Acta Astronautica 232 (2025) 296–306

Contents lists available at ScienceDirect

Acta Astronautica

journal homepage: www.elsevier.com/locate/actaastro

The protective effects of hyperbaric oxygen on ionising radiation injury: A systematic review

Amanda Holyer [a,*], Thomas Stewart [b], Edward T. Ashworth [c,d]

[a] Auckland University of Technology, Auckland, New Zealand
[b] AUT Human Potential Centre, School of Sport and Recreation, AUT University, New Zealand
[c] Department of Emergency Medicine, University of California San Diego, USA
[d] Te Pūnaha Ātea – Space Institute, University of Auckland, New Zealand

ARTICLE INFO

Keywords:
Hyperbaric oxygen
Ionising radiation
Space flight
Health

ABSTRACT

This systematic review evaluates the efficacy of hyperbaric oxygen therapy (HBOT) on treating ionising radiation injuries and discusses its applicability to space exploration. As human missions venture beyond Earth's magnetic field, astronauts are increasingly exposed to harmful levels of ionising radiation, posing significant health risks. Hyperbaric oxygen therapy, which has been traditionally used for treating diving illnesses and refractory wounds, could also be used to mitigate the effects of ionising radiation. A comprehensive systematic literature search was conducted using the Ovid and PubMed (MEDLINE) databases. Studies were examined to assess the effect of HBOT on different anatomical regions exposed to ionising radiation. Study quality was determined using the Risk of Bias Assessment Tool for Nonrandomized Studies (RoBANS), with random-effect estimates performed in R. While HBOT upregulates signalling factors beneficial for healing, only modest physical changes are seen at the cellular or tissue level on the timescales employed in current research. HBOT has potential benefits in the abdominal-pelvic and lower limb regions but complexities of HBOT's effects on bone health may invoke risks, such as radio-sensitisation of the spinal cord. While HBOT may offer some therapeutic benefits, its application to space flight requires careful consideration due to the unique challenges of space and the whole-body nature of space radiation. Effective strategies for maintaining astronaut health and safety during long-duration deep-space missions are still required.

1. Introduction

As humanity ventures beyond Earth's protective magnetic field in pursuit of space exploration, the physiological challenges and medical requirements of astronauts evolve accordingly. One significant challenge is the exposure to harmful levels of whole-body ionising radiation during missions to Mars or deep space [1,2]. This radiation, comprising galactic cosmic rays and solar particle events, stems from interstellar phenomena where atoms are stripped of electrons and accelerated to high velocities to produce free protons, alpha particles, and highly energetic, heavy charged (HZE) particles [3]. These particles, upon interacting with biological cells, can lead to severe health risks including tissue damage, cellular dysfunction, radiation sickness, and carcinogenesis [4,5]. The resultant DNA damage, particularly double-strand breaks, can impair cellular and organ function, posing a dire threat to astronaut health [6].

To counter these risks, strategies to mitigate ionising radiation injury are paramount. While mission planning and spacecraft design can reduce radiation exposure, the inevitability of some level of exposure necessitates effective treatment methods. Hyperbaric oxygen therapy (HBOT), a treatment traditionally associated with decompression sickness and refractory wounds, involves administering 100 % oxygen at an elevated barometric pressure, to increase tissue oxygenation and enhance the immune response [7,8]. The versatility of spacecraft design, particularly the presence of an airlock, offers a unique opportunity to utilise a pressurised compartment as an ad-hoc hyperbaric chamber, potentially providing a feasible solution for radiation injuries in space [9]. However, the effectiveness of HBOT in treating ionising radiation injuries, particularly in the context of space exploration, remains a subject of debate as research outcomes are equivocal [10,11].

Therefore, we systemically reviewed and performed a descriptive synthesis on the available literature to determine the viability of HBOT

* Corresponding author. 17 Antares Place, Rosedale, 0632, Auckland, New Zealand.
E-mail address: amanda.holyer98@gmail.com (A. Holyer).

https://doi.org/10.1016/j.actaastro.2025.03.011
Received 11 November 2024; Received in revised form 26 February 2025; Accepted 11 March 2025
Available online 18 March 2025

as a tool for treating ionising radiation injuries. This research will contribute to the body of evidence on the possible benefits of HBOT in spaceflight and long-duration missions beyond Earth's gravity.

2. Methods

2.1. Search strategy

A comprehensive, systematic literature search was conducted in November 2022 and repeated in October 2023 using the electronic databases Ovid and PubMed (MEDLINE). These databases were searched due to their extensive coverage of biomedical and life science literature. The search strategy employed specific terms related to radiation (e.g. "ionising radiation", "radiation injury"), hyperbaric oxygen therapy (e.g. "hyperbaric oxygen", "HBOT"), and randomised controlled trials (e.g. "randomised controlled trial", "clinical trial"), and were combined using Boolean operators. The exact combination of these terms, along with variations and Boolean logic, is detailed in Appendix A – Search strategy. The search was not restricted by publication date or language. The initial criteria for inclusion were studies that addressed the effects of hyperbaric oxygen therapy on ionising radiation injuries.

2.2. Selection criteria

Study selection criteria was informed by the PICOS (Population, Intervention, Comparison, Outcomes, Study Design) framework:

Population (P): Studies involving both human subjects and animal models were included. The inclusion of animal studies was intended to provide a broader understanding of the biological mechanisms and potential translational applications of HBOT in the context of ionising radiation exposure.

Intervention (I): The intervention of interest was HBOT administered prior to, during, or after partial or whole-body exposure to ionising radiation. Studies where HBOT was combined with other therapies were excluded unless the effect of HBOT could be isolated.

Comparison (C): The comparison group included subjects who received ionising radiation, but either had baseline measurements prior to HBOT intervention (within-subject) or were randomised to not receive HBOT in a clinical trial (between-subjects). Studies where the comparison group received a different form of intervention were excluded.

Outcomes (O): Relevant outcomes included health-related measurements, encompassing functional, anatomical, biochemical, and symptomatic assessments, and quality of life indicators. Studies focusing solely on theoretical or mechanistic outcomes without clear health-related implications were excluded.

Study Design (S): All experimental designs.

2.3. Study selection

Studies meeting the PICOS criteria were imported into Rayyan (Web Rayyan QCRI) for screening [12]. Two independent reviewers conducted the screening (AH and DS), with any disagreements resolved by consulting a third reviewer (EA). The process included removing

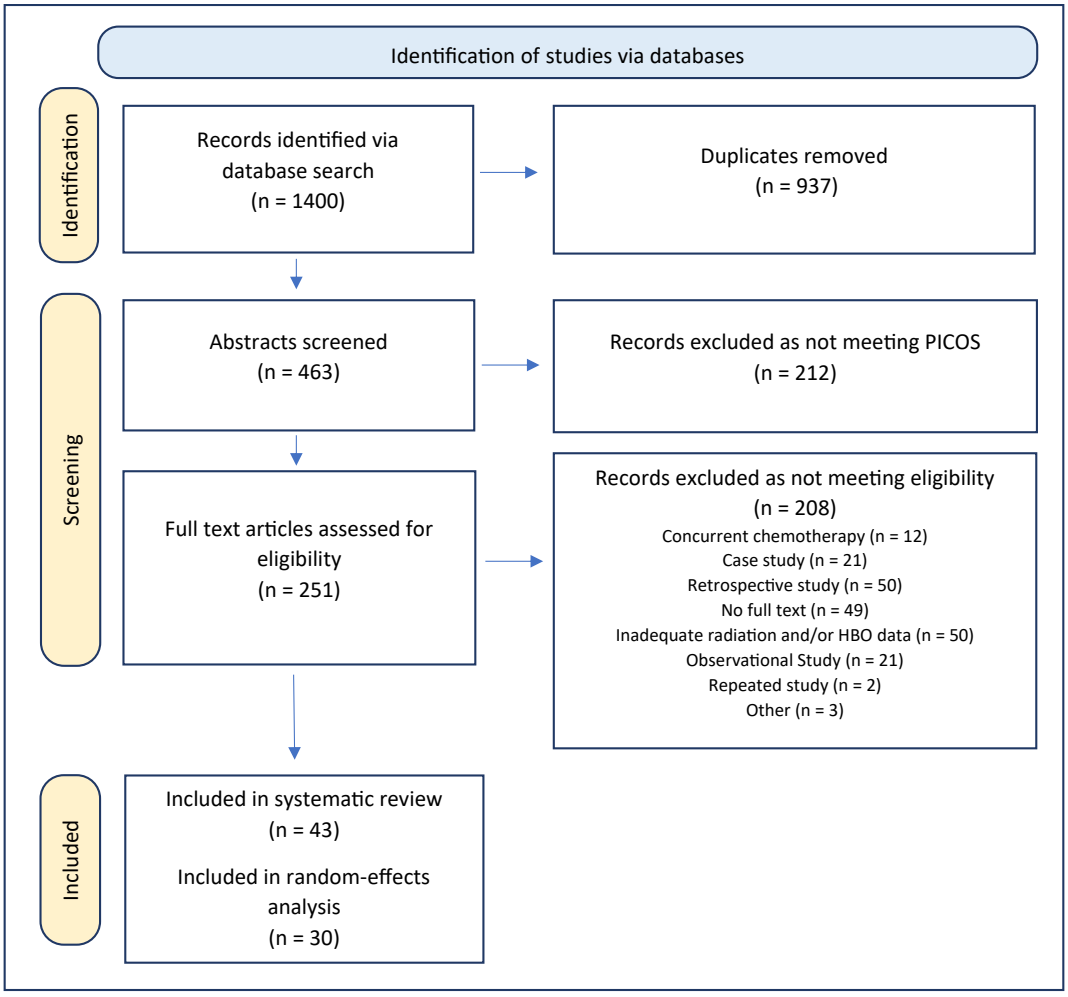

Fig. 1. Prisma flowchart summarising the literature search and screening process.

duplicates, followed by screening titles and abstracts. Criteria for this screening phase focused on relevance to the topic, and population characteristics. The full texts of the remaining articles were then assessed for inclusion. Studies were excluded if they met any of the following criteria: participants received concurrent chemotherapy or other therapies/drugs potentially affecting HBOT results; radiation exposure was non-ionising; articles in languages other than English without available translations; insufficient radiation or HBOT data; and reviews and theoretical analyses, case studies, observational studies, and retrospective study designs. These exclusions were documented in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) flowchart (Fig. 1).

2.4. Data extraction

Data was extracted from the selected studies using a modified version of the Space Biomedicine Systematic Review 'Data extraction and analysis' tool [13]. This tool was selected for its comprehensive approach to extracting relevant data in space biomedicine research. Data extraction from eligible articles encompassed key study details such as sample size, study design, subject characteristics (i.e. human or animal), details of the HBOT (i.e. frequency and duration of treatment, atmospheric pressure of chamber) and radiation exposure (dose measured in grays [*Gy*]), measured outcomes, and reported results. All outcome variables that met the PICOS inclusion criteria were extracted from eligible studies (i.e. functional; anatomical; biochemical health-related measurements; symptomatic assessments; quality of life indicators). Given the broad scope of these outcome variables, they were categorised by body region: head and neck; abdominal-pelvic region; spine; or lower limb. Body regions were chosen as whole body radiation exposure is rare; almost all study subjects received radiation at a specific site on the body.

2.5. Data synthesis

Means, standard deviations and sample sizes for each outcome were extracted from each study (Appendix B – Data table: random-effects analysis). In cases where standard deviations were not reported, they were calculated from confidence intervals or standard error values following Cochrane guidelines [14]. WebPlotDigitiser was used to estimate the data from studies that presented results solely in graphical formats [15]. Effect sizes were calculated via the *metafor* package, employing the *escalc* function for standardised mean differences (i.e. Hedges *g*; Equation A). This involved analysing the mean values, standard deviations, and sample sizes from HBOT and control groups.

2.6. Descriptive synthesis

A descriptive synthesis of the data was carried out to provide pooled effect sizes of the effects of HBOT on radiation injury. This is akin to a meta-analysis, although the lack of homogeneity in study methods and outcome assessments prevents the pooled and weighted quantification of a meta-analysis from being meaningful. All analysis was performed in R (v 3.6.1). The *metacont* function from the *meta* package generated a random-effects model for each grouping of variables (Appendix D). Extracted data was grouped by body region (i.e. head and neck, spine, abdominal-pelvic, lower limb) if possible, and a separate analysis was performed for each body region. Therefore, the mean random-effect produced by the analysis can be interpreted as the average HBOT treatment effect for all outcomes measured at that body region. A separate model was fit for each of the four body regions, and for the body mass outcome (which could not be assigned to a specific body region). A prediction interval was calculated for each of the five random-effect models; this is defined as the interval within which the effect size of a new study would fall if this study was selected at random from the same population of the studies already included in the analysis. Results are displayed in forest plots using the *forestplot* package, which effectively displays the effect sizes (Hedges *g*) for each study.

The heterogeneity of outcome measures across studies was reported when appropriate (i.e., >2 studies looking at the same variable). Two statistical methods were used to assess study heterogeneity: I^2 statistic and τ^2 (tau-squared). The I^2 statistic quantifies the proportion of total variation across studies that is due to heterogeneity rather than chance. An I^2 value of 0 % indicates no observed heterogeneity, and 25 %, 50 %, and 75 % were interpreted as low, moderate, and high heterogeneity, respectively [16]. Whereas τ^2 represents the between-study variance in the random-effects analysis. It provides an estimate of the actual variance of true effect sizes across studies. A larger τ^2 value suggests more variability in effect sizes between the studies, indicating a more diverse set of study results that may stem from different populations, interventions, methodologies, or study designs.

2.7. Assessment of study quality

To evaluate study quality and potential risk of bias, the Risk of Bias Assessment Tool for Nonrandomized Studies (RoBANS) was employed [17]. Despite focusing on randomised controlled trials, RoBANS was selected due to its comprehensive assessment across multiple domains relevant to this study. Each study was assessed in six domains: selection of participants, confounding variables, measurement of intervention (exposure), blinding of outcome assessments, completeness of outcome data, and selective outcome reporting. These domains were each assigned a risk level: high, low, or unclear, based on specific criteria detailed in RoBANS [17]. Uncertainties and disagreements were solved by discussion and required a consensus by at least two reviewers (AH, DS, EA).

3. Results

3.1. Search results

The initial search yielded 1400 articles. Among these, 937 were identified as duplicates and subsequently removed. The screening process, which involved a review of titles and abstracts, led to the exclusion of an additional 212 articles. The full-text review was conducted on 251 articles, culminating in the inclusion of 41 studies for the analysis. Of these, 30 provided sufficient quantitative HBOT, ionising radiation and outcome data (i.e. n, mean, sd) for a descriptive synthesis of the data and were additionally included in the random effects modelling.

3.2. Characteristics of included studies

For detailed characteristics of the studies included in this systematic review, refer to Appendix C – Summary of included studies. This summary table comprehensively outlines each study's title, publication date, subject characteristics, radiation doses, and HBOT exposure details. Studies where quantitative data were extracted or where data were unavailable are also indicated.

3.3. Methodological quality of included studies

The risk of bias in the included studies was assessed using RoBANS (Table 1). The inability to blind participants to HBOT is a notable limitation in these studies. This factor, along with any unclear risk due to missing or inadequately reported information, played a critical role in the risk-of-bias judgments. Eighteen out of the 43 papers included in this review achieved a low risk of bias result, 13 received a moderate risk of bias score and 12 received a high risk of bias.

3.4. Outcomes

The outcome variables assessed within each study varied drastically

Table 1
Risk of bias assessment of included studies using the cochrane RoBANS tool.

Study	Selection of participants	Confounding variables	Intervention (exposure) measurement	Blinding of outcome	Incomplete outcome data	Selective outcome reporting	Overall risk of bias
Aprilli et al., 2011 [18]	Low	Low	Low	Unclear	Low	Low	Low
Cankar et al., 2011 [19]	Low	Low	High	Unclear	Low	Low	Mod
Carl et al., 2001 [20]	Low	High	High	Unclear	Low	Low	High
Celik et al., 2010 [21]	Low	Low	Unclear	Unclear	Low	Low	Low
Chen et al., 1999 [22]	Low	Low	Low	Unclear	Low	Low	Low
Clark et al., 2006 [23]	Low	Low	Low	Unclear	Low	Low	Low
Demirci et al., 2016 [24]	Low	Low	Low	Unclear	Low	Low	Low
Dische et al., 1999 [25]	Low	High	Low	Unclear	High	Low	High
Feldmeier et al., 1995 [26]	Low	Low	Low	Unclear	Low	Low	Low
Feldmeier et al., 1993 [27]	Low	Low	Low	Unclear	Low	Low	Low
Forner et al., 2019 [28]	Low	Low	High	Unclear	Low	Low	Mod
Gerlach et al., 2008 [29]	Low	Low	High	Unclear	High	Low	High
Hillard et al., 2017 [30]	Low	Low	Low	Low	Low	Low	Low
Johnson et al., 1972 [31]	Low	Low	Low	Unclear	Low	Low	Low
Johnsson et al., 2000 [32]	Low	High	Low	Low	High	Low	High
Johnsson et al., 1999 [33]	Low	Low	Low	Low	Low	Low	Low
Junior et al., 2020 [34]	Low	Low	Low	Unclear	Low	Low	Low
Konak et al., 2016 [35]	Low	Low	Low	Low	Low	Low	Low
Larsen et al., 1993 [36]	Low	Low	High	Unclear	Low	Low	Mod
Lee et al., 1994 [37]	High	High	Low	Unclear	Low	Low	High
Mayer et al., 2001 [38]	Low	High	high	Unclear	Low	Low	High
Muhonen et al., 2004 [39]	Low	Low	Low	Unclear	High	Low	Mod
Muhonen et al., 2002a [40]	Low	Low	Low	Unclear	High	Low	Mod
Muhonen et al., 2002b [41]	Low	Low	Low	Unclear	High	Low	Mod
Muhonen et al., 2002c [42]	Low	Low	Low	Unclear	High	Low	Mod
Muhonen et al., 2002d [43]	Low	High	Low	Unclear	High	Low	High
Oscarsson et al., 2013 [44]	Low	High	High	Unclear	Low	Low	High
Poulton et al., 1985 [45]	Low	Low	High	Low	Low	Low	Mod
Rud et al., 2009 [46]	Low	Low	High	Unclear	High	Low	High
Safra et al., 2008 [47]	Low	High	High	Unclear	Low	Low	High
Schoen et al., 2007 [48]	Low	Low	Low	High	High	Low	High
Schwentker et al., 1998 [49]	Low	Low	Low	Unclear	High	Low	Mod
Shao et al., 2012 [50]	Low	Low	Low	Unclear	Low	Low	Low
Shaw et al., 2019 [51]	Low	Low	Low	Low	High	Low	Mod
Sønstevold et al., 2018 [52]	Low	Low	Low	Unclear	High	Low	Mod
Spiegelberg et al., 2014a [53]	Low	Low	Low	Unclear	Low	Low	Low
Spiegelberg et al., 2014b [54]	Low	Low	Low	Unclear	Low	Low	Low
Spiegelberg et al., 2015 [55]	Low	Low	Low	Unclear	Low	Low	Low
Suzuki et al., 1998 [56]	Low	Low	High	Unclear	Low	High	High
Svalestad et al., 2014 [57]	Low	Low	High	Unclear	Low	High	High
Tumerdem-Ulug et al., 2011 [58]	Low	Low	Low	Unclear	Low	Low	Low
Vidmar et al., 2022 [59]	Low	Low	High	Unclear	Low	Low	Mod
Wang et al., 1998 [60]	Low	Low	Low	Unclear	High	Low	Mod

in both human and animal studies. Outcome variables related to 'oral function' (i.e., head and neck body region) were the most prevalent, but were also highly variable across studies. There were eight oral function outcomes that were measured in more than one study, but all of these showed conflicting results as shown in Table 2. The complete list of outcome measures is shown in Appendix C – Summary of included studies.

Table 2
Conflicting results for outcome variables related to oral function after HBOT.

Outcome	Study and result direction
Xerostomia	↑Schoen et al., 2007
	↑Gerlach et al., 2008
	↓Cankar et al., 2011
Eating	↑Shaw et al., 2019
	↓Schoen et al., 2007
Bleeding	↑Shaw et al., 2019
	↓Schoen et al., 2007
Social limitations	↑Shaw et al., 2019
	↓Schoen et al., 2007
Physical limitations	↑Shaw et al., 2019
	↓Schoen et al., 2007
Swallowing	↑Gerlach et al., 2008
	↓Schoen et al., 2007
Saliva consistency	↑Schoen et al., 2007
	↓Gerlach et al., 2008
Saliva quantity/flow	↑Gerlach et al., 2008
	↓Spiegelberg et al., 2014a

Note: ↑ = studies that showed an improvement in oral function, ↓ studies that showed no improvement or a reduction in oral function.

3.5. Random effects modelling

The random effects modelling included 30 studies, split into five subsections (body mass and the four body regions) which are presented below. The forest plots below show the outcome measure assessed in each study, the HBOT treatment details (duration in days, minutes per day in the hyperbaric chamber, and the atmospheric pressure of treatment [atmosphere absolute; ATA]), the Hedges *g* effect size of the difference between HBOT and control group, and the weighting the random-effects model applied to each study.

Five studies reported the effect of HBOT on body mass (Fig. 2). The estimated random effect size of 0.85 (95 % CI = −0.11, 1.81) indicates HBOT favours weight gain; however, the random effect size is insignificant, and the prediction interval crossing zero suggests a need for further research. The heterogeneity across the five studies was high (I^2 = 84 %; τ^2 = 0.7857).

Fourteen studies reported the effect of HBOT on various outcomes assessed at the head and neck (Fig. 3). The random effect size of 0.16 (95 % CI = −0.01, 0.34) suggests HBOT may be a favourable treatment for radiation injury in the head and neck. However, the high heterogeneity (I^2 = 76 %; τ^2 = 0.7117) and relatively small sample sizes used in each study suggest there is insufficient evidence to draw this conclusion.

The effect of HBOT on various outcomes assessed at the spine was reported by three studies (Fig. 4). The random effect size of −2.22 (95 % CI = −3.57, −0.88) suggests HBOT is not a favourable treatment for radiation injury at the spine and is likely detrimental. As above, these results should be interpreted in the context of the wide prediction interval and high heterogeneity (I^2 = 78 %; τ^2 = 1.5235).

The effect of HBOT on various outcomes assessed at the abdominal-pelvic region was reported in eight studies (Fig. 5). The random effect size of 0.93 (95 % CI = 0.56, 1.30) suggests HBOT is most likely a favourable treatment for radiation injury in this area. No individual study showed a clear negative result. Although the prediction interval generally shows a positive treatment outcome, between-study heterogeneity was still high (I^2 = 78 %; τ^2 = 0.7621).

Lastly, three studies looked at the effect of HBOT on various outcomes assessed in the lower limbs (Fig. 6). The random effect size of 0.36 (95 % CI = −0.02, 0.75) suggests that HBOT was favoured when treating radiation injury in the lower leg. Although the prediction interval and random effect size confidence intervals both crossed zero, between-study heterogeneity was low (I^2 = ~0 %; τ^2 = 0).

4. Discussion

4.1. Overall impact of HBOT on ionising radiation injury

While the overall effectiveness of HBOT in treating healthy tissue exposed to ionising radiation in humans and animals remains limited there is upregulation of signalling factors to suggest healing is being augmented. This observation is consistent with the diverse outcomes and high study heterogeneity to reflect the complexity of HBOT's mechanisms.

4.2. Spine

Although spinal radiation myelitis in rodents tended to worsen more rapidly after HBOT [27], neurologic examination found no long-term benefit or harm of HBOT before or after radiation [45], including no change in movement capability or amount of healthy tissue [30]. The rapid progression of radiation myelitis in irradiated rats subjected to HBOT concurrently or within 4 h of irradiation suggests a sensitisation of the spinal cord to radiation from HBOT and therefore should be avoided [27]. The low or moderate risk of bias assessed across these studies suggests that their findings are likely to represent the true effects of HBOT on radiation induced spinal injury.

4.3. Head and neck region

Studies identified in the review revealed that radiation-induced saliva injury in animal models remained chronic after HBOT [53,52]. However, in human head and neck cancer patients with radiation induced injuries, HBOT improved saliva quantity, and reduced oedema in the affected head and neck region [19,29,35,59]. Patients receiving HBOT after radiation treatment needed fewer nutritional supplements and reported less pain, even when administered fewer pain killers, [48]. In terms of radiation injury to the salivary gland, HBOT significantly reduced damage and inflammation [35]. The reduced inflammation is likely due to an upregulation of genes that cause capillary formation and stem cell mobilisation which act to prevent tissue fibrosis [19,28]. Future research should investigate whether these same outcomes are

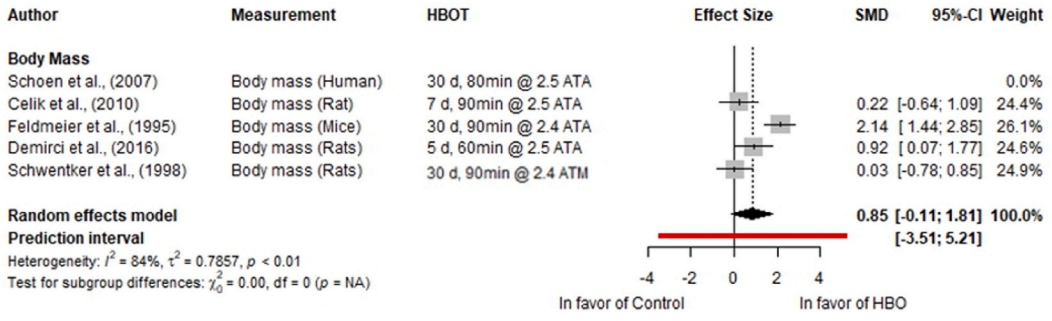

Fig. 2. Forest plot illustrating the effect of HBOT for changes in body mass. Note: when SD = 0 (no variability) data points cannot be seen in the forest plot.

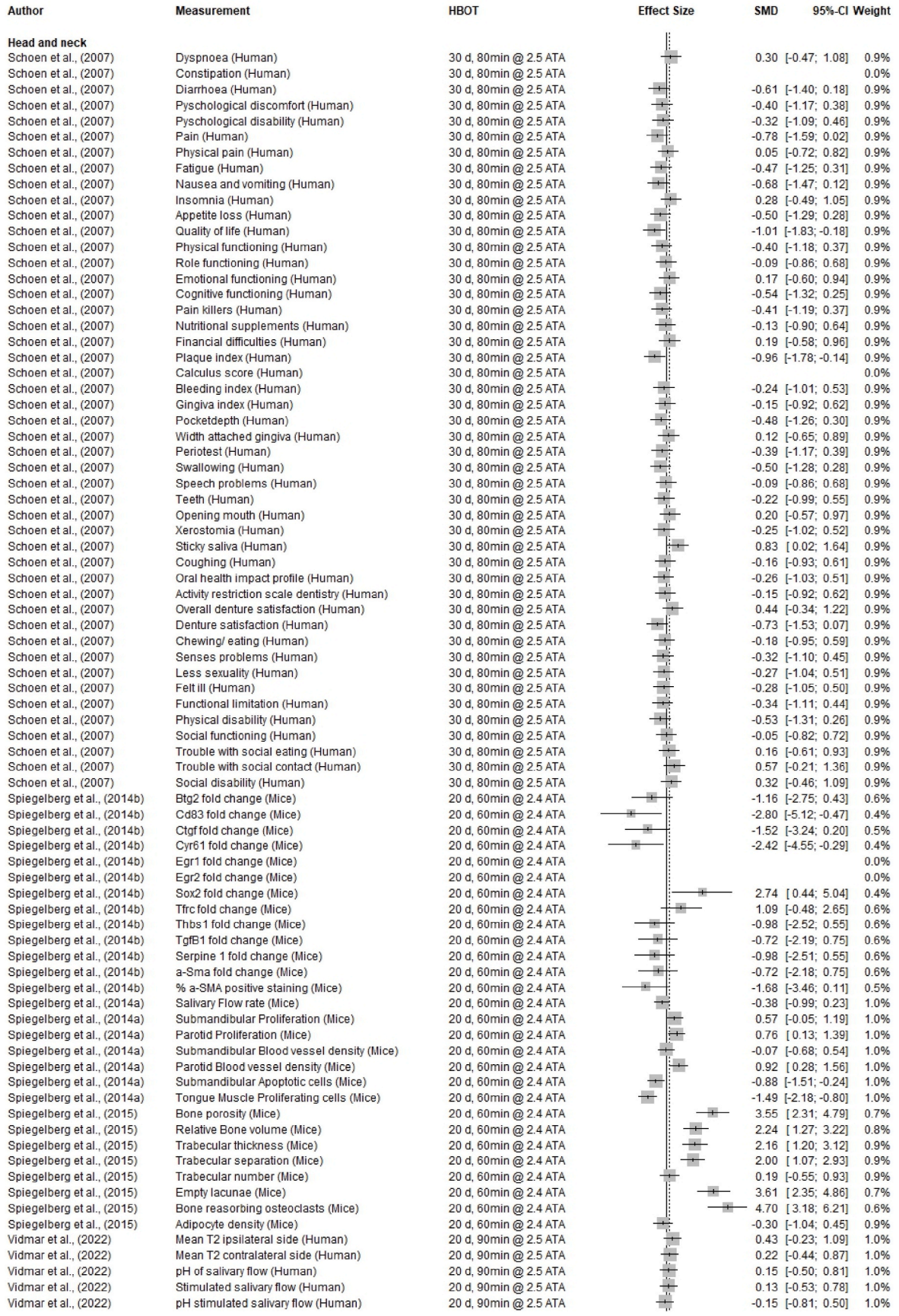

Fig. 3. Forest plot illustrating the effect of HBOT for treating ionising radiation injury outcomes at the head and neck. Note: when SD = 0 (no variability) data points cannot be seen in the forest plot.

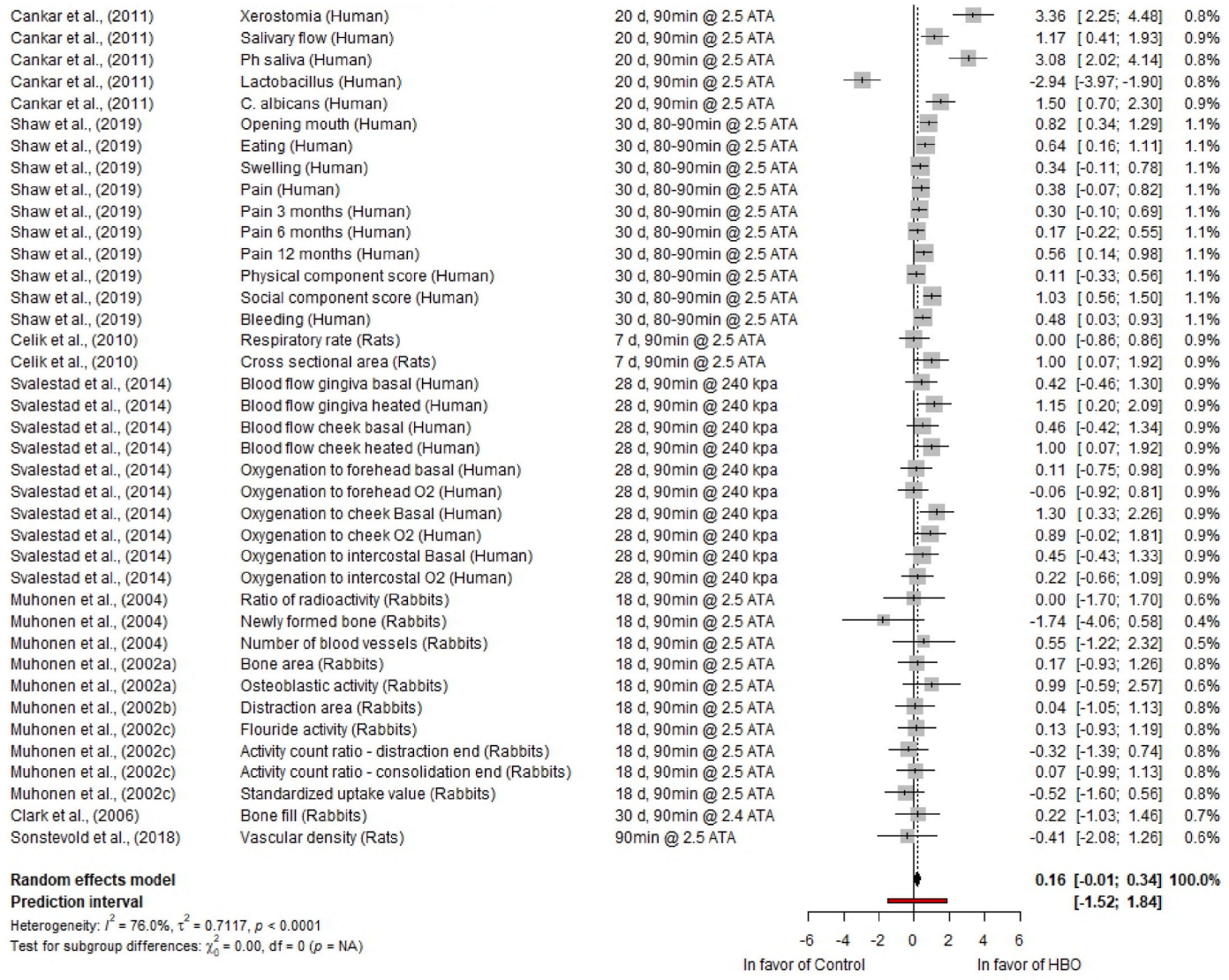

Fig. 3. (*continued*).

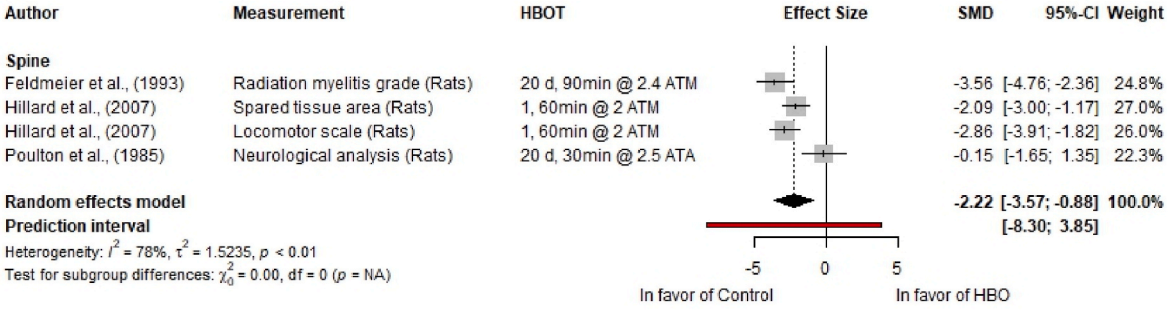

Fig. 4. Forest plot illustrating the effect of HBOT for treating ionising radiation injury outcomes at the spine.

replicated in other tissues, as the whole-body impact of HBOT would indicate widespread effects throughout the body.

In general, studies on human and rat mandibles suggest that while HBOT might not significantly prevent osteoradionecrosis (bone death) [52,51], it could potentially enhance osteoblastic activity (formation of new bone) over a longer period [23,40,42,55]. Muhonen et al. (2004) [39] and Svalestad et al. (2014) [57] supported the idea that with time, HBOT might positively impact bone-forming activity, blood vessel growth and tissue healing, but only one study on bone has looked beyond two months. With the exception of Spiegelberg et al. (2014a) [53], konak et al. (2016) [35] and Clark et al. (2006) [23], the moderate to high risk of bias across these studies reduces confidence in these results. To make more reliable claims, further research with stronger study designs and lower risk of bias is essential.

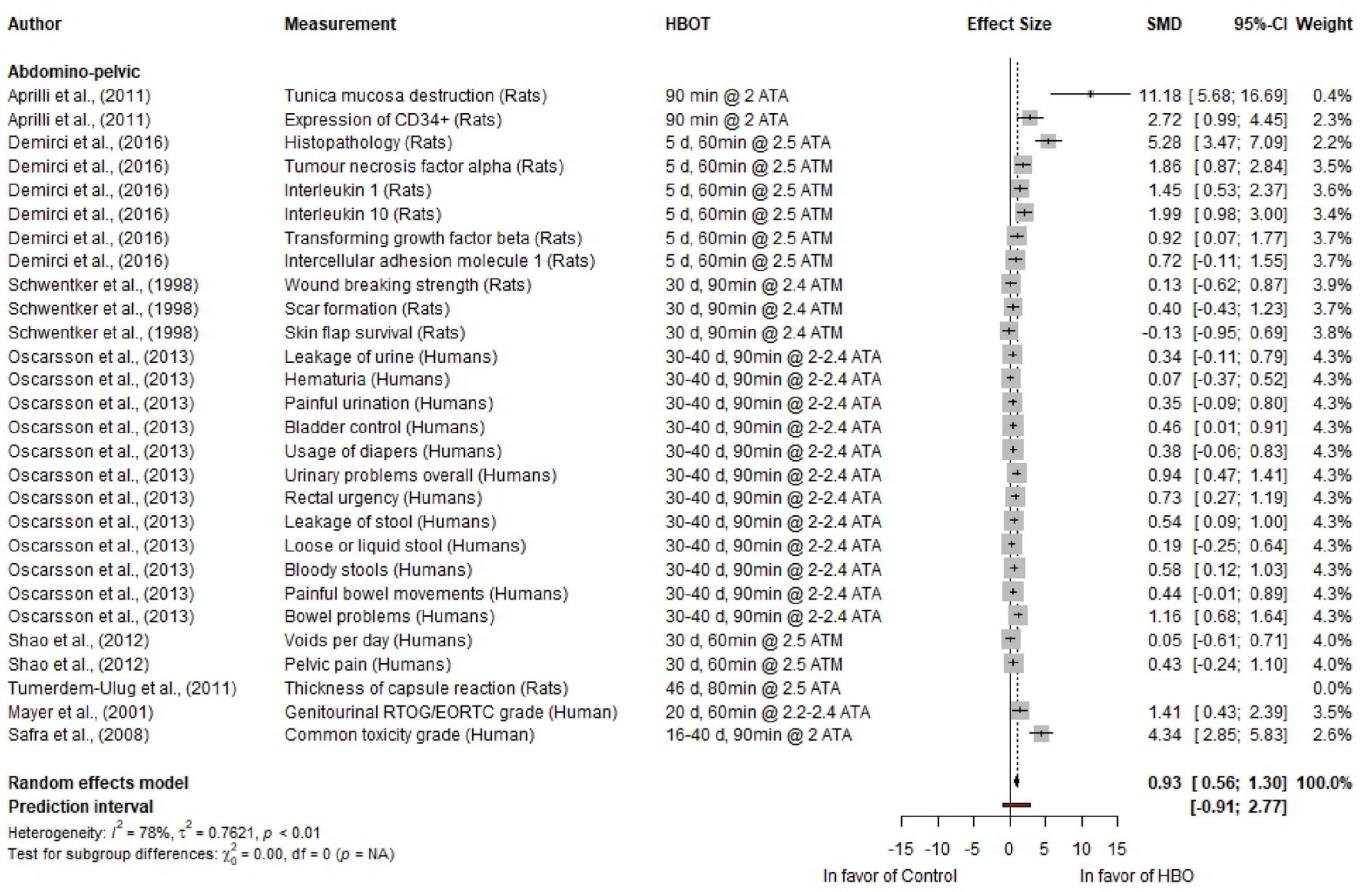

Fig. 5. Forest plot illustrating the effect of HBOT for treating ionising radiation injury outcomes at the abdominal-pelvic region. Note: when SD = 0 (no variability) data points cannot be seen in the forest plot.

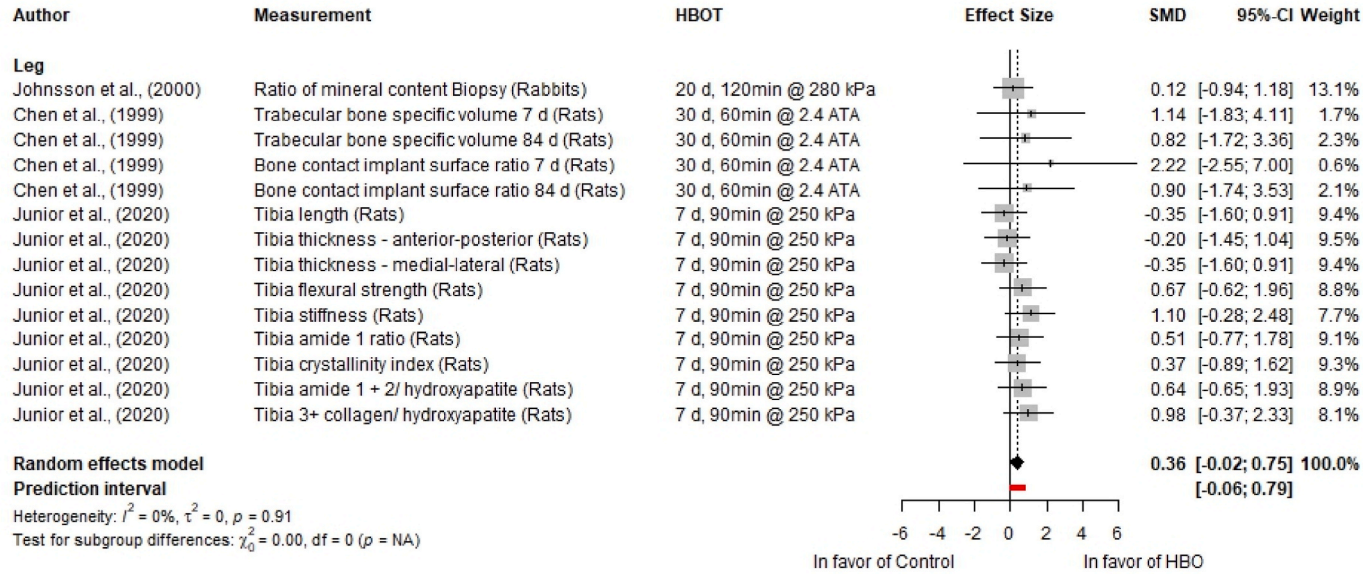

Fig. 6. Forest plot illustrating the effect of HBOT for treating ionising radiation injury outcomes at the lower limb.

4.4. *Abdominal-pelvic regions*

The potential of HBOT to treat radiation injuries in the abdominal-pelvic region were favourable, with a random effect size of 0.93 (Fig. 5). Only a single study included in the review examined HBOT for breast cancer patients who were exposed to radiation. This study was examined to have a high risk of bias. No change in fibrosis (thickening of tissue) or telangiectasia (dilated blood vessels) in the radiated breast

were observed. However, there was a significant reduction in erythema (redness of skin), oedema, and pain [20]. Encouragingly, no adverse effects were reported, and some patients experienced complete symptom relief at the end of treatment, whereas all subjects in the control group were still experiencing symptoms [20]. They found that complete symptom relief took on average 25 x 90-min sessions of HBOT.

In mice with abdominal-pelvic radiation-induced swelling to the small intestine, HBOT reduced the inflammation of the small intestine [26]. HBOT also prevented hair whitening in the radiation area, suggesting better melanocyte (skin pigment cell) survival [26]. HBOT has also protected the radiated intestines of rats by keeping the lining healthy and increasing the number of stem cells [18]. The above studies had a low risk of bias. Similarly, several studies showed positive signs for the use of HBOT in patients and rats with bladder or rectal problems caused by radiation [46,31], such as urinary and rectal pain, bleeding, and an overall better quality of life [38,44,47,50,56,58]. However, with the exception of Johnson, Wiseman & Hogg (1972) [31] and Shao, Lu & Shen (2012) [50], these studies were assessed as having a moderate or high risk of bias. Consequently, the positive outcomes reported may not fully reflect HBOT's actual efficacy in treating radiation-induced abdominal-pelvic injury, highlighting the need for further high-quality research to confirm these findings.

4.5. Lower limb

HBOT showed a potential benefit in treating lower limb radiation injuries, as evidenced by studies on rabbits with tibial implants where bone metabolism and strength improved [22,33,36]. In contrast, a study with similar methods found HBOT made no difference to bone mineral content [32] and a study by Junior et al. (2020) [34] had mixed results because although irradiated tibia became thinner and shorter after HBOT, they were significantly stronger. The variations in outcomes across studies, including conflicting results on bone mineral content and structural integrity, may be partially attributed to differences in the assessed risk of bias. These inconsistencies also highlight the complexity of HBOT's impact on bone health. The differing response times in animal models compared to humans (i.e. human bones take 3 times longer to heal compared to rabbits), [61], underscore the need for human-specific research in this area.

4.6. Quality of evidence

The heterogeneity in methodologies across the included studies reflects the significant challenge in synthesising conclusive evidence and as such these results should be treated as preliminary. While many studies had similar HBOT doses (2–3 ATA), there was considerable variation in HBOT duration (10–180min x 1–46 days), radiation dose (1–80Gy), and the time elapsed between radiation and HBOT, which affects study outcomes and makes direct comparison between studies challenging. This was evidenced by the high between-study heterogeneity observed for all body regions in the analysis. For some regions, single studies contributed a majority of the outcomes which could bias the effect estimates. For example, Junior et al., 2020 [34] contributed 9 out of the 14 outcomes in the lower limb region (Fig. 6). Further, many of the studies relied on self-reported, subjective measures for outcome variables, often gathered through non-standardised questionnaires or interviews which could create variability and bias in the results. Although most studies were assessed as low or moderate risk of bias, their small sample sizes and short follow-up durations limit the generalisability of the findings. Future research should address these limitations through longer trials that standardise radiation and HBOT based on the dosages shown herein to be effective. Consistency between trials is imperative to provide more definitive conclusions on the efficacy of HBOT in treating ionising radiation injuries especially in the areas which have already shown promise such as the abdominal-pelvic or lower limb region.

4.7. Relevance to space

The human clinical studies analysed in this analysis involved cumulative radiation doses ranging from 15 to 116 Gy that targets specific sites of the body. In contrast, space travel exposes the whole body to radiation at a much lower dose (approximately 0.48 mGy d^{-1}; [62]). However, during solar particle events, astronauts might be exposed to significantly higher doses — up to 10 Gy h^{-1}, or even 50 Gy h^{-1} — during extravehicular activities. Such exposure levels could lead to severe radiation damage akin to that experienced by radiotherapy patients [63]. While space missions often coincide with periods of low solar activity to minimise this risk [64], the possibility of encountering high radiation doses necessitates having effective onboard treatments. These treatments would ideally be independently administered by the crew to reverse the harmful physiological effects and provide symptomatic relief, thereby maintaining crew health and occupational productivity until ground-based medical treatment is available.

While the findings indicate that HBOT is effective for treating ionising radiation injuries in specific regions such as the abdominal-pelvic and lower limb areas, its application in the context of whole-body space radiation poses potential risks. The overall positive random effect size for body mass is encouraging, but the wide prediction interval we observed indicates the potential for HBOT to cause weight loss following radiation exposure. Given that astronauts already experience significant weight loss during space missions due to reduced gravity affecting the musculoskeletal system through muscle atrophy and loss of bone density [65,66], additional weight loss from HBOT is undesirable. Furthermore, the potential sensitisation of the spinal cord to radiation by HBOT [27] suggests that astronauts exposed to full-body irradiation may need to delay HBOT treatment to avoid a detrimental effect on spinal health. The research by Xin Wang et al. (1998) [60] suggests that injuries from low-level ionising radiation might remain treatable for an extended period post-exposure, which is crucial if astronauts on extravehicular missions cannot immediately access HBOT.

Despite HBOT being generally well-tolerated in clinical studies and its potential for integration into spacecraft design, the majority of outcomes in this review did not show clear beneficial effects. Moreover, it remains unclear how astronauts would react to HBOT in a microgravity environment especially dealing with side-effects. HBOT comes with risks of barotrauma and oxygen toxicity, which even in mild forms can induce oxidative stress that leads to fatigue, thereby compromising cognitive and physical performance [67]. Effects on the eyes, such as hyperoxic myopia and cataracts, could be exacerbated by spaceflight-associated neuro-ocular syndrome, impairing vision and incapacitating astronauts [67]. Mission planning should therefore carefully monitor and plan the duration and frequency of HBOT sessions, as well as the engineering challenges of providing sufficient hyperbaric pressure. For instance, a regimen requiring 90 min of HBOT for a total of 30 days would represent a significant time investment for astronauts, impacting their schedules and overall mission activities. While the use of HBOT to treat ionising radiation injuries in space has its limitations, the damage being done is likely comparable to alternate remedies and is the best analogue we currently have, especially in humans. Conversely, terrestrial application of these outcomes needs to also consider other clinical factors, such as concurrent chemotherapy, hormone therapy, and surgery, that we excluded from this review.

5. Conclusion

This systematic review highlights the nuanced and context-dependent nature of HBOT's effectiveness in mitigating ionising radiation-induced injuries. While showing promise in certain anatomical regions, the evidence does not uniformly support HBOT's efficacy across all areas including potential detrimental effects following spinal radiation. As we venture further into space exploration, the role of HBOT in maintaining astronaut health during and after exposure to ionising

radiation warrants continued investigation, guided by robust, comprehensive research.

CRediT authorship contribution statement

Amanda Holyer: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Thomas Stewart:** Writing – review & editing, Supervision, Project administration. **Edward T. Ashworth:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We would like to acknowledge the help and support of David M. Shaw (Royal New Zealand Air Force) in screening these articles.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.actaastro.2025.03.011.

References

[1] G. Reitz, Characteristic of the radiation field in low Earth orbit and in deep space, Z. Med. Phys. 18 (4) (2008) 233–243.
[2] M. Naito, S. Kodaira, Considerations for practical dose equivalent assessment of space radiation and exposure risk reduction in deep space, Sci. Rep. 12 (1) (2022) 13617.
[3] W. Suparta, S.K. Zulkeple, Spatial analysis of galactic cosmic ray particles in low earth orbit/near equator orbit using SPENVIS, in: Journal of Physics: Conference Series, vol. 495, IOP Publishing, 2014 012040. No. 1.
[4] Y. Ogawa, T. Kobayashi, A. Nishioka, S. Kariya, S. Hamasato, H. Seguchi, S. Yoshida, Radiation-induced reactive oxygen species formation prior to oxidative DNA damage in human peripheral T cells, Int. J. Mol. Med. 11 (2) (2003) 149–152.
[5] S. Furukawa, A. Nagamatsu, M. Nenoi, A. Fujimori, S. Kakinuma, T. Katsube, A. Takahashi, Space radiation biology for "living in space", BioMed Res. Int. 2020 (2020).
[6] S.P. Jackson, J. Bartek, The DNA-damage response in human biology and disease, Nature 461 (7267) (2009) 1071–1078.
[7] S. Sen, S. Sen, Therapeutic effects of hyperbaric oxygen: integrated review, Med. Gas Res. 11 (1) (2021) 30.
[8] S. Tejada, J.M. Batle, M.D. Ferrer, C. Busquets-Cortés, M. Monserrat-Mesquida, S. M. Nabavi, A. Sureda, Therapeutic effects of hyperbaric oxygen in the process of wound healing, Curr. Pharm. Des. 25 (15) (2019) 1682–1693.
[9] M. O'Connell, Hyperbaric oxygen therapy and spaceflight, 43rd COSPAR Scientific Assembly (2021). Held 28 January-4 February, 43, https://ui.adsabs.harvard.edu/abs/2021cosp...43E2021O/abstract.
[10] N. Skeik, B.R. Porten, E. Isaacson, J. Seong, D.L. Klosterman, R.F. Garberich, T. Sullivan, Hyperbaric oxygen treatment outcome for different indications from a single center, Ann. Vasc. Surg. 29 (2) (2015) 206–214.
[11] N. Jallali, S. Withey, P.E. Butler, Hyperbaric oxygen as adjuvant therapy in the management of necrotizing fasciitis, Am. J. Surg. 189 (4) (2005) 462–466.
[12] M. Ouzzani, H. Hammady, Z. Fedorowicz, A. Elmagarmid, Rayyan—a web and mobile app for systematic reviews, Syst. Rev. 5 (1) (2016) 210, https://doi.org/10.1186/s13643-016-0384-4.
[13] A. Winnard, N. Caplan, C. Bruce-Martin, P. Swain, R. Velho, R. Meroni, J. Laws, Developing, implementing, and applying novel techniques during systematic reviews of primary space medicine data, Aerospace Medicine and Human Performance 92 (8) (2021) 681–688.
[14] J.P. Higgins, J. Thomas, J. Chandler, M. Cumpston, T. Li, M.J. Page, V.A. Welch (Eds.), Cochrane Handbook for Systematic Reviews of Interventions, John Wiley & Sons, 2019.
[15] A. Rohatgi, WebPlotDigitizer. WebPlotDigitizer, 2021.
[16] J.P. Higgins, S.G. Thompson, Quantifying heterogeneity in a meta-analysis, Stat. Med. 21 (11) (2002) 1539–1558.
[17] H.J. Seo, S.Y. Kim, Y.J. Lee, J.E. Park, RoBANS 2: a revised risk of bias assessment tool for nonrandomized studies of interventions, Korean Journal of Family Medicine 44 (5) (2023) 249.
[18] R.R. Aprilli, R.S. Parra, H.F. de Oliveira, F. Aprilli, J.J.R. da Rocha, O. Féres, The effect of hyperbaric oxygenation on the distal intestine of rats subjected to ionizing radiation, Undersea & Hyperbaric Medicine: Journal of the Undersea and Hyperbaric Medical Society, Inc 38 (6) (2011) 503–507.
[19] K. Cankar, Z. Finderle, J. Jan, The effect of hyperbaric oxygenation on postradiation xerostomia and saliva in patients with head and neck tumours, Caries Res. 45 (2) (2011) 136–141.
[20] U.M. Carl, J.J. Feldmeier, G. Schmitt, K.A. Hartmann, Hyperbaric oxygen therapy for late sequelae in women receiving radiation after breast-conserving surgery, Int. J. Radiat. Oncol. Biol. Phys. 49 (4) (2001) 1029–1031.
[21] B. Celik, A.D. Meydan, M. Kefeli, E.K. Gülen, N.Ö. Okumus, The effects of hyperbaric oxygen treatment on the healing of tracheal anastomosis following irradiation in rats, Thorac. Cardiovasc. Surg. 58 (8) (2010) 481–485.
[22] X. Chen, Y. Matsui, K. Ohno, K.I. Michi, Histomorphometric evaluation of the effect of hyperbaric oxygen treatment on healing around hydroxyapatite implants in irradiated rat bone, Int. J. Oral Maxillofac. Implants 14 (1) (1999) 61–68.
[23] C.L. Clark, J. Strider, C. Hall, H.W. Ferguson, K.L. Armstrong, R.R. Runner, D. A. Baur, Distraction osteogenesis in irradiated rabbit mandibles with adjunctive hyperbaric oxygen therapy, Journal of oral and maxillofacial surgery 64 (4) (2006) 589–593.
[24] H. Demirci, Z. Polat, A. Uygun, A. Kadayifci, O. Sager, K. Oztutk, S. Bagci, The effect of the iNOS inhibitor S-methylisothiourea and hyperbaric oxygen treatment on radiation colitis in rats, Acta Gastroenterol. Belg. 79 (1) (2016) 8–13.
[25] S. Dische, M.I. Saunders, R. Sealy, I.D. Werner, N. Verma, C. Foy, S.M. Bentzen, Carcinoma of the cervix and the use of hyperbaric oxygen with radiotherapy: a report of a randomised controlled trial, Radiother. Oncol. 53 (2) (1999) 93–98.
[26] J.J. Feldmeier, I. Jelen, D.A. Davolt, P.T. Valante, M.L. Meltz, R. Alecu, Hyperbaric oxygen as a prophylaxis for radiation-induced delayed enteropathy, Radiother. Oncol. 35 (2) (1995) 138–144.
[27] J.J. Feldmeier, J.D. Lange, S.D. Cox, L.J. Chou, V. Ciaravino, Hyperbaric oxygen as prophylaxis or treatment for radiation myelitis, Undersea & hyperbaric medicine: journal of the Undersea and Hyperbaric Medical Society, Inc 20 (3) (1993) 249–255.
[28] L. Forner, A. Berkowicz, E. Dickmeiss, O. Hyldegaard, E.C. Jansen, A. Fischer-Nielsen, Only minor stem cell mobilization in head and neck irradiated patients treated with hyperbaric oxygen, Diving and Hyperbaric Medicine 49 (3) (2019) 175.
[29] N.L. Gerlach, R. Barkhuysen, J.H.A.M. Kaanders, G.O.R.J. Janssens, W. Sterk, M.A. W. Merkx, The effect of hyperbaric oxygen therapy on quality of life in oral and oropharyngeal cancer patients treated with radiotherapy, Int. J. Oral Maxillofac. Surg. 37 (3) (2008) 255–259.
[30] V.H. Hillard, H. Peng, K. Das, R. Murali, C.R. Moorthy, J.D. Etlinger, R.J. Zeman, Inhibition of x-irradiation–enhanced locomotor recovery after spinal cord injury by hyperbaric oxygen or the antioxidant nitroxide tempol, J. Neurosurg. Spine 6 (4) (2007) 337–343.
[31] R.J. Johnson, N. Wiseman, G.R. Hogg, Radiation induced bowel damage in rats treated under conditions of air or hyperbaric oxygen, Clin. Radiol. 23 (1) (1972) 106–109.
[32] Å.A. Johnsson, M. Jacobsson, G. Granström, C.B. Johansson, K.G. Strid, I. Turesson, A microradiographic investigation of cancellous bone healing after irradiation and hyperbaric oxygenation: a rabbit study, Int. J. Radiat. Oncol. Biol. Phys. 48 (2) (2000) 555–563.
[33] Å.A. Johnsson, T. Sawaii, M. Jacobsson, G. Granström, I. Turesson, A histomorphometric study of bone reactions to titanium implants in irradiated bone and the effect of hyperbaric oxygen treatment, Int. J. Oral Maxillofac. Implants 14 (5) (1999).
[34] L.H.F. Júnior, P.H.J.O. Limirio, P.B.F. Soares, P. Dechichi, L. de Souza Castro Filice, P.S. Quagliatto, F.S. Rocha, The effect of hyperbaric oxygen therapy on bone macroscopy, composition and biomechanical properties after ionizing radiation injury, Radiat. Oncol. 15 (1) (2020) 1–8.
[35] M. Konak, H. Cincik, E. Erkul, Z. Kucukodaci, A. Gungor, S. Ozdemir, M. Salihoglu, The protective effects of different treatments on rat salivary glands after radiotherapy, Eur. Arch. Otorhinolaryngol. 273 (2016) 4501–4506.
[36] P.E. Larsen, M.J. Stronczek, F.M. Beck, M. Rohrer, Osteointegration of implants in radiated bone with and without adjunctive hyperbaric oxygen, Journal of oral and maxillofacial surgery 51 (3) (1993) 280–287.
[37] H.C. Lee, C.S. Liu, C. Chiao, S.N. Lin, Hyperbaric oxygen therapy in hemorrhagic radiation cystitis: a report of 20 cases, Undersea & Hyperbaric Medicine: Journal of the Undersea and Hyperbaric Medical Society, Inc 21 (3) (1994) 321–327.
[38] R. Mayer, H. Klemen, F. Quehenberger, O. Sankin, E. Mayer, A. Hackl, F.M. Smolle-Juettner, Hyperbaric oxygen–an effective tool to treat radiation morbidity in prostate cancer, Radiother. Oncol. 61 (2) (2001) 151–156.
[39] A. Muhonen, M. Haaparanta, T. Grönroos, J. Bergman, J. Knuuti, S. Hinkka, R. P. Happonen, Osteoblastic activity and neoangiogenesis in distracted bone of irradiated rabbit mandible with or without hyperbaric oxygen treatment, Int. J. Oral Maxillofac. Surg. 33 (2) (2004) 173–178.
[40] A. Muhonen, J. Muhonen, T.C. Lindholm, H. Minn, J. Klossner, J. Kulmala, R. P. Happonen, Osteodistraction of a previously irradiated mandible with or without adjunctive hyperbaric oxygenation: an experimental study in rabbits, Int. J. Oral Maxillofac. Surg. 31 (5) (2002) 519–524.
[41] A. Muhonen, T. Peltomäki, S. Hinkka, R.P. Happonen, Effect of mandibular distraction osteogenesis on temporomandibular joint after previous irradiation and hyperbaric oxygenation, Int. J. Oral Maxillofac. Surg. 31 (4) (2002) 397–404.
[42] A. Muhonen, J. Muhonen, H. Minn, J. Kulmala, J. Klossner, M. Teräs, R. P. Happonen, The effects of irradiation and hyperbaric oxygen on bone formation during rabbit mandibular distraction, Arch. Oral Biol. 47 (10) (2002) 701–707.
[43] A. Muhonen, T. Peltomäki, J. Knuuti, O. Raitakari, R.P. Happonen, Osteoblastic activity of the rabbit temporomandibular joint during distraction osteogenesis

assessed by [18F] fluoride positron emission tomography, Eur. J. Oral Sci. 110 (2) (2002) 144–148.
[44] N. Oscarsson, P. Arnell, P. Lodding, S.E. Ricksten, H. Seeman-Lodding, Hyperbaric oxygen treatment in radiation-induced cystitis and proctitis: a prospective cohort study on patient-perceived quality of recovery, Int. J. Radiat. Oncol. Biol. Phys. 87 (4) (2013) 670–675.
[45] T.J. Poulton, R.L. Witcofski, Hyperbaric oxygen therapy for radiation myelitis, Undersea Biomed. Res. 12 (4) (1985) 453–458.
[46] A.K. Rud, S. Bjørgo, G.B. Kristensen, U.E. Kongsgaard, Hyperbaric oxygen therapy for late radiation tissue injury in gynaecological patients, Support. Care Cancer 17 (2009) 1517–1521.
[47] T. Safra, G. Gutman, G. Fishlev, V. Soyfer, N. Gall, J.B. Lessing, D. Grisaru, Improved quality of life with hyperbaric oxygen therapy in patients with persistent pelvic radiation-induced toxicity, Clin. Oncol. 20 (4) (2008) 284–287.
[48] P.J. Schoen, G.M. Raghoebar, J. Bouma, H. Reintsema, A. Vissink, W. Sterk, J. L. Roodenburg, Rehabilitation of oral function in head and neck cancer patients after radiotherapy with implant-retained dentures: effects of hyperbaric oxygen therapy, Oral Oncol. 43 (4) (2007) 379–388.
[49] A. Schwentker, S.M. Evans, M. Partington, B.L. Johnson, C.J. Koch, S.R. Thom, A model of wound healing in chronically radiation-damaged rat skin, Cancer letters 128 (1) (1998) 71–78.
[50] Y. Shao, G.L. Lu, Z.J. Shen, Comparison of intravesical hyaluronic acid instillation and hyperbaric oxygen in the treatment of radiation-induced hemorrhagic cystitis, BJU Int. 109 (5) (2012) 691–694.
[51] R.J. Shaw, C.J. Butterworth, P. Silcocks, B.T. Tesfaye, M. Bickerstaff, R. Jackson, M. Glover, HOPON (Hyperbaric Oxygen for the Prevention of Osteoradionecrosis): a randomized controlled trial of hyperbaric oxygen to prevent osteoradionecrosis of the irradiated mandible after dentoalveolar surgery, Int. J. Radiat. Oncol. Biol. Phys. 104 (3) (2019) 530–539.
[52] T. Sønstevold, A.C. Johannessen, R.K. Reed, G.S. Salvesen, L. Stuhr, Hyperbaric oxygen treatment did not significantly affect radiation injury in the mandibular area of rats, Oral surgery, oral medicine, oral pathology and oral radiology 125 (2) (2018) 112–119.
[53] L. Spiegelberg, J.A. Braks, U.M. Djasim, E. Farrell, K.G. van der Wal, E.B. Wolvius, Effects of hyperbaric oxygen therapy on the viability of irradiated soft head and neck tissues in mice, Oral Dis. 20 (3) (2014) e111–e119.
[54] L. Spiegelberg, S. Swagemakers, W.F. Van Ijcken, E. Oole, E.B. Wolvius, J. Essers, J. A. Braks, Gene expression analysis reveals inhibition of radiation-induced TGFβ-signaling by hyperbaric oxygen therapy in mouse salivary glands, Molecular Medicine 20 (1) (2014) 257–269.
[55] L. Spiegelberg, J.A. Braks, L.C. Groeneveldt, U.M. Djasim, K.G. van der Wal, E. B. Wolvius, Hyperbaric oxygen therapy as a prevention modality for radiation damage in the mandibles of mice, J. Cranio-Maxillofacial Surg. 43 (2) (2015) 214–219.
[56] K. Suzuki, K. Kurokawa, T. Suzuki, H. Okazaki, N. Otake, K. Imai, H. Yamanaka, Successful treatment of radiation cystitis with hyperbaric oxygen therapy: resolution of bleeding event and changes of histopathological findings of the bladder mucosa, Int. Urol. Nephrol. 30 (1998) 267–271.
[57] J. Svalestad, E. Thorsen, G. Vaagbø, S. Hellem, Effect of hyperbaric oxygen treatment on oxygen tension and vascular capacity in irradiated skin and mucosa, Int. J. Oral Maxillofac. Surg. 43 (1) (2014) 107–112.
[58] B. Tumerdem-Ulug, I. Kuran, B.C. Ozden, O. Mete, G. Kemikler, S. Aktas, B. Calik, Does hyperbaric oxygen administration before or after irradiation decrease side effects of irradiation on implant sites? Ann. Plast. Surg. 67 (1) (2011) 62–67.
[59] J. Vidmar, K. Cankar, M. Groselj, Z. Finderle, I. Sersa, Assessment of hyperbaric oxygenation treatment response in parotid glands by mapping following radiotherapy for head and neck tumours, Radiol. Oncol. 56 (1) (2022) 60–68.
[60] M.D. Xin Wang, I. Ding, H. Xie, T. Wu, N. Wersto, K. Huang, P. Okunieff, Hyperbaric oxygen and basic fibroblast growth factor promote growth of irradiated bone, Int. J. Radiat. Oncol. Biol. Phys. 40 (1) (1998) 189–196.
[61] W.E. Roberts, R.K. Smith, Y. Zilberman, P.G. Mozsary, R.S. Smith, Osseous adaptation to continuous loading of rigid endosseous implants, Am. J. Orthod. 86 (2) (1984) 95–111.
[62] C. Zeitlin, D.M. Hassler, F.A. Cucinotta, B. Ehresmann, R.F. Wimmer-Schweingruber, D.E. Brinza, G. Reitz, Measurements of energetic particle radiation in transit to Mars on the Mars science laboratory, science 340 (6136) (2013) 1080–1084.
[63] G. Onorato, E. Di Schiavi, F. Di Cunto, Understanding the effects of deep space radiation on nervous system: the role of genetically tractable experimental models, Frontiers in Physics 8 (2020) 362.
[64] R. Turner, What we must know about solar particle events to reduce the risk to astronauts, Geophys. Monogr. 125 (2001) 39–44.
[65] A. Matsumoto, K.J. Storch, A. Stolfi, S.R. Mohler, M.A. Frey, T.P. Stein, Weight loss in humans in space, Aviat Space Environ. Med. 82 (6) (2011) 615–621.
[66] T.P. Stein, Weight, muscle and bone loss during space flight: another perspective, Eur. J. Appl. Physiol. 113 (2013) 2171–2181.
[67] M. Heyboer III, D. Sharma, W. Santiago, N. McCulloch, Hyperbaric oxygen therapy: side effects defined and quantified, Adv. Wound Care 6 (6) (2017) 210–224.