Note: this is the final draft of the article:

Winnard A, Nasser M, Debuse D, Stokes M, Evetts S, Wilkinson M, Hides J, Caplan N

Systematic Review of countermeasures to minimise physiological changes and risk of injury to the lumbopelvic area following long-term microgravity

Musculoskelet Sci Pract 2017; 27(Suppl 1): 5-14

Accepted 1st November 2016
for publication in
Musculoskeletal Science and Practice
Supplement Issue on **"Terrestrial neuro-musculoskeletal rehabilitation and astronaut reconditioning: reciprocal knowledge transfer"**
Guest Editors: Maria Stokes, Simon Evetts, Julie Hides

The final, fully proofed and peer-reviewed journal article will be available online in:
https://www.journals.elsevier.com/musculoskeletal-science-and-practice

For *Musculoskeletal Science and Practice* Supplement: "Terrestrial neuro-musculoskeletal rehabilitation and astronaut reconditioning: reciprocal knowledge transfer"
Guest Editors: Maria Stokes, Simon Evetts, Julie Hides

Systematic Review of countermeasures to minimise physiological changes and risk of injury to the lumbopelvic area following long-term microgravity

Andrew Winnard[1], Mona Nasser[2], Dorothee Debuse[1], Maria Stokes[3], Simon Evetts[1,4], Mick Wilkinson[1], Julie Hides[5], Nick Caplan[1]

1. Faculty of Health and Life Sciences, Northumbria University, Newcastle upon Tyne, UK.
2. Peninsula Dental School, Plymouth University, Plymouth, UK.
3. Faculty of Health Sciences, University of Southampton, Southampton, UK.
4. Wyle GmbH, Cologne, Germany.
5. Centre for Musculoskeletal Research, Mary MacKillop Institute for Health Research, Australian Catholic University, Brisbane, Australia.

Corresponding author:

Dr Nick Caplan
Faculty of Health and Life Sciences
Northumbria University
Northumberland Building
Newcastle upon Tyne
NE1 8ST
United Kingdom

Tel: +44(0)191 243 7382
Email: nick.caplan@northumbria.ac.uk

Abstract

Background: No studies have been published on an astronaut population to assess the effectiveness of countermeasures for limiting physiological changes in the lumbopelvic region caused by microgravity exposure during spaceflight. However, several studies in this area have been done using spaceflight simulation via bed-rest. The purpose of this systematic review was to evaluate the effectiveness of countermeasures designed to limit physiological changes to the lumbopelvic region caused by spaceflight simulation by means of bed-rest.

Methods: Electronic databases were searched from the start of their records to November 2014. Studies were assessed with PEDro, Cochrane Risk of Bias and a bed-rest study quality tool. Magnitude based inferences were used to assess countermeasure effectiveness.

Results: Seven studies were included. There was a lack of consistency across studies in reporting of outcome measures. Some countermeasures were found to be successful in preventing some lumbopelvic musculoskeletal changes, but not others. For example, resistive vibration exercise prevented muscle changes, but showed the potential to worsen loss of lumbar lordosis and intervertebral disc height.

Conclusion: Future studies investigating countermeasures should report consistent outcomes, and also use an actual microgravity environment. Additional research with patient reported quality of life and functional outcome measures is advocated.

Keywords: spinal stability, muscle, exercise, countermeasure

Highlights

- No countermeasure limited or prevented all musculoskeletal changes successfully;
- Future studies investigating countermeasures should use consistent outcome measures;
- Population-reported outcomes and relevant functional measures should be used.

1. Introduction

Human spaceflight results in exposure to an altered gravity state. This environment eliminates most weight bearing and axial loads, resulting in physiological changes and increased injury risk [1-3]. Gernand [1] reported the implications of these physiological changes on subsequent safe functioning on return to a gravity loaded environment, highlighting the need for both countermeasures during spaceflight and rapid and effective rehabilitation following spaceflight. For longer duration spaceflight of around six months, Gernand [1] noted significant bone and muscle loss, as well as altered postural control, leaving the body susceptible to bone fracture, muscle injury and the potential to develop osteoporosis. Muscle atrophy and altered motor control have been specifically observed in the lumbopelvic region [4].

Snijders et al. [5] reported low back pain (LBP) in 12 out of 20 astronauts during spaceflight, and highlighted the importance of maintaining spinal movements, because end range flexion and extension exercises were anecdotally noted as being employed to ease pain during spaceflight. A relationship was highlighted between LBP and atrophy of lumbopelvic stability musculature, particularly multifidus, during bed-rest studies [6].

Wing et al. [7] reported that 53-68% of astronauts experienced moderate to severe back pain while in space. On landing after a shuttle mission, one astronaut reported severe LBP associated with a herniated nucleus pulposus at the L4-5 intervertebral disc requiring surgical intervention [8]. Johnston et al. [8] found that astronauts had a four-fold increased incidence of herniated disc pulposus within the first year following spaceflight, compared with matched controls. Sayson and Hargens [4] suggested that back pain and disc injury in astronauts could be caused by a range of factors linked to spinal lengthening and reduced loading. Belavy et al. [9] argued that the increased lumbar intervertebral disc herniation risk in astronauts was most likely caused by long term disc tissue deconditioning which results from swelling of the discs due to unloading during spaceflight.

Lumbopelvic adaptations to microgravity include adoption of a flexed posture (Figure 1)[3], spinal lengthening, increased disc height and deconditioning, altered spinal curvatures [4] and atrophy of lumbopelvic musculature. A general pattern of selective extensor muscle atrophy over flexors has been seen throughout the body [10, 11]. Spinal extensor volume decreases have been reported as greater than hip flexor (psoas muscle) decline in astronauts [12]. Anecdotal accounts appear to show selective atrophy of trunk extensor muscles concomitant with improved flexor muscle performance immediately post mission [13]. Hides et al. [14] suggested that local muscle changes such as atrophy of the lumbar multifidus and transversus abdominis muscles, and selective hypertrophy of spinal flexors over extensors [15], may impact on the ability of the spine to distribute loads appropriately after spaceflight simulation via bed-rest. Selective atrophy of spinal extensors without corresponding atrophy of the psoas muscle was also seen in terrestrial individuals with LBP compared to healthy controls [16]. Atrophy and motor control changes in the lumbar multifidus muscle have been linked with LBP [17, 18] and development of poor intersegmental control of the lumbar spine [19-22], which can potentially cause increased loads on spinal structures, resulting in pain [23-25].

While deconditioning and reduced physiological loading occur during spaceflight, some strenuous physical tasks are still performed (e.g. extra-vehicular activity, physically demanding medical procedures, landing and return to a g-loaded environment), which have the potential to be at least as demanding as those undertaken in normal Earth gravity [1]. It is necessary, therefore, to develop countermeasures to minimise physiological compromise.

The aim of this systematic review was to determine what interventions are effective at counteracting changes, and reducing injury risks, to the lumbopelvic region, during exposure to microgravity in humans. Specifically, this systematic review focussed on the lumbopelvic region due to its vital role in the maintenance of lumbar posture, intersegmental control of the lumbar spine and its link with LBP [5, 14, 25].

2. Material and Methods

2.1. Search strategy

A range of terms (rehabilitate, rehabilitation, recover*, recovery, spaceflight, space*, space flight, astronaut*, microgravity, micro gravity, bed-rest, bedrest, weightless*, muscle*, bone*, skeletal, musculoskeletal, neuromusculoskeletal, intervention*, treat, treatment*, physio, physiotherapy, physical therapy, therapy, exercise, program*, exercise program*, lumb*, pelv*, low back, lower back, countermeasure*, counter*, protect*, maintain, prevent*, train*) were used in combinations to search the following databases in November 2014: Pubmed, CINAHL, Web of Science, Science Direct and The Cochrane Collaboration Library. The full search strategy can be seen in Supplementary Table A.

2.2. Inclusion criteria

Inclusion criteria were that studies had to report on either astronaut or bedrest populations, to compare countermeasures to each other or to no intervention or placebo/sham, to report outcomes relating to lumbopelvic health, and they had to be either randomised controlled trials (RCT), controlled clinical trials (CT), interrupted time series or before and after studies.

2.3. Study selection & data extraction

Initial screening was performed using abstracts and titles by the lead author. Where it was unclear whether the study met the inclusion criteria from initial screening the full text was obtained. An adapted version of The Cochrane Collaboration "Data collection form for intervention reviews: RCTs only" version 3, April 2014 [26], was used by two authors (AW and MN) to extract data from each paper, and disagreements were discussed to reach consensus.

2.3.1. Quality Assessment

The Physiotherapy Evidence Database scale (PEDro)[27] and The Cochrane Collaboration risk of bias analysis for randomised trials [28] were used by two authors (AW and MN) to assess each study, and disagreements discussed to reach consensus.

2.3.2. Methodological quality of bed-rest studies

Bed-rest is commonly used to simulate axial unloading which occurs during spaceflight [29]. There are currently no tools for assessing bed-rest methodological quality. A methodological tool was developed to assess how bed-rest studies compare to an "ideal design" (Table 1). The key features of an ideal "bed rest" study were based on literature and expert consultation [29-31], including European Space Agency protocols [32]. Bed-rest duration was also recorded, as simulation studies can only relate to spaceflight of similar duration. Two authors (AW and MN) independently rated studies using this tool, and disagreements were discussed to reach consensus.

2.4. Data analysis

The raw change across all outcome measures in the inactive control groups from baseline to end of bed-rest was extracted. The effect size that exists between the changes seen in the intervention and control groups provides an indication of the effectiveness of each treatment. Data were pooled across the same outcomes within each intervention when they were tested at multiple spinal levels and had effects of similar size, with changes in the same direction.

All the studies used bed-rest and measured surrogate outcomes. The assumption with the outcome measures was that any change in the control group is "undesirable" and success is evaluated by the ability of an intervention to demonstrate changes in the opposite direction. In the comparison between intervention and control group, four scenarios were used to judge interventions as effective, neutral or ineffective:

1. Training effect: changes in “desirable” direction beyond baseline.
2. Full protective effect: changes reduced completely back to baseline.
3. Partially protective effect: changes in “desirable” direction but not reaching baseline.
4. Worsening effect: further changes in “undesirable direction”.

To quantify the amount by which the interventions altered the change relating to baseline, the intervention difference was expressed as a percentage of the change recorded in the inactive control groups.

$$Intervention\ ability\ to\ restore\ change\ to\ baseline\ (\%) = x_i/x_c \times 100$$

where x_i is the difference in the intervention group between baseline and end of bed-rest/spaceflight and x_c is the same difference in the control group.

The percentages are reported as negative where the intervention partially prevented the change and by how much (% off baseline), and positive where the intervention caused a training effect. A negative percentage of more than 100% shows the intervention making the change worse than having no treatment. Where data from a single study were pooled across vertebral levels, a standard deviation is presented with this value.

Magnitude based inference was used to calculate the probability of the true effect being positive or negative using 90% confidence intervals [33], in relation to a smallest worthwhile change of 0.2 (small) and 0.6 (moderate) effect size.

3. Results

In total, 3147 papers were identified, which reduced to 2104 after duplicates were removed. A further 2095 were excluded following screening of title and abstract. The nine remaining papers were acquired in full text

and two further exclusions made (Supplementary Figure A). Seven papers were included in the final review. No further eligible papers were found through screening the reference lists of the included papers.

3.1. Characteristics of included studies

All seven studies shared the RCT design. All seven studies were included in the quantitative synthesis. All studies used bed-rest; no astronaut population studies were found. Interventions included resistance exercise (RE)[34], resistive vibration exercise (RVE)[34, 35], lower body negative pressure treadmill exercise (LBNP)[36, 37], low magnitude mechanical signals (LMMS)[38], flywheel exercise (FE)[39], and spinal mobilisation exercise (SME)[39]. Belavy et al. [35] and Belavy et al. [40] both used the first Berlin Bed-rest study population to assess the same countermeasure but with different outcome measures. Belavy et al. [35] had one less participant than Belavy et al. [40] due to one individual's MRI data being unavailable. A summary of included study characteristics can be seen in Table 2.

3.2. Quality Scoring

3.2.1. PEDro Scores

All studies failed to conceal group allocations and blind participants and therapists. This made the highest scores eight, which were attained by Belavy et al. [34] and Belavy et al. [35]. Cao et al. [36], Holguin et al. [38] and Marcias et al. [37] all failed to blind assessors, scoring seven. Belavy et al. [39] failed to take measures from at least 85% of participants and did not perform intention to treat analysis, scoring six. Belavy et al [40] also failed to take measures from at least 85% of participants and did not perform intention to treat analysis, in addition to not blinding assessors, scoring five.

3.2.2. The Cochrane Collaboration Risk of Bias

All of the studies were classed as having a high overall risk of bias. The risks were mostly performance and measurement bias due to not concealing group allocation and failing to blind participants and assessors. No papers reported a clear randomisation method. The overall risks were similar across all the studies except for Holguin et al. [38] which had high or unclear risks for all points except for selective reporting.

3.2.3. Bed-rest Methodological Quality

Belavy et al. [34] achieved the highest bed-rest methodological quality score (six). All the other studies scored between three and five except for Cao et al. [36] which only scored two. While all studies indicated the days on which measures were taken, none specified that the measures were taken at the same time of day for all participants. While six degree head down tilt bed-rest (the standard for simulating microgravity) was satisfied in six studies, the protocols did allow participants to raise the head on occasions, such as for eating. Two studies specifically mentioned allowing participants to raise the head up to thirty degrees for "daytime activities" [35, 40]. No studies indicated fulfilling the sunlight criteria.

A summary of the overall quality scores for all studies across all quality assessments can be seen in Table 4.

3.3. Outcomes assessed

The only outcomes where good comparability existed between countermeasures were lordosis angle, disc volume and spinal length. Overall, RVE was the most frequently tested intervention, although SME and FE were tested against the most spinal morphology outcomes. A summary of the interventions tested for each outcome can be seen in Supplementary Table B.

3.4. Effect of countermeasures on muscle

Table 4 shows the effects of all muscle related changes assessed across all studies.

Resistive vibration exercise had a training effect on tonic activity in the lumbar erector spinae muscle, lumbopelvic extensor-flexor co-contraction ratio, lumbopelvic extensor-flexor activity ratio and external oblique muscle tonic activity. The intervention was able to partially protect lumbar multifidus muscle cross sectional area (CSA) L1-L5, erector spinae muscle CSA L1-L5, quadratus lumborum muscle CSA L1-L4, inferior gluteus maximus muscle tonic activity and internal oblique muscle tonic activity. The RVE programme worsened erector spinae muscle thoracic tonic activity and psoas CSA L1-L5.

Flywheel exercise had no observed training effect, partially protected lumbar multifidus muscle volume L1-S1, erector spinae muscle volume L1-S1, psoas muscle volume L1-S1 and isokinetic trunk extension strength. The intervention worsened quadratus lumborum muscle volume L1-S1 and isokinetic strength trunk flexion.

Spinal mobilisation exercise had no observed training effect. It partially protected lumbar multifidus muscle volume L1-S1, psoas muscle volume L1-S1 (although it is unclear what the true effect is), isokinetic trunk extension strength and isokinetic trunk flexion strength. It worsened erector spinae muscle volume L1-S1 and quadratus lumborum muscle volume L1-S1.

Lower body negative pressure treadmill was only tested for one muscle change and was able to partially protect erector spinae muscle CSA at L4.

Resistance exercise had no observed training effect, partially protected multifidus muscle CSA L1-S1, erector spinae muscle CSA L1-S1 and quadratus lumborum muscle CSA L1-L4, and worsened psoas muscle CSA L1-L5.

3.5. Effect of countermeasures on spinal morphology

Table 5 shows the effects of interventions on spinal morphology changes across all studies.

Resistive vibration exercise did not have any training effect. It partially protected intervertebral disc volume L1-S1, intervertebral disc sagittal CSA L1-S1, posterior intervertebral disc height L1-S1 and spinal length L1-S1. It failed to prevent changes to and, in fact, worsened lordosis angle L1-S1 and anterior intervertebral disc height L1-S1.

Flywheel exercise had training effects for intervertebral disc anterior-posterior diameter L1-S1 and intervertebral disc sagittal CSA L1-S1. It partially protected anterior intervertebral disc height L1-S1 and lordosis angle and worsened intervertebral disc transverse diameter L1-S1, intervertebral disc axial CSA L1-S1, posterior intervertebral disc height L1-S1 and spinal length L1-S1.

Spinal mobilisation exercise had training effects for intervertebral disc anterior-posterior diameter L1-S1 and intervertebral disc sagittal CSA L1-S1. The intervention partially protected intervertebral disc volume L1-S1 and anterior intervertebral disc height L1-S1, and worsened lordosis angle L1-S1, intervertebral disc transverse diameter L1-S1, intervertebral disc axial CSA L1-S1, posterior intervertebral disc height L1-S1 and spinal Length L1-S1.

Lower body negative pressure treadmill had training effects for lumbar spine compressibility with 50% body weight and partially protected lordosis angle L1-S1, lumbar spine extension strength at various flexion angles and spinal length L1-S1.

Low magnitude mechanical signals had no observed training effects and partially protected intervertebral disc volume L1-S1, intervertebral disc nuclei pulposi volume L1-S1, intervertebral disc convexity L1-S1 and spinal length L1-S1.

Resistive exercise had no observed training effects. The intervention was able to partially protect lordosis angle L1-S1, posterior intervertebral disc height L1-S1, anterior intervertebral disc height L1-S1 and spinal length L1-S1, and worsened intervertebral disc volume L1-S1.

4. Discussion

Only seven bed-rest studies were found for inclusion. No single countermeasure was found to be successful in preventing all lumbopelvic musculoskeletal adaptations.

4.1. Muscle changes

The most effective countermeasure for preventing muscle changes appeared to be RVE, being the only one to have training effects, increasing external oblique and lumbar erector spinae muscle tonic activity during lower limb movements. Resistive vibration exercise also protected more against decreases in the size of the lumbar multifidus muscle than RE. This is relevant as preventing lumbar multifidus muscle atrophy maybe more important for mitigating spinal pain and injury risk, as this muscle has been linked to low back pain and injury [17-19, 25]. Resistance exercise (without vibration) had slightly larger effects than RVE for preventing decreases in quadratus lumborum and lumbar erector spinae muscle CSA. Flywheel exercise and SME had small or trivial effect sizes for protecting against all muscle changes for which they were assessed, except for SME, which partially prevents trunk flexion strength loss. Spinal mobilisation exercise effects on trunk strength may have been due to the way the exercises were performed, being large amplitude active spinal

movements in three planes [39]. Lower body negative pressure treadmill exercise was only trialled for preventing decreases in erector spinae muscle CSA at L4, for which it had a moderate effect. Erector spinae muscle CSA may not be as relevant to lumbopelvic injury and pain prevention as lumbar multifidus muscle atrophy. Resistive vibration exercise appears to be the most effective countermeasure for protecting against muscle changes. However, both RVE and RE would appear to cause further increases in psoas muscle CSA, and RVE would appear to cause additional increases in thoracic erector spinae muscle activity, all above the magnitude of change seen with no treatment. Psoas musce hypertophy may increase inbalances in the trunk flexion-extension strength ratio with greater flexion bias. Hypertrophy of the lumbopelvic flexors coupled with atrophy of the lumbopelvic extensors has been reported during inactive axial unloading simulation via bed-rest [35], and such an inbalance is a risk factor for LBP [41].

4.2. Spinal morphology changes

Lower body negative pressure treadmill exercise appeared to be most successful in protecting against spinal morphology changes as it was the only intervention able to fully prevent loss of lumbar lordosis and increased spinal length. Prolonged and maintained increased spinal length may be particularly relevant to injury and pain risk, having been linked to disc degeneration through interuption of the diurnal cycle of disc compression and expansion [4]. A diurnal disc cycle is needed for normal fluid and nutrition turnover observed during typical terrestrial sleep-wake/loading-unloading cycles, which become disrupted in bed-rest and spaceflight [4, 8, 9]. Decreased lordosis angle may also be a key outcome, as prolonged periods of flexed lumbar postures have been linked to tissue creep changes in disc and posterior spinal ligaments and disc prolapse on subsequent axial loading [42]. However, LBNP treadmill exercise has not been assessed for preventing any intervetebral disc changes specifically. Prolonged increases in disc volume due to lack of axially loaded compression periods are also considered to be a risk factor for disc degeneration [4]. Moreover, Adams and Hutton [42] suggested that the differences in anterior and posterior disc heights may be relevant to both lack of compression periods and prolonged flexion postures causing tissue creep. Future studies should assess the effectiveness of LBNP treadmill exercise against these outcomes.

Resistive vibration exercise was found to be partially effective for preventing increases in lumbar disc volume and spinal length. While it appeared detrimental to lumbar lordosis, it further increased anterior disc height, over the amount of change seen with no intervention. While increasing anterior disc height may be useful for reducing the posterior tissue creep caused by prolonged flexed posture, loss of lumbar lordosis could be an aggravating factor for posterior tissue creep, therefore maintaining stress on the intervertebral discs. These results call into question the effectiveness of resistive vibration exercise to prevent spinal morphology changes in bed-rest and un-loading situations. Low magnitude mechanical signals, partially protected lordosis angle, spinal length and disc volume. However, the LMMS effect sizes were very small and sometimes unclear. Resistance exercise partially protected lordosis angle, spinal length and anterior and posterior disc heights. However, it worsened disc volume and its protective effects were all small, being potentially mechanistically trivial, and less than RVE for protecting spinal length.

Flywheel exercise and SME were able to fully prevent some of the disc area and diameter changes. However, they both resulted in increased spinal length and posterior disc height compared to controls, which could increase risks of disc damage. Flywheel exercise was able to reduce anterior disc height. However, it increased posterior disc height, possibly due to the flexed posture adopted during the exercise. In combination with the fact that flexed postures have been linked to tissue creep and disc prolapse [42], this would appear to make FE an inappropriate countermeasure for the lumbopelvic region.

4.3. Current intervention evidence base

Six countermeasures for the lumbopelvic region have been trialled across seven published bed-rest studies. Two papers were based on data from the First Berlin Bed-rest Study [35, 40], which when combined with the bed rest populations used in the other five studies, resulted in six distinct trial populations. Comparibility between interventions was limited due to outcome heterogenity across the studies. Consequently, the quality of intervention recommendations for clinical use is restricted. Further research is advocated in this area as countermeasures have been shown to be unable to adequately protect against many lumbopelvic changes. Standardisation of outcome measures in the research community is recommended. None of the studies

attempted to blind participants, resulting in performance bias. While blinding participants in exercise intervention trials is acknowledged as being difficult due to potentially obvious sham interventions, potential methods to counter this, within back pain exercise therapy trials, have been suggested [43].

No population-reported outcome measures were used in the included studies. There is a risk of mismatch between clinician reported outcomes and population-reported outcomes regarding how effectively interventions meet the population's needs and preferences [44]. Additionally, there are no reported minimal worthwhile changes for lumbopelvic outcome measures. Missing patient-reported outcomes and known minimal clinically significant changes make it difficult to establish the clinical and patient-relevant effectiveness of interventions. In effect, the research performed in this area, to date, has only shown that mechanistic and statistically relevant changes can be achieved through use of the tested interventions. However, it remains unknown if the reported changes in surrogate outcome measures are ones which the astronauts consider relevant to their quality of life or if the intervention effects are clinically meaningful. It is recommended that future research attempts to establish clinically meaningful changes in lumbopelvic outcome measures and make use of population-reported outcome measures such as quality of life, activity scores and return to normal functional activity measures.

Interventions for the lumbopelvic region should not negatively impact the wider physiological changes caused by spaceflight or bed-rest simulation. Treatment effectiveness data could be combined from further systematic reviews, similar to this one, conducted across all physiological areas affected by unloading due to spaceflight or bed-rest. Resistance exercise, for example, may be required for maintenance of global lower limb muscles [30, 45]. Therefore, suggesting ways to modify axially loaded RE to reduce any increased risk of causing lumbopelvic damage, while still being effective outside the lumbopelvic region, may be preferable. An overall appraisal may be required to deal with conflicting recommendations from individual studies should differing effects be reported at various physiological regions in isolation.

4.4. Limitations of the systematic review

The small evidence base and heterogeneity of outcomes across studies limits conclusions. No true spaceflight population trials have been conducted in this area. Definitive data to determine if mechanisms of back pain and spinal injury are the same between bed-rest and spaceflight populations do not yet exist. Without data to compare bed-rest and astronaut populations, it is unknown if the effectiveness seen in analogue research will be the same in astronauts. Included studies used only surrogate, clinician reported outcome measures. Gaining access to patient views and the use of patient-reported outcome measures relating to quality of life, and ability to perform population-relevant functions post spaceflight, may also help drive intervention recommendations which are more clearly relevant to astronauts' and study participants' preferences and needs [44].

The duration of bed-rest across the included studies varied between 28 days and 90 days, which impacts on the comparability of studies. Additionally, the results reported from the bed-rest studies can be assumed as valid only for space flight of similar duration [32]. For example, the LBNP treadmill exercise results may only relate well to shorter duration spaceflight missions of around 28 days. Resistance exercise, RVE, LMMS, FE and SME, however, may relate more to longer duration spaceflight missions of 60-90 days.

5. Conclusions

This systematic review highlights the lack of consistency in the reporting of outcome measures to demonstrate the effectiveness of countermeasures to reduce the negative effect of microgravity exposure on the lumbopelvic musculoskeletal system, Despite the difficulty this creates in making meaningful comparisons between studies and between countermeasures, the analysis presented here showed that no countermeasure was successful in limiting or preventing all musculoskeletal changes seen. For example, LBNP treadmill exercise showed some training effects on spinal morphology, but was limited in its effects on muscle physiology. Conversely, resistive vibration exercise was successful in limiting or preventing some muscular changes, but had little beneficial effect on spinal morphology. More research is required into the different

mechanisms of interventions. Knowledge of effective mechanisms will be an important basis for the development and subsequent trial of interventions that are effective in minimising or even mitigating the effects of exposure to micro-gravity. These investigations should use standardised outcome measures which, in turn, should include population-reported outcomes and functional measures relevant to astronauts. Importantly, countermeasure studies should be developed to take place on the International Space Station (ISS), making use of an actual spaceflight environment, rather than solely in simulated microgravity. The fact that no countermeasure has been shown to be completely successful in preventing lumbopelvic musculoskeletal changes during spaceflight or simulated microgravity, at this time, highlights the need for an appropriate rehabilitation programme to be completed on return to upright gravitational loading.

6. References

[1] J.M. Gernand, Risk Assessment and Control Through Countermeasure System Implementation For Long-Term Crew Exposure to Microgravity, in: Proceedings of the International Mechanical Engineering Congress and Exposition, IMECE, Anaheim, CA, 2004.

[2] P.E. di Prampero, M.V. Narici, Muscles in microgravity: from fibres to human motion, Journal of Biomechanics, 36 (2003) 403-412.

[3] J.C. Buckey, Space Physiology, Oxford University Press, New York, 2006.

[4] J. Sayson, A. Hargens, Pathophysiology of Low Back Pain during Exposure to Microgravity, Aviation, Space and Environmental Medicine, 79 (2008) 365-373.

[5] C.J. Snijders, C.A. Richardson, J.A. Hides, A.L. Pool-Doudzwaard, D.L. Belavy, Low Back Pain during Flight - 1 Year Post-Flight Science Report, European Space Agency Report, ESA Proposal number 2003-DSM-MUS-100 (2011).

[6] A.L. Pool-Goudzwaard, D.L. Belavy, J.A. Hides, C. Richadson, A., C.J. Snijders, Low Back Pain in Microgravity and Bed Rest Studies, Aerospace Medicine and Human Performance, 86 (2015) 541-547.

[7] P. Wing, I. Tsang, L. Susak, R. Gagnon, J. Potts, Back pain and spinal changes in microgravity, Orthopedic Clinics of North America, 22 (1991) 255-262.

[8] S. Johnston, M. Campbell, R. Scheuring, A. Feiveson, Risk of hernated nucleus pulposus among US astronauts, Aviation, Space and Environments Medicine, 81 (2010) 566-574.

[9] D.L. Belavy, M. Adams, H. Brisby, B. Cagnie, L. Danneels, J. Fairbank, A.R. Hargens, S. Judex, R.A. Scheuring, R. Sovelius, J. Urban, J.H. van Dieen, H.-J. Wilke, Disc herniations in astronauts: What causes them, and what does it tell us about herniation on earth?, European Spine Journal, 24 (2015).

[10] V.R. Edgerton, G.E. McCall, J.A. Hodgeson, J. Gotto, C. Goulet, K. Fleischmann, R.R. Roy, Sensorimotor adaptations to microgravity in humans, The Journal of Experimental Biology, 204 (2001) 3217-3224.

[11] J.J. Widrick, J.G. Romatowski, K.M. Norenberg, S.T. Knuth, W. Bain, A.A. Riley, S.W. Trappe, T.A. Trappe, D.L. Costill, R.H. Fitts, Functional properties of slow and fast gastrocnemius muscle fibers after a 17-day spaceflight, Journal of Applied Physiology, 90 (2001) 2203-2211.

[12] A. LeBlanc, Rowe, R, Schneider, V, Evans, H,Hedrick, T., Regional muscle loss after short duration spaceflight, Aviation, Space, and Environmental Medicine, 66 (1995) 1151.

[13] S. Evetts, Anecdotal accounts of selective atrophy of trunk extensors over flexors in an astronaut population, personal communication, (2015).

[14] J.A. Hides, G. Lambrecht, R.C. A., W.R. Stanton, G. Armbrecht, C. Pruett, V. Damann, D. Felsenberg, D.L. Belavy, The effects of rehabilitation on the muscles of the trunk following prolonged bed rest, European Spine Journal, 20 (2011) 808-818.

[15] J.A. Hides, D.L. Belavy, W. Stanton, S.J. Wilson, J. Rittweger, D. Felsenberg, C.A. Richardson, Magnetic Resonance Imaging Assessment of Trunk Muscles During Prolonged Bed Rest, Spine, 32 (2007) 1687-1692.

[16] L.A. Danneels, G.G. Vanderstaeten, D.C. Cambier, E.E. Witvrouw, H.J. Cuyper, CT imaging of trunk muscles in chronic low back pain patients and healthy control subjects, European Spine Journal, 9 (2000) 266-272.

[17] J.A. Hides, M.J. Stokes, G.A. Jull, D.H. Cooper, Evidence of Lumbar Multifidus Muscle Wasting Ipsilateral to Symptoms in Patients with Acute/Subacute Low Back Pain, Spine, 19 (1994) 165-172.

[18] J. Hides, C. Gilmore, W. Stanton, E. Bohlscheid, Multifidus size and symmetry among chronic LBP and healthy asymptomatic subjects, Manual Therapy, 13 (2008) 43-49.

[19] A. Bergmark, Stability of the lumbar spine - A study in mechanical engineering, in, Department of Solid Mechanics, Lund Institute of Technology, Copenhagen, 1989.

[20] P. Hodges, Lumbopelvic stability: A functional model of the biomechanics and motor control, in: . Richardson C, Hodges P, and Hides J (eds) Therapuetic Exercise for Lumbopelvic Stabilization, Churchull Livingston, Edinburgh, 2004, pp. 13-28.

[21] P. Hodges, J. Cholewicki, Functional control of the spine, in: In Vleeming A, Mooney V and Stoeckart R(eds), Churchill Livingstone, Edinburgh, 2007, pp. 489-512.

[22] P. Hodges, G. Moseley, Pain and motor control of the lumbopelvic region: Effect and possible mechanisms., Journal of Electromyography and Kinesiology, 13 (2003) 361-370.

[23] M.M. Panjabi, The Stabilizing System of the Spine. Part 1. Function, Dysfunction, Adaptation, and Enhancment, Journal of Spinal Disorders & Techniques, 5 (1992a) 383 - 389.

[24] M.M. Panjabi, The Stabilizing System of the Spine. Part 2. Neutral Zone and Instability Hypothesis, Journal of Spinal Disorders & Techniques, 5 (1992b) 390 - 397.

[25] M.M. Panjabi, Clinical spinal instabiilty and low back pain, Journal of Electromyography and Kinesiology, 13 (2003) 371 - 379.

[26] C. Cochrane, Data collection form for intervention reviews: RCTs only, The Cochrane Collaboration, community.cochrane.org (2015) version 3.1 April 2014.

[27] PEDro, PEDro scale, The George Institute for Global Health, www.pedro.org.au (accessed: 8th July 2015), 1999.

[28] J. Higgins, D. Altman, J. Sterne, Chapter 8: Assessing risk of bias in included studies., in: Higgins JPT, Green A. (editors) Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0, The Cochrane Collbaboration, 2011.

[29] E.R. Morey-Holton, Ground-Based Models for Studying Adaptation to Altered Gravity, NASA Ames Research Centre Report - Moffet Field, CA, (2000).

[30] A. Pavy-Le Traon, M. Heer, M.V. Narici, J. Rittweger, J. Vernikos, From space to Earth: advances in human physiology from 20 years of bed rest studies (1986-2006), European Journal of Applied Physiology, 191 (2007) 143-194.

[31] G.R. Adams, V.J. Caiozzo, K.M. Baldwin, Skeletal muscle unweighting: spaceflight and ground-based models, Journal of Applied Physiology, 95 (2003) 2185-2201.

[32] E. Mulder, Bed rest protocols, Personal Communication, (2014).

[33] W.G. Hopkins, A Spreadsheet for Deriving a Confidence Interval, Mechanistic Inference and Clinical Inference from a P Value, Sportscience, 11 (2007) 16-20.

[34] D.L. Belavy, G. Armbrecht, U. Gast, C. Richadrson, J.A. Hides, D. Felsenberg, Countermeasures against lumbar spine deconditioning in prolonged bed rest: resistive exercise with and without whole body vibration, Journal of Applied Physiology, 109 (2010) 1801-1811.

[35] D.L.l. Belavy, J.A. Hides, S.J. Wilson, W. Stanton, F. C., J. Rittweger, D. Felsenberg, C.A. Richardson, Resistive Simulated Weightbearing Exercise with Whole Body Vibration Reduces Lumbar Spine Deconditioning in Bed-Rest, Spine, 33 (2008) 121-131.

[36] P. Cao, S. Kimura, B.R. Marcias, T. Ueno, D.E. Watenpaugh, A.R. Hargens, Exercise within lower body negative pressure partially counteracts lumbar spine deconditioning associated with 28-day bed rest, Journal of Applied Physiology, 99 (2005) 39-44.

[37] B.R. Marcias, P. Cao, D.E. Watenpaugh, A.R. Hargens, LBNP treadmill exercise maintains spine function and muscle strength in identical twins during 28-day simulated microgravity, Journal of Applied Physiology, 102 (2007) 2274-2278.

[38] N. Holguin, J. Muir, C. Rubin, S. Judex, Short applications of very low-magnitude vibrations attenuate expansion of the intervertrbral disc during extended bed rest, The Spine Journal, 9 (2009) 470-477.

[39] D.L. Belavy, H. Ohshima, M.-P. Bareille, J. Rittweger, D. Felsenberg, Limited effect of fly-wheel and spinal mobilisation exercise countermeasures on lumbar spine decondtioning during 90 d bed-rest in the Toulouse LTBR study, Acta Astronautica, 69 (2011) 406-419.

[40] D.L. Belavy, S.J. Wilson, G. Armbrecht, J. Rittweger, F. .Dieter, C.A. Richardson, Resistive vibration exercise during bed-rest reduces motor control changes in the lumbo-pelvic musculature., Journal of Electromyography and Kinesiology, 22 (2012) 21-30.

[41] J.-H. Lee, Y. Hoshino, K. Nahamura, Y. Kariya, k. Saita, K. Ito, Trunk Muscle Weakness as a Risk Factor for Low Back Pain - A 5 Year Prospective Study, Spine, 24 (1999) 54-57.

[42] M.A. Adams, W.C. Hutton, Prolapsed Intervertebral Disc - A Hyperflexion Injury, Spine, 7 (1982) 184-191.

[43] P.H. Helmhout, B.J. Staal, C.G. Maher, T. Petersen, J. Rainville, W.S. Shaw, Exercise Therapy and Low Back Pain Insights and Proppsals to Improve the Design, Conduct and Reporting of Clinical Trials, Spine, 33 (2008) 1782-1788.

[44] E. Nelson, E. Eftimovska, C. Lind, A. Hager, J. Wasson, S. Lindblad, Patient reported outcome measures in practice, British Medical Journal, 350 (2015) 7818.

[45] A. Ferrando, K. Tipton, M. Bamman, R. Wolfe, Resistance exercise maintains skeletal muscle protein synthesis during bed rest, Journal of Applied Physiology, 82 (1997) 807-810.

[46] M. Stokes, S. Evetts, J. Hides. Guest Editorial: Terrestrial neuro-muscular rehabilitation and astronaut reconditioning: reciprocal knowledge transfer. Musculoskelet Sci Pract 2017; 27(Suppl1): 1-4.

Acknowledgements

We acknowledge members of the European Space Agency (ESA) Topical Team on “Exercise after space (rehabilitation)” for their contributions to this review (see Stokes et al. [46] for team members). Specifically, we thank Gunda Lambrecht (ESA Physiotherapist, Space Medicine Office) and Dan Barry (retired NASA astronaut).

Table captions

Table 1. Bed-rest methodological quality assessment

Table 2. Characteristics of included studies

Table 3. Results of all quality control assessments performed across all included studies

Table 4. The effects of all muscle related changes assessed across all studies

Table 5. The effects of interventions on spinal morphology changes across all studies.

Table 1

Point	Criteria
1	Was the bed-rest six degree head down tilt to simulate cephlad fluid shift?
2	Was diet individualised and controlled?
3	Was the daily routine fixed – with set wake – sleep times and same routines for all?
4	Are all phases of bed-rest standardised for all participants – same baseline data collection period, same bed-rest time and same recovery phase?
5	Was the bed-rest 'horizontal posture' maintained except for when the test condition required it? I.e. personal hygiene, bowel movements, urination should all occur in bed, no visitors should be allowed and knees should not be flexed?
6	Was sunlight exposure prohibited and participants supplemented with vitamin D?
7	Were all measurements scheduled the same for all participants and done at the same time of day?
8	Was the duration of bed-rest stated?

Table 2

Study	Design	Population	Interventions	Control	Outcomes Measures
Cao et al. (2005)	Randomised controlled trial	Twelve sets of identical twins. One twin randomly assigned to control and other to the intervention group during 28 days of six degree head down tilt bed-rest.	Test group (n=12) exercising in a lower body negative pressure treadmill in a supine suspended position for 40mins 6 days per week. Loaded to one body weight. All % are of VO2 max (maximal Oxygen uptake): 7mins warm up at 40%, 3mins at 60%, 2mins at 40%, 3mins at 70%, 2mins at 50%, 3mins at 80%, 2mins at 60%, 3mins at 80%, 2mins at 50%, 3mins at 70%, 2mins at 40%, 3mins at 60% and 5mins cool down at 50%.	Control group (n=12); no intervention during bed-rest	MRI measures of: spinal length, lumbar disc heights, lumbar intervertebral angle, cross sectional area of Psoas and Erector Spinae muscles.
Marcias et al. (2007)	Randomised controlled trial	Fifteen sets of identical twins. One twin randomly assigned to control and the other to the intervention group. In six degree head down tilt bed-rest for 30 days.	Test group (n=15) exercise using a lower body negative pressure treadmill in a supine suspended position. 40min exercise period at 40-80% peak oxygen consumption 6 days a week for 30 days. Loaded to one body weight.	Control group (n=15);no intervention during bed-rest	MRI 1 day before bed-rest, on day 28 of bed-rest. MRI measures of: Spinal length, spinal compressibility, disc height. Lumbar strength pre and post bed-rest determined with lumbar extension dynamometer.
Belavy et al. (2008) Berlin bed-rest study 1	Randomised controlled trial.	Nineteen healthy males during 56 days of head down tilt bed-rest. One test group and one control group.	Test group (n=9) Two RVE sessions daily, lasting 5-10 minutes each. RVE: Squat, heel raise and toe raise. In morning session also did explosive kick (full force knee extension). Resistance set greater than body weight. Whole body vibration set at 19-26Hz frequency and 3.5-4mm amplitude. Loaded to 1.2-1.9 times body weight.	Control group (n=10); no intervention during bed-rest.	MRI on day one of bed-rest and then at two week periods during bed-rest. Follow up scans at recovery days 4, 14, 28, 90 and 180. MRI measures of: Lumbar spine length, disc area, and height, intervertebral angles, cross sections of Lumbar Multifidus, Erector Spinae, Quadratus Lumborum, Psoas, Rectus Abdominis, External and Internal Oblique and Transversus Abdominialis muscles.

Study	Design	Population	Interventions	Control	Outcomes Measures
Holguin et al. (2009)	Randomised controlled trial	Twenty nine healthy volunteers during 90 days of supine bed-rest One test group and one control group.	Test group (n=18) low magnitude vibration exercise at 30Hz delivered at the feet while loaded to 60% of their body mass using a harness system for 10mins each day. Knees straight but not locked out during the stimulation.	Control group (n=11); no intervention during bed-rest	MRI at start of bed-rest, day 60 and 90 and 7 days post bed-rest at the S1-L1 area. MRI Disc volume and convexity and spinal length L1-S1. CT scan of intrinsic back muscle volume.
Belavy et al. (2010) Berlin bed-rest study 2	Randomised controlled trial. Two test groups and one control group.	Twenty four healthy males during 60 days of six degrees head down tilt bed-rest.	Test group one (n=7) RE only. Test group two (n=8) RVE. Exercise performed three days per week. RE: Bilateral squat, single leg heel raise, double leg heel raise, back and toe raise. Resistance set greater than body weight. RVE: Same as RE with whole body vibration of 24Hz frequency and 3.5-4mm amplitude. Loaded to 1.3-1.5 times body weight	Control group (n=9); no intervention during bed-rest.	MRI pre bed-rest and on bed-rest days 27/28 and 55/56: Spine length L1-S1, disk volume, disk height, lumbar lordosis angle. MRI measures of: Cross sectional areas of Lumbar Multifidus, Erector Spinae, Quadratus Lumborum and Psoas muscles. Low back pain questionnaire pre bed-rest, every day during first two weeks, then weekly throughout remaining bed-rest period.
Belavy et al. (2011)	Randomised controlled trial. Two test groups and one control group.	Twenty five healthy males during 90 days of six degrees head down tilt bed-rest.	Test group one (n=8) fly wheel exercise sessions every third day during bed-rest. Exercises used an ergometer utilising the inertia of a rotating flywheel to provide resistance during concentric and eccentric actions. The flywheel device was configured to exercise during 6 degree head down bedrest. Flywheel exercises used were supine squat and calf press. Test group two (n=7) spinal mobilisations, by performing large amplitude low load slow trunk movements of the frontal, sagittal and longitudinal plane five times daily. Mobilisations were done as a self-mobilisation exercise.	Control group (n=9); no intervention during bed-rest.	MRI 17 days prior to bed-rest and on day 89 of bed-rest and either 13 or 90 days after bed-rest. MRI measures of: Disc heights, disc CSA, lumbar lordosis angle. Cross section of Multifidus, Erector Spinae, Quadratus, Psoas and Iliacus muscles.

Study	Design	Population	Interventions	Control	Outcomes Measures
Belavy et al. (2012) Berlin bed-rest study 1	Randomised controlled trial.	Twenty healthy males, aged 20-45 years, during 56 days of six degree head down tilt bed-rest. One test group and one control group.	Test group (n=10) RVE sessions daily, lasting 5-10 minutes each. Squat, heel raise, toe raise and explosive kicks (knee extension) with whole body vibration at 19-26Hz frequency and 4mm amplitude. Loaded to 1.2-1.9 times body weight.	Control group (n=10); no intervention during bed-rest	Electromyography of Erector Spinae, Internal and External Obliques, Gluteus Maximus and Lumbar Multifidus muscles. Specifically measured: lumbopelvic extensor-flexor co-contraction ratio, change in muscles tonic activity and extensor-flexor activity ratio.

Abbreviations: RVE; resistance vibration exercise, RE; resistance exercise, BBR; Berlin Bed-rest Study

Table 3

	Belavy et al. (2010)	**Belavy et al. (2008)**	**Belavy et al.** (2011)	**Belavy et al** (2012)	**Cao et al.** (2005)	**Holguin et al.** (2009)	**Marcias et al.** (2007)
PEDro criteria (short description)							
Eligibility criteria specified	✓	✓	✓	✓	✓	✓	✓
Random allocation	✓	✓	✓	✓	✓	✓	✓
Concealed allocation	×	×	×	×	×	×	×
Similar baseline groups	✓	✓	✓	✓	✓	✓	✓
Blinding of participants	×	×	×	×	×	×	×
Blinding of therapists	×	×	×	×	×	×	×
Blinding of assessors	✓	✓	✓	×	×	×	×
Measures obtained from 85% of participants	✓	✓	×	×	✓	✓	✓
All participants received treatment or intention to treat analysis performed	✓	✓	×	×	✓	✓	✓
Between groups statistics	✓	✓	✓	✓	✓	✓	✓
Point and variability measures	✓	✓	✓	✓	✓	✓	✓
Total score	**8**	**8**	**6**	**5**	**7**	**7**	**7**
Risk of bias criteria (short description)							
Random sequence generation	?	?	?	?	?	?	?
Allocation concealment	↑	↑	?	↑	↑	↑	↑
Blinding of participants and assessors	↑	↑	↑	↑	↑	↑	↑
Blinding of outcome assessment	↓	↓	↓	↑	↑	↑	↑
Incomplete outcome data	↓	↓	?	?	↓	↑	↓
Selective reporting	↓	↓	↓	↓	↓	↓	↓
Total score	**↑**	**↑**	**↑**	**↑**	**↑**	**↑**	**↑**
Bed-rest criteria (short description)							
Six degree head down tilt	✓	?*	✓	?*	✓	✓	✓
Individualised and controlled diet	✓	✓	✓	✓	?	✓	?
Set daily routine with fixed wake/seep time	✓	?	?	?	?	?	?
Bed-rest phases standardised for all participants	✓	✓	✓	✓	?	✓	✓
Uninterrupted bed-rest except for test condition	✓	?	?	?	✓	?	?
Sunlight exposure prohibited	?	?	?	?	?	?	?
All measures taken same day and time	✓	✓	✓	✓	?	✓	✓
Bed-rest duration (days)	60	56	90	60	28	90	28
Total points met	**6**	**4**	**3**	**5**	**2**	**3**	**2**

*Participants were allowed to raise trunk to 30 degrees tilt during day activities

Table 4

	N	Increase/ decrease in inactive controls	Effect size ±90% CI	Probability of true effect being mechanistically (±SD when pooled)		% recovered off baseline
				Small	Moderate	(±SD when pooled)
Resistance Vibration Exercise						
Multifidus muscle CSA L1-L5 pooled	16	↓	0.9±0.8 [1]	86.8±18.2%↑	80.3±15.8%↑	-36±30%
Multifidus muscle CSA at L4	19	↓	2.7±1.0 [2]	100%↑	100%↑	-30%
Erector Spinae muscle CSA L1-L5 pooled	16	↓	0.6±0.9 [1]	86±9.5 %↑	77.1±13.4%↑	-65±14%
Erector Spinae muscle lumbar tonic activity	20	↑	-2.9±1.1 [5]	100%↓	100%↓	+20% (training)
Erector Spinae muscle thoracic tonic activity	20	↑	0.6±0.8 [5]	89.2%↑	80.5%↑	-220%
Psoas muscle cross sectional area L1-L5 pooled	16	↑	0.7±0.9 [1]	89.5±19.3%↑	84.9±24.9%↑	-280±144%
Quadratus Lumborum muscle CSA L1-L4 pooled	16	↓	0.7±0.9 [1]	85.3±17.5%↑	78±23.9%↑	-31±21%
Lumbopelvic extensor-flexor co-contraction	20	↓	4.3±1.3 [5]	100%↑	100%↑	+80% (training)
Lumbopelvic extensor-flexor activity	20	↑	-3.0±1.0 [5]	100%↓	100%↓	+433% (training)
Inferior Gluteus Maximus muscle tonic activity	20	↓	2.6±1.0 [5]	100%↑	100%↑	-3.60%
External Oblique muscle tonic activity	20	↓	2.7±1.0 [5]	100%↑	100%↑	+200% (training)
Internal Oblique muscle tonic activity	20	↑	-1.1±0.8 [5]	98.7%↓	97.1%↓	-13%
Flywheel Exercise						
Multifidus muscle volume L1-S1	17	↓	0.3±0.8 [3]	68.1%↑	52.8%↑	-80%
Erector Spinae muscle volume L1-S1	17	↓	0.4±0.8 [3]	71.2%↑	56.7%↑	-70%
Psoas muscle volume L1-S1	17	↑	-0.3±0.8 [3]	68.2%↓	53.1%↓	-40%
Quadratus Lumborum volume L1-S1	17	↑	-0.2±0.8 [3]	61.3%↓	46.5%↓	-183%
Isokinetic strength trunk extension	17	↓	0.2±0.8 [3]	58.1%↑	42.9%↑	-80%
Isokinetic strength trunk flexion	17	↓	-1.0±0.8 [3]	96%↓	92%↓	-184%
Spinal Mobilisations						
Multifidus muscle volume L1-S1	16	↓	0.3±0.8 [3]	67.1%↑	52.5%↑	-85%
Erector Spinae muscle volume L1-S1	16	↓	-0.1±0.8 [3]	48.3%↓	32.1%↓	-110%
Psoas muscle volume L1-S1	16		0.0±0.8 [3]	Unclear	Unclear	-96%
Quadratus Lumborum muscle volume L1-S1	16	↓	-0.4±0.8 [3]	72.4%↓	59.4%↓	-250%
Isokinetic strength trunk extension	16	↓	0.4±0.8 [3]	70.3%↑	56.5%↑	-60%

Isokinetic strength trunk flexion	16	↓	1.1±0.9 [3]	97%↑	94%↑	-14%
Lower Body Negative Pressure Treadmill						
Erector Spinae muscle CSA at L4	24	↓	1.0±0.8 [4]	97.5%↑	94.7%↑	-79.49±14%
Resistance Exercise						
Multifidus muscle CSA L1-L5 pooled	16	↓	0.6±0.8 [1]	80.3±15.8%↑	70.3±21.8%↑	-56±15%
Erector Spinae muscle CSA L1-L5 pooled	16	↓	1.3±0.9 [1]	98.2±1.3%↑	96.2±2.6%↑	-33±16%
Psoas muscle cross sectional area L1-L5 pooled	16	↑	0.5±0.8 [1]	84±33.3%↑	81.2±37.3%↑	-257±172%
Quadratus Lumborum muscle CSA L1-L4 pooled	16	↓	1.0±0.8 [1]	93±9%↑	88.1±14%↑	-6±6%

1= Belavy et al. [36], 2 = Belavy et al. [34], 3= Belavy et al. [40], 4= Cao et al. [37]. 5 = Belavy et al. [35], 6= Marcias et al. [39] and 7 = Holguin et al. [38].

Table 5

	n	Increase/ decrease in inactive controls	Effect size ±90% CI	Probability of true effect being mechanistically		% recovery off baseline
				Small	Moderate	
Resistance Vibration Exercise						
Lordosis angle L1-S1	16	↓	-0.1±0.8 [1]	52.7%↓	37.5%↓	-124%
IV disc volume L1-S1	16	↑	-0.36±0.8 [1]	71%↓	56.6%↓	-73%
IV disc sagittal CSA L1-S1		↓	-2.9±1.1 [2]	100%↓	100%↓	-9%
Posterior IV disc height L1-S1	16	↑	-0.1±0.8 [1]	52.1%↓	37.1%↓	95%
Anterior IV disc height L1-S1	16	↑	0.4±0.8 [1]	75.2%↑	61.5%↑	-126%
Spinal length L1-S1	16	↑	-1.1±0.9[1]	81.5±26.1%↓	73.8±37%↓	-60±41%
Flywheel Exercise						
Lordosis angle L1-S1	17	↑	-0.2±0.8 [3]	57.3%↓	41.8%↓	-62%
IV disc volume L1-S1	17	↑	-0.5±0.8 [3]	79.2%↓	66.4%↓	-56.00%
IV disc anterior-posterior diameter L1-S1	17	↑	-1.4±0.9 [3]	99.2%↓	85.5%↓	+550% (training)
IV disc transverse diameter L1-S1	17	↓	-1.8±0.9 [3]	99.9%↓	99.8%↓	-600%
IV disc axial CSA L1-S1	17	↓	-1.9±1.0 [3]	99.9%↓	93.9%↓	-2900%
IV disc sagittal CSA L1-S1	17	↑	-1.0±0.9 [3]	95.8%↓	91.6%↓	+117% (training)
Posterior IV disc height L1-S1	17	↑	0.7±0.8 [3]	88.5%↑	79.6%↑	-260%
Anterior IV disc height L1-S1	17	↑	-0.2±0.8 [3]	56.2%↓	40.6%↓	-87%
Spinal length L1-S1	17	↑	0.1±0.8 [3]	51%↑	36%↑	-108%
Spinal Mobilisations						
Lordosis angle L1-S1	16	↑	0.4±0.8 [3]	71.2%↑	57%↑	-171%
IV disc volume L1-S1	16	↑	-0.1±0.8 [3]	51.1%↓	36.1%↓	-92%
IV disc anterior-posterior diameter L1-S1	16	↑	-0.6±0.9 [3]	98.3%↓	75.5%↓	+200% (training)
IV disc transverse diameter L1-S1	16	↓	-1.8±1.0 [3]	99.7%↓	99.6%↓	-600%
IV disc axial CSA L1-S1	16	↓	-0.9±0.9 [3]	99.8%↓	88.2%↓	-1400%
IV disc sagittal CSA L1-S1	16	↑	-0.7±0.9 [3]	87%↓	78.1%↓	+33% (training)
Posterior IV disc height L1-S1	16	↑	0.9±0.9 [3]	93.6%↑	88.1%↑	-283%
Anterior IV disc height L1-S1	16	↑	-0.2±0.8 [3]	60.6%↓	46.1%↓	-85%

Spinal length L1-S1	16	↑	0.2±0.8 [3]	53.9%↑	37.8%↑	-117%
Lower Body Negative Pressure Treadmill						
Lordosis angle L1-S1	24	↓	1.2±0.7 [4]	99.4%↑	98.7%↑	-58%
Lordosis angle with 50% body weight	30	-	-0.7±0.7 [6]	95.1%↓	90%↓	No change in inactive bed-rest to compare
Lumbar spine compressibility with 50% body weight	30	↓	3.2±0.9 [6]	100%↑	100%↑	+20% (training)
Lumbar spine extension strength at various flexion angles	30	↓	1.4±0.7 [6]	99.9%↑	99.8%↑	-28%
Spinal length L1-S1	24	↑	-2.7±0.9[4]	100%↓	100%↓	-65%
Low Magnitude Mechanical Signals						
IV disc volume L1-S1	24	↑	-0.1±0.7 [7]	51±8.21%↓	34.6±6.2%↓	-82.1±18.4%
IV disc nucleusi pulposi volume L1-S1 pooled	24	↑	**At L1, 2, 4** 0.1±0.7 [7] **At L3, 5** -0.3±0.7 [7]	**At L1, 2, 4** 47.5±5%↑ **At L3, 5** 66.9±12%↓	**At L1, 2, 4** 32.1±6%↑ **At L3, 5** 49.5±11%↓	-90±54%
IV disc convexity L1-S1 pooled	24	↓	1.2±0.8 [7]	96.8±3.5%↑	92.8±7.2%↑	-10±25%
Spinal length L1-S1	24	↑	-0.3±0.7[7]	66.5%↓	48.9%↓	-58%
Resistance Exercise						
Lordosis angle L1-S1	16	↓	0.1±0.8 [1]	50.9%↑	35.3%↑	-76%
IV disc volume L1-S1	16	↑	0.1±0.8 [1]	47.5%↑	32.1%↑	-104%
Posterior IV disc height L1-S1	16	↑	-0.1±0.8 [1]	52.1%↓	36.8%↓	-95%
Anterior IV disc height L1-S1	16	↑	-0.1±0.8 [1]	54.8%↓	39.3%↓	-91%
Spinal length L1-S1	24	↑	-0.6±0.8[3]	85.7%↓	75.5%↓	-75%

1= Belavy et al. [36], 2 = Belavy et al. [34], 3= Belavy et al. [40], 4= Cao et al. [37]. 5 = Belavy et al. [35], 6= Marcias et al. [39] and 7 = Holguin et al. [38].

Figure captions

Figure 1. Postural adaptation to microgravity, showing loss of normal spinal curvature and increased flexion of the spinal column. Illustration ©2004 William Scavone (Kestrel Illustration Studio).

Figure 1

Supplementary Table Captions

Supplementary Table A. Search term construction

Supplementary Table B. Results of all quality control assessments performed across all included studies

Supplementary Table C. Indication of which interventions were assessed against the various outcomes used across all studies

Supplementary Table A

Search number	Term	Key words in Boolean search format	Reason
1	Rehabilitation	rehabilitate OR rehabilitation OR recover* OR recovery	Locate studies which consider rehabilitation
2	Spaceflight /analogues	spaceflight OR space* OR space flight OR astronaut* OR microgravity OR micro gravity OR bed-rest OR bedrest OR weightless*	To find studies using spaceflight or simulating microgravity terrestrially using bed-rest.
3	Musculoskeletal	muscle* OR bone* OR skeletal OR musculoskeletal OR neuromusculoskeletal	Limiting search to musculoskeletal area
4	Intervention	intervention* OR treat OR treatment* OR physio OR physiotherapy OR physical therapy OR therapy OR exercise OR program* OR exercise program*	To find research which considered actual interventions
5	Lumbopelvic	lumb* OR pelv* OR low back OR lower back	Limiting search to interventions for the lumbopelvic region
6	Countermeasures	countermeasure* OR counter* OR protect* OR maintain OR prevent* OR train*	Locate studies which consider countermeasures
7	Combined rehab search	1 AND 2 AND 3 AND 4 AND 5	Search for musculoskeletal rehabilitation interventions for

			lumbopelvic region linked to spaceflight or bed-rest
8	Combined countermeasures search	2 AND 3 AND 4 AND 5 AND 6	Search for musculoskeletal countermeasure interventions for lumbopelvic region linked to spaceflight or bed bed-restrest
9		1 AND 2 AND 3	Less specific combination
10		4 AND 2 AND 3	Less specific combination
11		1 AND 2 AND 5	Less specific combination
12		4 AND 2 AND 5	Less specific combination
13		6 AND 2 AND 3	Less specific combination
14		6 AND 2 AND 5	Less specific combination
15		7 OR 8 OR 9 OR 10 OR 11 OR 12	Increased sensitivity search to check for any missed studies

Supplementary Table B

	Belavy et al. (2010)	**Belavy et al. (2008)**	**Belavy et al.** (2011)	**Belavy et al** (2012)	**Cao et al.** (2005)	**Holguin et al.** (2009)	**Marcias et al.** (2007)
PEDro criteria (short description)							
Eligibility criteria specified	✓	✓	✓	✓	✓	✓	✓
Random allocation	✓	✓	✓	✓	✓	✓	✓
Concealed allocation	×	×	×	×	×	×	×
Similar baseline groups	✓	✓	✓	✓	✓	✓	✓
Blinding of participants	×	×	×	×	×	×	×
Blinding of therapists	×	×	×	×	×	×	×
Blinding of assessors	✓	✓	✓	×	×	×	×
Measures obtained from 85% of participants	✓	✓	×	×	✓	✓	✓
All participants received treatment or intention to treat analysis performed	✓	✓	×	×	✓	✓	✓
Between groups statistics	✓	✓	✓	✓	✓	✓	✓
Point and variability measures	✓	✓	✓	✓	✓	✓	✓
Total score	**8**	**8**	**6**	**5**	**7**	**7**	**7**
Risk of bias criteria (short description)							
Random sequence generation	?	?	?	?	?	?	?
Allocation concealment	↑	↑	?	↑	↑	↑	↑
Blinding of participants and assessors	↑	↑	↑	↑	↑	↑	↑
Blinding of outcome assessment	↓	↓	↓	↑	↑	↑	↑
Incomplete outcome data	↓	↓	?	?	↓	↑	↓
Selective reporting	↓	↓	↓	↓	↓	↓	↓
Total score	**↑**	**↑**	**↑**	**↑**	**↑**	**↑**	**↑**
Bed-rest criteria (short description)							
Six degree head down tilt	✓	?*	✓	?*	✓	✓	✓
Individualised and controlled diet	✓	✓	✓	✓	?	✓	?
Set daily routine with fixed wake/seep time	✓	?	?	?	?	?	?
Bed-rest phases standardised for all participants	✓	✓	✓	✓	?	✓	✓
Uninterrupted bed-rest except for test condition	✓	?	?	?	✓	?	?
Sunlight exposure prohibited	?	?	?	?	?	?	?
All measures taken same day and time	✓	✓	✓	✓	?	✓	✓
Bed-rest duration (days)	60	56	90	60	28	90	28
Total points met	**6**	**4**	**3**	**5**	**2**	**3**	**2**

*Participants were allowed to raise trunk to 30 degrees tilt during day activities

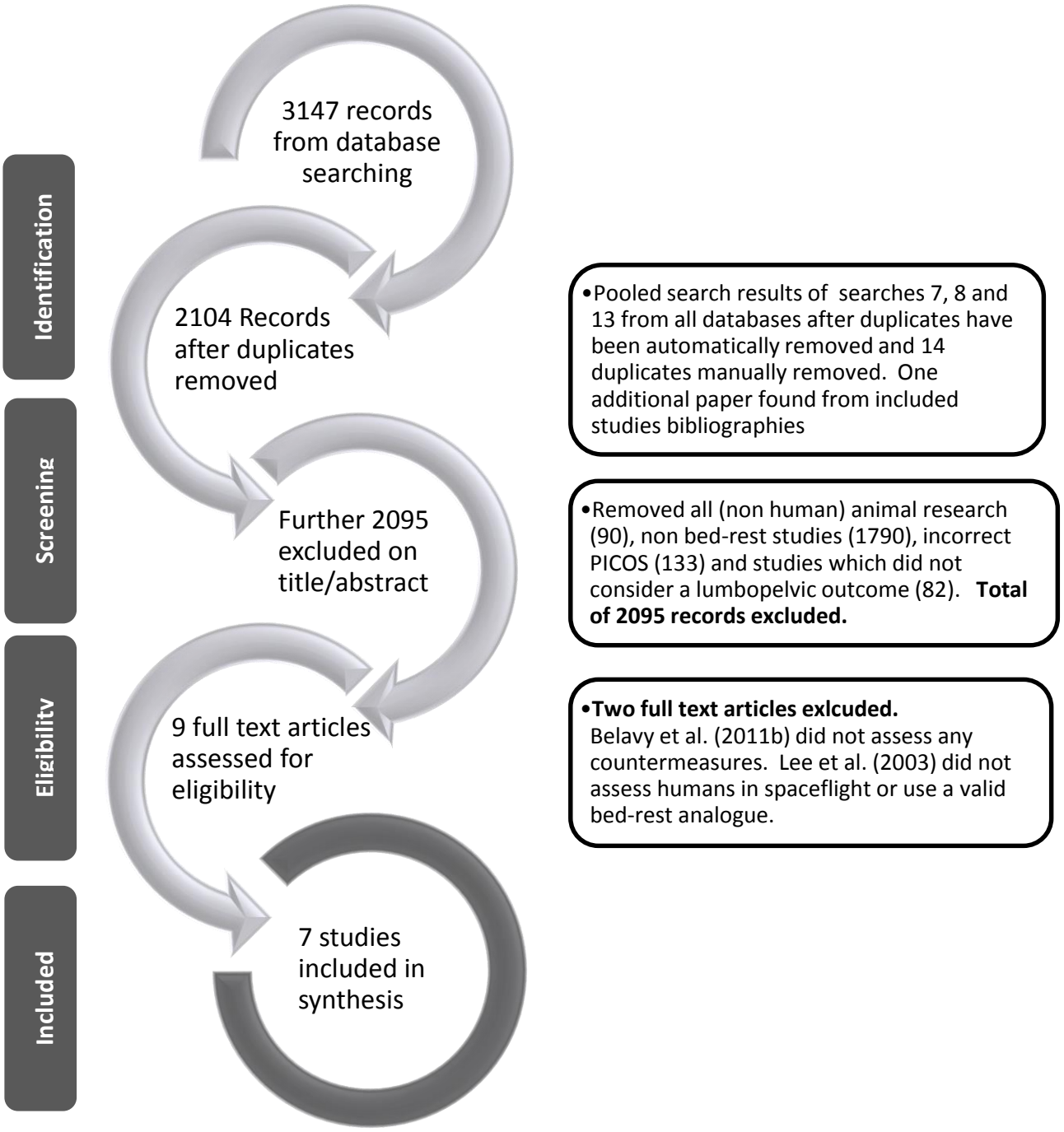
Supplementary Table C

Outcomes	RVE	Flywheel	Spinal mobs	LBNP treadmill	LMMS	RE
Multifidus muscle CSA L1-L5 averaged	✓					✓
Multifidus muscle CSA at L4	✓					
Multifidus muscle volume L1-S1		✓	✓			
Erector Spinae muscle CSA L1-L5 averaged	✓					✓
Erector Spinae muscle CSA at L4				✓		
Erector Spinae muscle volume L1-S1		✓	✓			
Erector Spinae muscle lumbar tonic activity	✓					
Erector Spinae muscle thoracic tonic activity	✓					
Psoas muscle cross sectional area L1-L5 averaged	✓					✓
Psoas muscle volume L1-S1		✓	✓			
Quadratus Lumborum muscle CSA L1-L4 averaged	✓					✓
Quadratus Lumborum muscle volume L1-S1		✓	✓			
Lumbopelvic extensor-flexor co-contraction	✓					
Lumbopelvic extensor-flexor activity	✓					
Inferior Gluteus muscle Maximus tonic activity	✓					
External Oblique muscle tonic activity	✓					
Internal Oblique muscle tonic activity	✓					
Isokinetic strength trunk extension		✓	✓			
Isokinetic strength trunk flexion		✓	✓			
Lordosis angle L1-S1	✓	✓	✓	✓		✓
Lordosis angle with 50% body weight				✓		
Lumbar spine compressibility with 50% body weight				✓		

Outcomes	RVE	Flywheel	Spinal mobs	LBNP treadmill	LMMS	RE
Lumbar spine extension strength at various flexion angles				✓		
IV disc volume L1-S1	✓	✓	✓		✓	✓
IV disc anterior-posterior diameter L1-S1		✓	✓			
IV disc transverse diameter L1-S1		✓	✓			
IV disc axial CSA L1-S1		✓	✓			
IV disc sagittal CSA L1-S1	✓	✓	✓			
IV disc nucleus pulposa volume L1-S1 averaged					✓	
IV disc convexity L1-S1 averaged					✓	
Posterior IV disc height	✓	✓	✓			✓
Anterior IV disc height	✓	✓	✓			✓
Spinal length L1-S1	✓	✓	✓	✓	✓	✓

RVE: resistive vibration exercise, RE: resistive exercise, IV: intervertebral, CSA: cross sectional area, L# and S# refer to lumbar and sacral spinal regions, LMMS: low magnitude mechanical stimulation, SMC: specific motor control.

Supplementary Figure A



Supplementary Figure A. Search and screening results shown in PRISMA flow diagram standard