engorgement is associated with increased jugular venous pressure (JVP) and cerebral venous congestion^{15,19}. These can then result in a rise in ICP that may be transferred to the ONS, leading to ONS expansion, stasis of axoplasmic flow and globe flattening³. Using the same kind of countermeasure, Sater et al.²⁴ studied possible changes of the optic nerve and ONS, seen by MRI. No change in the optic nerve area was found, but there were important increases in optic nerve deviations and ONS area, suggesting that CSF pressures were elevated during HDT. Kermorgant et al.²⁵ reported a small increase in ONS diameter and found a decrease in intraocular pressure (IOP)²⁴ when using dry-immersion as a microgravity analog. Thus, a spectrum of results can be seen from the above-described studies that try to correlate ICP and SANS. In general, the results do not reinforce the theory that ICP is pathologically elevated in microgravity, indeed to the contrary, they suggest the possibility of other factors existing that are involved in the development of SANS.

A second theory that tries to explain the development of SANS is the compartmentalization of CSF within the orbital subarachnoid space³, in which a one-way valve mechanism traps pressurized CSF within the optic nerve and ONS, without requiring elevated ICP⁴. This hypothesis is explained by several possible mechanisms, the first one being based on MRI findings showing an upward shift of the brain, with a retraction posteriorly of the optic nerve and globe⁴. Wåhlin et al.¹⁸ supported this theory through a study involving 22 astronauts that showed the optic nerve to be structurally altered after spaceflight. More precisely, they detected an anterior displacement of the optic nerve head (related to mission duration), superior

displacement of the optic chiasm, and an overall increase in length of the optic nerve. However, they could not prove these alterations were caused by general white matter swelling, associated with CSF¹⁸.

Research by Ombergren et al.¹³ using MRI exams of a group of astronauts before and after LDSF found an increased ventricular CSF volume in supratentorial ventricular structures, with results revealing that the greater the lateral ventricular expansion, the more visual acuity was decreased postflight¹³. Findings from another report showed the development of significant peripapillary neural, retinal, and choroid tissue thickening in both eyes during early spaceflight, persisting throughout the mission²⁶. Furthermore, the authors discuss the limitation of axoplasmic flow when CSF is chronically elevated, which can result in neuronal swelling of retinal nerve fibers. Additionally, the headward fluid shift could result in a chronic elevation of arterial or venous pressure at the optic nerve head, increasing local capillary filtration and, consequently, contributing to edema formation or direct compression of neural tissue^{17,26,27}.

One of the astronauts accompanied by Mader et al.¹⁴ presented with postflight unilateral disc swelling, asymmetric globe flattening and ONS expansion. These findings suggest asymmetric CSF flow, volume and pressure changes within the ONS that worsened during LDSF, which supports the idea of asymmetric CSF flow along the ONS cul-de-sac and CSF compartmentalization. These investigators also reached the same conclusion earlier, in 2013, when one of the astronauts returning from LDSF presented with unilateral disc swelling and unilateral loss of spontaneous venous pulsations in the same eye¹.

The second mechanism that tries to explain this optic nerve compartment syndrome is the existence of a glymphatic system, responsible for

Table 2 | Results and analysis of the included papers, presenting the studies description, main findings and significance

a)	Author, year	Mader et al. ²	Mader et al. ¹	Lawley et al. ²³	Laurie et al. ³¹
Description	Analysis of ophthalmic findings in 7 astronauts and of postflight questionnaires about vision changes in 300 astronauts.	Case study of an astronaut with 2 long-duration (6 months) exposures to microgravity, with complete eye examination and brain imaging.		Collection of data on changes in ICP in 4 different conditions (change from sitting to spine position, parabolic flight, prolonged exposure to simulated microgravity with -6° HDT and with hypercapnia), in 8 participants.	Investigation of possible mechanisms for ocular changes, using 6° HDT, in 8 male subjects, during three 1 h conditions (seated, HDT and HDT + CO2).
Main findings	1. After 6 months of spaceflight, all 7 astronauts had ophthalmic findings. 2. The 300 postflight questionnaires documented a significant percentage of astronauts as experiencing a degradation in distant and near visual acuity.	1. After his first long-duration mission, the astronaut was documented as having eye findings limited to unilateral choroidal folds and a single cotton wool spot. 2. During a subsequent 6-month mission, the astronaut developed more widespread choroidal folds and new onset of optic disc edema in the same eye.	1. ICP was lower when seated in the 90° upright posture compared to lying supine. 2. In the supine posture, central venous pressure and ICP were reduced in acute zero gravity. 3. Prolonged periods of simulated microgravity did not cause progressive elevations in ICP. 4. Complete removal of gravity does not pathologically elevate ICP but does prevent the normal lowering of ICP when upright.	1. Relative to the seated position, IOP, ICP, ONS diameter (ONSD) and subfoveal choroidal thickness increased and TLPD decreased during HDT. 2. During HDT + CO2, IOP increased. 3. Between the HDT conditions, TLPD maintained unchanged. 4. Visual acuity and ocular structures did not change across conditions. 5. Genetic polymorphisms were associated with differences in IOP, ICP and end-tidal PCO2.	
Significance	The first study to report neuroocular changes in astronauts after LDSF.	Documents the recurrence of ophthalmological changes in an astronaut after a second LDSF.	First study to measure directly ICP during weightlessness conditions.	Reports that the combination of mild hypercapnia with an acute headward fluid shift (HDT) does not increase cardiovascular outcomes, ICP and TLPD.	
b)	Author, year	Scott et al. ¹⁵	Ombergren et al. ¹³	Mekhavić et al. ¹⁶	Galdamez et al. ¹⁷
Description	Analysis of the effect of exercise, supine posture, -15° HDT and aerobic in 22 participants and the use of swimming goggles in 10 participants, on cerebro-ocular hemodynamic and ICP.	Study to assess and quantify ventricular volume changes in cosmonauts and give an analysis of CSF spaces derived from structural MRI brain scans before, shortly after, and 7 months after LDSF.		This study assesses the effect on IOP of 6° head down prone tilt during rest and exercise, in normocapnic and hypercapnic conditions, in 10 participants.	Systematic review of the literature published about the pathophysiology of cerebral and optic disc edema.
Main findings	1. 15° HDT showed increased IOP and JVP and decreased TLPG. 2. Exercise at -15° HDT presented decreased IOP and TLPG. 3. Both IOP and TLPG were higher in participants who wore swimming goggles compared with those not wearing goggles. 4. Exercise was associated with decreased IOP and estimated transmamillary pressure gradient in HDT, while the addition of swimming goggles was associated with increased IOP and TLPG in HDT.	1. Found an increased ventricular CSF volume after spaceflight in supratentorial ventricular structures, while the infratentorial fourth ventricle was not enlarged. 2. Found a progressive enlargement of the subarachnoid CSF space. 3. Periventricular white matter changes might be a direct consequence of transependymal water diffusion from the enlarged ventricles into periventricular structures, due to pressure peaks in a backed-up CSF circulation.	1. In the prone 6° HDT position, IOP increased. 2. Normocapnic isometric exercise caused a significant increase in MAP, with a corresponding increase in IOP. 3. Hypercapnia did not significantly modify the responses of MAP, but increased the IOP response. 4. Substantial individual variation in the IOP response was observed.	1. Cerebral edema occurs through redistribution of ions and water intracellularly and displacement of ions and water from the vascular compartment to the brain parenchyma. 2. Venous and local circulatory stasis in the optic nerve head may lead to increased hydrostatic pressure and local ATP depletion resulting in increased oxidative stress and inflammation, in SANS.	
Significance	Establishes a relation between exercise, neuro-ocular changes and ICP.	Study, in first-hand, the ventricular volume changes in cosmonauts, analyzing MRI brain scans.	Uses LDSF and exercise, in an environment with CO2 variations, as a countermeasure to study the alterations associated with SANS.	Studies the pathophysiology of cerebral and optic disc edema and its relation to SANS.	
c)	Author, year	Macias et al. ²⁶	Elwy et al. ⁵	Wählin et al. ¹⁸	Mader et al. ¹⁴
Description	This study quantifies changes in ocular structures of 11 astronauts, testing before, during, and up to 1 year after LDSF.	Systematic review of literature contrasting simulation and spaceflight studies, focusing on the pathophysiology of SANS.	Registration of pre- and post-spaceflight MRI scans and generation of representations of the optic nerve, of 22 astronauts.	Report of the long-term follow-up and persistence of globe flattening and hyperopic refractive shifts for 7 years or more following LDSF in 3 of the 7 astronauts described in Mader et al. ² .	

Table 2 (continued) | Results and analysis of the included papers, presenting the studies description, main findings and significance

c)	Author, year	Macias et al. ²⁶	Elwy et al. ⁵	Wählin et al. ¹⁸	Mader et al. ¹⁴
Main findings		1. Optic nerve head rim tissue and peripapillary choroidal thickness increased significantly during spaceflight. 2. Spaceflight induced significant thickening of retinal tissue layers near the optic nerve head and choroidal engorgement early in flight that progressively increased across the mission. 3. Chronic elevation in retrobulbar cerebrospinal fluid pressure and/or engorgement of the choroidal vasculature may directly deform tissues at the optic nerve head.	1. Intracranial filling pressure reflects changes in intracranial tissue volumes. 2. ICP is proportional to the pressure gradient driving CSF flow through the resistance of its anatomical pathways and that of the absorptive arachnoid villi. 3. Microgravity prevents circadian variations in ICP, possibly inducing the ophthalmic and ICP changes. 4. Microgravity may alter intraorbital flow dynamics resulting in compartmentalized optic nerve compression, independent of ICP.	1. Optic nerve length increased, reflecting forward optic nerve head displacement. 2. Upward displacement of the optic chiasm was detected, indicative of brain movement, but it was not possible to correlate it with the development of SANS. 3. Elevated ONS pressures, during LDSF, may create sufficient mechanical stress on the sclera to cause permanent structural change with secondary globe flattening in the absence of persistent orbital subarachnoid space pressure elevation.	1. Report of persistent globe flattening after LDSF. 2. Permanent structural change may result from elevated CSF pressures within the ONS in SANS. 3. Elevated ONS pressures, during LDSF, may create sufficient mechanical stress on the sclera to cause permanent structural change with secondary globe flattening in the absence of persistent orbital subarachnoid space pressure elevation.
Significance		Documents spaceflight-induced optic disc edema and ocular changes, post-flight recovery and the consequences after spaceflight.	Shows that ICP and ophthalmic effects of microgravity increase with duration of exposure.	Establishes a relationship between optic nerve structural alterations, ICP and the development of SANS.	Suggests that pre-existing increased ICP, asymmetric ONS structure or globe flattening may pre-dispose to prominent anatomic changes.
d)	Author, year	Rohr et al. ²²	Paez et al. ⁴	Roberts et al, 2021a ³⁰	Iwasaki et al. ²¹
Description		Quantitative analysis of optic nerve and ONS cross-sectional areas, and optic nerve tortuosity, in 10 astronauts before and after spaceflight (6-month missions).	Systematic review of current body of literature surrounding SANS.	Compares cerebral perfusion before, during, and after HDT + CO ₂ in participants who developed SANS (n = 5) with those who did not (n = 6).	Using a model-based analysis of cerebral blood velocity and arterial blood pressure waveforms, intracranial pressure was estimated noninvasively in 11 astronauts, before and after LDSF.
Main findings		1. Most individuals did not have changes in ONS anatomy after LDSF. 2. The single subject diagnosed with grade 1 optic disc edema had an optic nerve cross-sectional area reduction and displayed the largest increases in ONS cross-sectional area. 3. The degree of optic nerve deviation lacked correlation with ONS cross-sectional area. 4. Optic nerve cross-sectional area tended to decrease in our cohort immediately post-flight.	1. Two major hypotheses exist for SANS: elevated ICP and compartmentalization of CSF to the globe and optic nerve. These are not mutually exclusive. 2. Determination of ICP during LDSF remains a challenge to be met and represents a critical need with respect to understanding SANS pathophysiology and designing interventions.	1. All participants had a decrease in perfusion during HDT + CO ₂ . 2. The SANS group had a reduction in perfusion earlier than the non-SANS group. 3. In contrast, by day 29 of HDT + CO ₂ , the SANS group had significantly higher perfusion than the non-SANS group. 4. Inverse correlation between increased mean MCAV and decreased Hb concentration.	1. Supine nICP decreased or did not change after spaceflight. 2. No link between the change in supine nICP and the development of ocular changes. 3. Mean Cerebral blood velocity in the MCA (MCAV) increased after spaceflight independently of the nICP changes and ocular alterations. 4. Inverse correlation between increased mean MCAV and decreased Hb concentration.
Significance		Establishes a relation between changes in optic nerve tortuosity and ONS distension and cerebrospinal fluid dynamics.	Provides the literature about the pathophysiology of SANS, the technology and potential countermeasures and treatment.	Shows that the combination of strict HDT along with chronic CO ₂ results in altered cerebral perfusion that is SANS dependent.	Compares ICP values before and after spaceflight.
e)	Author, year	Sater et al. ²⁴	Roberts et al, 2021b ³⁶	Kermorgant et al. ²⁵	Rosenberg et al. ¹⁹
Description		This study developed non-invasive magnetic resonance imaging-based techniques to quantify ophthalmic structural changes under acute 15° HDT.	Comparison of percent ventricular volume change per year (PVVC/yr) documented on pre- to post-flight MRI in 18 astronauts with two groups who underwent longitudinal MRI.	Analysis of the possible neuroophthalmological impact of microgravity, through a microgravity analog (dry-immersion), in 18 participants.	Quantitative and qualitative assessments of the intracranial venous system on preflight and postflight MR venograms in 12 astronauts.
Main findings		1. Under HDT, - ONS cross-sectional area and optic nerve deviation increased. - Optic nerve cross-sectional area remained unchanged. - Vitreous chamber depth decreased. 2. The significant ONS distension identified in this study, in HDT subjects, potentially supports that	1. Concerning total ventricular volume change, astronauts showed a significantly greater increase in PVVC/yr. 2. As the older adults had larger total ventricular volumes at baseline, there was no significant difference in total ventricular volume change per year between both groups. 3. 7 astronauts presented features of SANS following spaceflight. These 7 astronauts had	1. Higher thickness of the retinal nerve fiber layer (RNFL) in the temporal quadrant was observed after dry-immersion (D). 2. ONSD increased significantly during D and remained higher during the recovery phase. 3. IOP did not significantly change during and after D.	1. Astronauts who presented clinically with SANS had enlargement of the dural venous sinuses consistent with intracranial venous congestion 2. There was no evidence of intracranial dural venous sinus thrombosis.

Table 2 (continued) | Results and analysis of the included papers, presenting the studies description, main findings and significance

e)	Author, year	Sater et al. ²⁴	Roberts et al, 2021b ³⁶	Kernmorgant et al. ²⁵	Rosenberg et al. ¹⁹
	HDT could result in a higher ICP than would be expected in microgravity.	significantly smaller total PVVC/yr. 4. PVVC/yr appeared to be inversely associated with SANS.	Reports that astronauts who were in LDSF experienced an annual rate of ventricular expansion more than three times than expected from normal aging.	Utilizes a microgravity analog to study its impact on IOP and establishes a relation with ICP and SANS.	This study suggests an association between intracranial venous congestion and SANS.
Significance	First study to measure optic nerve area during HDT.				

a) – Results and analysis of the included papers, presenting the studies description, main findings and significance. b) – Results and analysis of the included papers, presenting the studies description, main findings and significance. c) – Results and analysis of the included papers, presenting the studies description, main findings and significance. d) – Results and analysis of the included papers, presenting the studies description, main findings and significance. e) – Results and analysis of the included papers, presenting the studies description, main findings and significance

the exchange of CSF with interstitial fluid⁴. Wostyn et al.²⁸ hypothesized that the glymphatic outflow from the eye into the optic nerve might be blocked under prolonged microgravity conditions, since elevation of ONS pressure due to a rise in ICP or sequestration of CSF within the orbital subarachnoid space, might lead to a reduction or reversal of the normal posteriorly directed trans-lamina pressure difference (TLPD). This results in fluid stasis within the prelaminar optic nerve head, and, consequently, various degrees of papillary edema can be seen without an increase in ICP²⁹. Macias et al.²⁶ noted that the lack of a retinal-blood barrier in the prelaminar region of the optic nerve head may be associated with greater extravasation of fluid due to the headward fluid shift in weightlessness, and may be a contributing factor to the retinal thickening quantified in this location^{26,28}. It is therefore understandable that gravitational dependency for the functioning of the glymphatic system³⁰ may exist.

In addition to the aforementioned theories and considering the variety of conditions affecting the spaceflight environment, many other factors for the development of SANS and variations in ICP have been proposed. Laurie et al.³¹ studied hypercapnia, one of the most important environmental conditions on the International Space Station (ISS), where values of CO₂ can be 15-20 times higher than found on Earth¹⁶. The investigators compared the effects of 60 minutes acute exposure to a seated position breathing room air, -6° HDT breathing room air, and -6° HDT breathing 1% CO₂ (HDT + CO₂). A small increase in IOP was found after HDT, in comparison to seated, while the addition of CO₂ to HDT resulted in a significant increase in IOP. A significant rise in nICP was seen in HDT, when compared to seated, however, no difference was found between HDT and HDT + CO₂. No participant showed significant ophthalmic changes³¹.

Roberts et al. (2021a)³⁰ developed a study with a similar countermeasure (-6°HDT + 0.5% CO₂), but the 11 participants were exposed to the conditions for 30 days. No neurological symptoms of chronic hypercapnia were revealed, however, 5 subjects developed optic disc edema. These same participants also presented a greater decrease in perfusion, when compared to the rest of the group, progressively recovering towards the end of the exposure³⁰. Comparing these two studies and knowing that CO₂ has a strong impact on cerebrovascular modulation, we believe a time effect on the progression of neuro-ocular changes may exist, and CO₂ may be an important environmental factor for the development of SANS.

Another risk factor associated with LDSF is the intense resistive and aerobic exercise that astronauts must practice 6 days per week, for at least two hours a day. Mekjavić et al.¹⁶, using HDT, sought to observe the acute effect of isometric exercise. Their findings showed that exercise caused a significant increase in mean arterial pressure (MAP), as well as an increase in IOP. Scott et al.¹⁵ used the same countermeasure, but with additional participant exposure to moderate-intensity aerobic, resistance, or high-intensity interval aerobic exercise. Interestingly, compared with HDT rest, they observed a decrease in IOP during HDT exercises. Fischman et al.³² exposed six volunteers to low level resistance exercise on the Advanced Resistive Exercise Device (ARED), and measured noninvasive ICP, assessing tympanic membrane displacement (Vm) in the inner ear following auditory stimulus. Knowing that Vm and ICP have an inverse relationship, a slight decrease in Vm in the supine position was observed, indicating a nonsignificant increase in ICP. The authors suggest that the use of ARED is unlikely to have a prominent impact on the development of SANS during spaceflight³². These divergent results highlight the current lack of understanding and need for more studies when discussing the effect of exercise on astronaut cerebro-ocular hemodynamics.

A further important topic to consider in relation to astronauts as individuals is genetics. As already mentioned, not all astronauts develop ophthalmic symptoms and neuro-ocular changes, which could suggest the possibility of existing predisposing factors that increase susceptibility. The one-carbon metabolic pathway and its link with single-nucleotide polymorphisms (SNPs) has been associated with genetic differences between astronauts and the development, or not, of neuro-ocular alterations, such as choroidal fold, optic disc edema and cotton-wool spots³¹. A study in which individuals bearing the GG allele of the MTRR 66 gene (associated with

ocular alterations) were identified, grouped the participants according to their genetic polymorphisms (SNP+ and SNP-) and exposed them to HDT + CO₂. The results revealed both groups to demonstrate a similar TLPD and no differences in cerebral blood flow and nICP were seen during HDT + CO₂³¹.

As previously stated, SANS is one of the biggest causes of concern for aerospace professionals, so further research to gain a better understanding of its development and consequences becomes very important. The present review systematically analyzed data about SANS and its development, reporting information on variations in ICP and how this relates to the other theories regarding SANS pathophysiology. Considering all the information discussed above, we believe that SANS has a multifactorial etiology, where ICP variation and its relationship with CSF shifts and compartmentalization, together with environmental factors have an important influence on the development of neuro-ocular changes.

We believe this work gives an interesting view on the development of this syndrome and provides a step forward to better understand it. We further recognize how essential it is to study astronauts and to find new ways of analyzing, in real-time, the alterations that occur during spaceflight.

Methods

This systematic review was structured according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 checklist³³.

Eligibility Criteria

Inclusion and exclusion criteria were defined before the study selection process, respecting the PICO method³⁴. The inclusion criteria considered all clinical trials, cohort studies, case studies and systematic reviews that discussed SANS and its pathophysiology, established a relationship with ICP variation and/or CSF fluid shifts and/or studied neuro-ocular changes in the spaceflight environment or analog conditions and countermeasures. Furthermore, all studies were required to be in English and published in 2011 or after.

Studies that did not discuss SANS or the effect of microgravity and space environmental conditions on astronaut health were not considered. Animal studies, narrative reviews, background literature, letters, editorials, reports, thesis, and commentaries were also excluded from our review. Studies that met the inclusion criteria, but were considered by the reviewers to be unclear, insufficient, or did not add new data for the analysis were excluded.

Information sources and Search Strategy

The search was conducted in five databases, PubMed, Web of Science, Scopus, Google Scholar and Wiley Online Library. The search terms used were “Brain”, “Neuroocular”, “Astronaut”, “Spaceflight” and “Microgravity”. In all five databases, the search strategy was based on applying the keywords in the following way: “((brain) and (eye) or (neuro-ocular)) AND ((astronaut) or (spaceflight) or (microgravity))”. The search was conducted in August 2022.

The search returned 244 results in Pubmed, 149 in Web of Science, 121 in Scopus, 310 in Google Scholar and 28 in Wiley Online. The 852 results were then imported to RAYYAN³⁵, a systematic review screening software and automation tool, to remove duplicates. The remaining 738 results were subsequently screened for inclusion by two reviewers.

Selection and data collection processes

Two reviewers (GR and EO) worked independently, applying, individually, the inclusion and exclusion criteria to the 738 results. An important factor in permitting this independent work was the blinding (each reviewer worked without access to the other reviewer's work), made possible by using the Rayyan tool. Firstly, each reviewer applied the eligibility criteria based on the titles and abstracts of each result. If this information was not sufficient for decision-making, the study would have a full-text review. Coincidentally, each reviewer

included 250 results and excluded 488. After screening and the final discussion between reviewers, 240 results were included and 498 excluded.

Following the screening process, the studies were again included or excluded based on the study type. Additionally, the two reviewers read all the studies and applied the eligibility criteria, excluding those articles that did not consider a relationship between the findings and SANS and/or ICP. Six studies met the inclusion criteria but were excluded based on different reasons. Therefore, after this final selection and discussion between the reviewers, 20 studies were included.

Data items

Population (P) data comprised of all astronauts who had completed a long-duration spaceflight and developed neuro-ocular symptoms, independently of gender, age or background.

Intervention (I) data comprised of the descriptions about ICP variations in the different conditions, such as spaceflight and countermeasures.

Comparison (C) data comprised of all astronauts who completed a long-duration spaceflight and did not develop neuro-ocular symptoms, independently of gender, age or background.

Outcomes (O) data comprised of the development of SANS and description of different neuro-ocular findings, after spaceflight or analogs.

Data on general information (title, DOI, authors, year, month and country), type of publication, and study characteristics (study design) were also extracted. Where data was missing, protocols and project overviews cited were consulted.

Study risk of bias assessment

Two independent reviewers (GR and EO) carried out a risk of bias assessment. The included research articles were divided according to study type.

The risk of bias of the eleven non-randomized studies^{2,13,14,21–24,26,30,31,36} was evaluated using the “ROBINS-I” tool, developed by the BMJ³⁷. This tool evaluates the presence of bias due to confounding (D1), due to the selection of study participants (D2), in classification of interventions (D3), due to deviations from intended interventions (D4), due to missing data (D5), in measurement of outcomes (D6), and in the selection of the reported result (D7). Each parameter and the overall study were then rated using a scale comprising of “Low risk”, “Moderate risk”, “Serious risk”, and “Critical risk” of bias levels, as well as a “No information” level, for risk of bias assessment. The “Robvis” web-app was then used to create risk of bias plots for our study, to present the results of the risk of bias assessment³⁸.

The risk of bias assessment for the three randomized trials^{15,16,25} was performed using the “RoB 2 tool”³⁹. This instrument evaluates the presence of bias arising from the randomization process (D1), due to deviations from intended interventions (D2), due to missing outcome data (D3), in measurement of the outcome (D4) and in selection of the reported result (D5). Each parameter and the overall study were then evaluated according to a scale comprising of “Low”, “Some concerns” and “High” risk of bias levels. The “Robvis” web-app was then used to create risk of bias plots for our study, to present the results of the risk of bias assessment³⁸.

The “ROBIS” tool, developed by Bristol Medical School⁴⁰, was used to assess the risk of bias of the three systematic reviews^{4,5,17}. This tool evaluates the presence of Concerns regarding Study eligibility criteria, Identification and selection of studies, Data collection and study appraisal, and Synthesis and findings. Each parameter and the overall study were then evaluated in a scale with “Low”, “High” and “Uncertain” risk of bias levels.

The Newcastle-Ottawa Quality Assessment Form⁴¹ was used to evaluate the risk of bias of the two cohort studies^{18,19}. This form evaluates the quality of Selection (Representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure and demonstration of the outcome of interest), Comparability (Comparability of Cohorts on the Basis of the Design or Analysis) and Outcome (Assessment of Outcome, duration of follow-up and Adequacy of Follow-up of Cohorts). After the evaluation of each parameter, the quality of the study is designated as “Good”, “Fair” or “Poor”.

The risk of bias of the only case study¹ was evaluated using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Reports⁴². This tool evaluates the demographic characteristics, description of patient history, presentation of the current clinical condition, description of diagnostic/treatment procedures, description of post-intervention clinical condition, adverse effects, and takeaway lessons of the report. The end results in a decision to “Include”, “Exclude” or “Seek further information”.

Any disagreement between the two reviewers concerning risk of bias assessment was resolved through discussion. Consensus was reached on all articles included in the review.

Synthesis methods

The research synthesis for the present review was conducted based on analysis of each included article and subsequent creation of Table 2, in which the main findings and significance of each study were summarized by the reviewers.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon request.

Code availability

No code was developed during the analysis and review of this manuscript.

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Author contributions

Gabriela Alves Rodrigues, the main author, was responsible for the search and selection of studies and writing the article, under the supervision of Thaís Russomano and Edson Santos Oliveira, who also contributed to the study inclusion process and article review. All authors have read and approved the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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