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To the Moon, Mars and Beyond: Recommending Exercise Countermeasures Against Musculoskeletal and Cardiovascular Deconditioning During Microgravity Exposure, for Future Spacecraft Applications

Jonathan Michael Laws

PhD

2021

To the Moon, Mars and Beyond: Recommending Exercise Countermeasures Against Musculoskeletal and Cardiovascular Deconditioning During Microgravity Exposure, for Future Spacecraft Applications

Jonathan Michael Laws

A thesis submitted in partial fulfilment of the requirements of the University of Northumbria at Newcastle for the degree of Doctor of Philosophy

Research undertaken in the Faculty of Sport, Exercise, and Rehabilitation

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Abstract

Exposure to the microgravity environment during spaceflight can lead to the deconditioning of physiological systems that are concerned with mechanical loading, the musculoskeletal and cardiovascular systems. Deconditioning of the musculoskeletal and cardiovascular systems can impact astronaut health and operational performance both during and after spaceflight. Physical exercise is a common countermeasure that has been implemented to reduce or eliminate these negative physiological outcomes. The Orion Multi Purpose Crew Vehicle (MPCV) is the next generation of exploration capsular spacecraft intended for use during crewed missions beyond low Earth orbit, however, it is constrained by technical limitations that might prevent the use of the exercise countermeasures currently used on-board the International Space Station. To prepare for future spaceflight using the MPCV, it is necessary to investigate the constraints of the MPCV and recommend new exercise countermeasures against musculoskeletal and cardiovascular deconditioning that are effective within these constraints.

To achieve this, the thesis identified the technical constraints of the Orion MPCV and transferable capsular spacecraft that prevent the use of current ISS exercise countermeasures using a qualitative systematic review. Next, a mixed-methods systematic review investigating the musculoskeletal and cardiovascular outcomes of greatest relevance to astronaut health and operational success was conducted to enable selection of exercise recommendations based on the highest priority space medical needs. Having identified both the technical constraints of the Orion MPCV and the most important outcomes, it was then possible to identify the most effective exercise countermeasures that may work within the constraints of the MPCV for space medicine priority outcomes using a quantitative systematic review and meta-analysis. Self-reported outcomes from astronauts on their preferences for an exercise device during spaceflight were collected via a qualitative survey and analysed to provide additional context and input to help inform final exercise recommendations.

The findings indicate that a flywheel device may be the most effective exercise countermeasure for use during spaceflight to reduce musculoskeletal and cardiovascular deconditioning for missions of up to 30 days. Any potential countermeasure, including flywheel, must be assessed against the technical constraints of the Orion MPCV identified within this thesis to ensure its suitability. For missions of longer than 30 days, astronauts indicated a single countermeasure alone might not be sufficient as limited options may induce boredom, reducing adherence to exercise prescriptions and risking their health and the chance of operational mission success. Missions of longer than 30 days should consider implementing a larger spacecraft or deep-space habitat for use alongside the Orion MPCV in which the volume and mass constraints preventing the use of only a single exercise device can be negated. Considerations should be made for the entertainment of astronauts during exercise (such as access to podcasts) to prevent boredom and increase adherence to exercise. Additional social considerations,

including the implementation of team exercises, or exercise that utilises the spaceflight environment might also be useful in increasing adherence to exercise.

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Where a colleague has been directly involved beyond advice or supervision (e.g. secondary reviewer for inclusion/exclusion screening) their initials are noted within the main thesis text to clarify their contribution(s).

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Declaration

I declare that the work contained in this thesis has not been submitted for any other award and that it is all my own work. I also confirm that this work fully acknowledges opinions, ideas and contributions from the work of others.

Any ethical clearance for the research presented in this thesis has been approved. Approval has been sought and granted by the Faculty Ethics Committee on 19/10/20.

I declare that the Word Count of this Thesis is 61290 words

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Date: 27/09/2021

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1. Chapter One: Introduction

1.1. Introduction

1.1.1. Rationale

Since the SkyLab and Mir space missions it has been clear that exposure to microgravity during spaceflight can result in the deconditioning of human physiological systems that are concerned with mechanical loading, the musculoskeletal and cardiovascular systems (Hargens, Bhattacharya, & Schneider, 2013; Rittweger et al., 2018; Williams, Kuipers, Mukai, & Thirsk, 2009). These adaptations to the microgravity environment may affect crew performance during spaceflight, impacting their capability to perform prolonged or strenuous tasks or affect their safety both during spaceflight and upon return to a gravity-loaded environment (Evans, Knapp, & Goswami, 2018). These negative physiological outcomes may become amplified as a result of longer duration spaceflight beyond Low Earth Orbit (LEO) (Kanas & Manzey, 2008), such as during transit periods to the Moon, Mars, and beyond (Williams et al., 2009). Physical exercise can be used to reduce the adverse effects of microgravity exposure (Perusek et al., 2015), however, the use of current exercise countermeasures may be constrained by the technical limitations of future spacecraft designed for use beyond LEO (Anderson & Stambaugh, 2015).

During microgravity exposure astronauts are no longer subject to the weight-bearing or axial loads they experience on Earth, leading to deconditioning of the physiological systems that concern mechanical loading (Baker, Barratt, & Wear, 2008). For the muscular system, the most significant adverse changes are a reduction in muscle strength and power (Akima, Foley, Prior, Dudley, & Meyer, 2002; Alkner & Tesch, 2004) and the atrophy of muscles, particularly within the postural muscles of the trunk and lower limbs (English, Lee, Loehr, Ploutz–Snyder, & Ploutz–Snyder, 2015) that are adapted to oppose gravity on Earth (Scheuring, 2010; Shackelford, 2019). For example, some astronauts experience more than a 20% reduction in muscle strength during spaceflight (Ploutz-Snyder, Ryder, English, Haddad, & Baldwin, 2015). Deconditioning of the deep spinal muscles, such as the lumbar multifidus and transversus abdominis, have also been linked to reduced motor control and low back pain which may present additional challenges to the safety and performance of astronauts (Hides et al., 2020).

Specific to the skeletal system, the most significant adverse change is the development of osteopenia which demineralises the bones that provide support in opposing gravity on Earth (Shackelford, 2019). Decreases in bone density may lead to an increased risk of bone fracture and kidney stones (Richter, Braunstein, Winnard, Nasser, & Weber, 2017; Wang et al., 2019). For example, over an average of 4.5 months astronauts may experience bone loss of 1-3% under microgravity conditions (Smith et al., 2012).

In the case of the cardiovascular system, decreased gravitational input leads to an immediate fluid shift towards the head and the alteration and disruption of cardiovascular regulatory mechanisms and

systems (Evans et al., 2018; Norsk, Asmar, Damgaard, & Christensen, 2015). These alterations may include atrophy of the cardiac muscle, a decrease in central venous pressure, blood pressure, and plasma volume (Buckey, Lane, et al., 1996; Dorfman et al., 2008; Tanaka, Nishimura, & Kawai, 2017). One of the most common cardiovascular problems stemming from these alterations is the development of orthostatic intolerance, which has been reported in up to 64% of astronauts (Buckey, Lane, et al., 1996; Platts et al., 2014). Orthostatic intolerance is concerning upon return to a gravity-loaded environment, where astronauts may lose their tolerance for standing, leading to increased risks of syncope and presyncope (Evans et al., 2018; Kaderka, Young, & Paloski, 2010).

In order to mitigate this deconditioning, a range of countermeasures are used. The most frequently used countermeasure for musculoskeletal and cardiovascular deconditioning during microgravity exposure is physical exercise (LeBlanc, Spector, Evans, & Sibonga, 2007). To function within the microgravity environment, exercise countermeasures are designed with specific adaptations, such as the fitting of a harness and loading system, which provides a force to keep astronauts attached to the exercise device (De Witt & Ploutz-Snyder, 2014). Current exercise countermeasures used on-board the International Space Station (ISS) include: the Advanced Resistive Exercise Device (ARED), Cycle Ergometer with Vibration Isolation System (CEVIS), and a treadmill (T2) (Loehr et al., 2015; Petersen et al., 2016).

To reduce musculoskeletal and cardiovascular deconditioning, astronauts need to use these exercise countermeasures for up to 2.5 hours per day, 6 to 7 days per week, including 60 minutes preparation time for equipment set-up and storage (Petersen et al., 2016; Richter et al., 2017). Despite the general effectiveness of current ISS exercise countermeasures, such as ARED (Jagodnik et al., 2016), they have not historically been capable of fully protecting the musculoskeletal and cardiovascular systems of all individuals during microgravity exposure (Hargens et al., 2013; Rittweger, 2019; Tanaka et al., 2017). While other physiological systems are also impacted by microgravity exposure, for example the neurovestibular system (Hallgren et al., 2015; Van Ombergen et al., 2017), these are not attenuated by exercise countermeasures (Mulavara et al., 2018) and, therefore, beyond the scope of this thesis.

The future of human spaceflight will take us beyond LEO: back to the Moon; to asteroids; and, within 30 years by current estimates, to the planet Mars (Kanas, 2013; Williams et al., 2009). The Orion Multi-Purpose Crew Vehicle (MPCV) (Figure 1.1 and 1.2) is the newest generation of exploration mission spacecraft that has been planned for use during many of these missions beyond LEO (Thompson et al., 2014). The Orion MPCV has been designed for exploration beyond LEO of up to 21 days (Burns et al., 2013). A number of other future spacecraft are planned for spaceflight beyond LEO, although they are still in the early process of development (SpaceX, 2017). The MPCV is already undergoing test flights (Cichan, Norris, & Marshall, 2015); and the first human flight is

expected by 2022 (Hambleton, 2018); the current focus of preparing for spaceflight beyond LEO is, therefore, on the MPCV.

Figure 1.1 The Orion MPCV crew module (top) with European Service Module (base) attachment (Etherington, 2020)

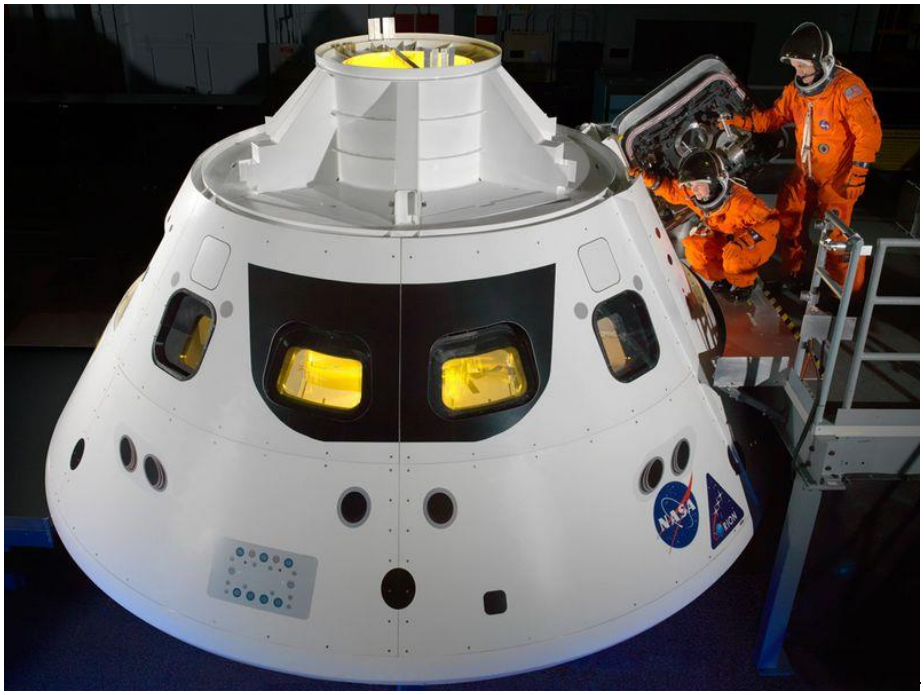

Figure 1.2 Mock-up of the Orion MPCV crew module with astronauts for size comparison (Klesius, 2007)

Relative to orbital space stations and non-capsular spacecraft, the MPCV is constrained by technical limitations that hinder astronauts' capabilities to effectively exercise as a countermeasure to musculoskeletal and cardiovascular deconditioning (Thompson et al., 2014). Whilst exercise can be used to reduce the adverse effects of microgravity exposure (Perusek et al., 2015), it is not yet fully understood what constraints the MPCV's design may place upon such countermeasures (Anderson et al., 2015). This is because there is currently no publicly available synthesis of how these constraints might impact the delivery of exercise countermeasures (Anderson et al., 2015).

Previous literature has identified that some limitations of future exploration vehicles include: volume and mass restrictions, which do not provide an adequate area for current exercise countermeasure technologies (De la Torre, 2014) and may limit the storage of consumables such as food and water (Scott, Weber, & Green, 2019); limited electrical power, which will prevent the use of exercise technologies that require a large power supply (Sheehan et al., 2016); logistical constraints, such as the maintenance and repair of exercise devices; operational constraints, such as time allocation for exercises that do not conflict with the crewmembers work (Scott et al., 2019); and life support systems, which will be unable to effectively filter exercise by-products such as heat, water vapour and carbon dioxide produced at their average rates per 90 minutes (up to 30 minutes of exercise per person in a crew of three) (Ryder, Scott, Ploutz-Snyder, & Ploutz-Snyder, 2016). Whilst these limitations have been identified, it is not clear which of these are specifically in reference to the MPCV and similar spacecraft, and which of these are in reference to much larger spacecraft that will not experience the same mass and volume constraints. This is because a majority of the literature refers

only to “exploration vehicles” when discussing future spaceflight beyond LEO, rather than specifying a certain spacecraft such as the MPCV (e.g. Richter et al., 2017; Scott, Weber, & Green, 2019). This is problematic because the term “exploration vehicle” can refer to a range of diverse spacecraft including the ISS (Thompson et al., 2015); the multi-mission space exploration vehicle, and the lunar lander (Metcalf, Peterson, Carrasquillo, & Bagdigian, 2012).

As space agencies and commercial spaceflight enterprises aim to expand beyond low Earth orbit (SpaceX, 2017; Thompson et al., 2014) it is essential that astronaut health and the success of those missions will not be placed at risk. To prepare astronauts for crewed spaceflight using the MPCV, new exercise countermeasures will need to be recommended and developed for use during these missions. NASA have designed a number of potential exercise countermeasures for this purpose, including the Resistive Overload Combined with Kinetic Yo-yo (ROCKY) (Williams, 2016) and the Advanced Twin Lifting and Aerobic System (ATLAS) (Funk et al., n.d), however there are no trial data available to indicate their effectiveness or to determine their suitability for use within Orion. In order to recommend new exercise countermeasures, it will be necessary to first identify all known technical constraints of the MPCV in order to determine which exercise devices are able to work within its limitations. The musculoskeletal and cardiovascular outcomes of greatest relevance to astronaut health and operational success will also need to be identified to ensure that any recommended exercise countermeasures are effective for maintaining the health of astronauts during microgravity exposure. Exercise countermeasures will then need to be assessed for their effectiveness on the outcomes of greatest relevance to astronaut health. Patient-reported outcomes should also be identified to assess if astronauts will have any concerns or preferences regarding the implementation of an MPCV exercise countermeasure device. Final recommendations on the most effective exercise device for use on-board the Orion MPCV and transferable capsular spacecraft can then be made.

1.1.2. Aims and Objectives

The aim of this thesis is to recommend exercise countermeasures to mitigate against musculoskeletal and cardiovascular deconditioning for use on-board the Orion MPCV during future spaceflight missions.

To achieve this, the thesis objectives are to:

1) identify the technical constraints of the Orion MPCV that will prevent or reduce the capability of astronauts to exercise effectively during spaceflight.
    a. This will be achieved through a qualitative systematic review of the current evidence base (Chapter 2).

2) determine the most important musculoskeletal and cardiovascular outcomes, from a medical operations perspective, that should be considered when recommending exercise countermeasures for use on the Orion MPCV
    a. This will be achieved through a mixed-methods systematic reviews identifying the musculoskeletal and cardiovascular outcomes of greatest relevance to astronaut health and operational success (Chapter 3).
3) determine the most effective exercise countermeasure, based upon actual and simulated microgravity trials.
    a. This will be achieved by a quantitative systematic review and meta-analysis to identify the most effective exercise countermeasure, for the greatest benefit on the outcomes identified in Chapter 3. This chapter will further consider the suitability of these countermeasures for use within the technical constraints of Orion identified in Chapter 2 (Chapter 4).
4) determine astronaut preferences for the design, development and implemtation of an exercise device in the Orion MPCV
    a. This will be achieved through a qualitative survey of astronauts exploring patient-reported preferences for the design, development and implementation of an exercise device, to supplement and inform the final recommendation for an MPCV exercise countermeasure (Chapter 5).

Chapter 6 will provide an overall summary of the original contribution to knowledge made by this thesis, implications of the research in terms of both systematic review methodology and spaceflight medical operations policy, limitations of the research, and final recommendations for the development of exercise countermeasures for use on the Orion MPCV.

2. Chapter Two: Technical constraints of the Orion Multi-Purpose Crew Vehicle that affect the capability of astronauts to exercise effectively during spaceflight, a systematic review

This chapter has been peer-reviewed and published as:

Laws, J. M., Caplan, N., Bruce, C., McGrogan, C., Lindsay, K., Wild, B., ... & Winnard, A. (2020). Systematic review of the technical and physiological constraints of the Orion Multi-Purpose Crew Vehicle that affect the capability of astronauts to exercise effectively during spaceflight. *Acta Astronautica*, *170*, 665-677.

2.1. Introduction

The first step in recommending exercise countermeasures for use on-board the Orion MPCV and transferable capsular spacecraft was to identify the technical constraints that will limit or prevent the use of current ISS countermeasures for musculoskeletal and cardiovascular deconditioning. By systematically reviewing the evidence base of this field to determine the technical constraints of the MPCV it will be possible to consider future exercise countermeasure design within the framework of the MPCV's technical limitations. Systematic reviews form an essential role within evidence-based research by providing a comprehensive assessment of existing evidence and identifying gaps or obstacles within the literature to research goals (Robinson, Saldanha, & Mckoy, 2011). Conducting a systematic review on the technical constraints of the MPCV and transferable capsular spacecraft will aid in the development of future research questions and inform the types of questions and research designs necessary to answer those questions (Robinson et al., 2011); such as determining the most effective exercise countermeasures that can work within the constraints of the MPCV and transferable capsular spacecraft. The aim of the systematic review in this chapter was to identify the technical constraints of the Orion MPCV or transferable capsular spacecraft that will have an impact on the capability of astronauts to exercise effectively during spaceflight.

2.2. Methods and Materials

The following systematic review was conducted following the protocols set out in the Aerospace Medicine Systematic Review Group (AMSRG) methods guides (Winnard et al., 2021), which adapt the gold standard terrestrial medical systematic review Cochrane Collaboration guidelines (Higgins et al., 2019), thematic analysis (Braun & Clarke, 2006; Braun, Clarke, Hayfield, & Terry, 2019), and thematic synthesis (Thomas & Harden, 2008) to space medicine reviews. The PRISMA standards (Preferred Reporting Items for Systematic reviews and Meta Analyses) (Moher et al., 2015) checklist was followed to ensure gold standard, transparent and complete reporting of results.

2.2.1. Search Strategy

A range of terms (mpcv, orion mpcv, exploration vehicle, exercise*, physical exercise, exercise area, exercise test, test, training, squat, technical constraint*, physical constraint, biomechanical, modelling, hybrid, lifting kit, grey water, gray water, humidity, oxygen, O2, straps, fire risk, friction, respiration, volume, energy consumption, stabilization, sweat, gaseous composition, isolation, crew time, vibration, habitation module) were used in combinations to search the NASA Technical Reports Server (NTRS), NASA Life Science Data Archive (LSDA), and the Texas Digital Library (TDL) in December 2018. The range of search terms for each database were decided by a pre-scoping search of the literature and through a meeting of the supervision team and academic colleagues (JL, AW, KL)

to ensure that each search would capture the most relevant results possible. Separate search strategies (Table 1) using Boolean logic were developed for each of the databases included in the final review. Due to limitations of the databases examined (discussed in detail in section 2.4.7.), the search strategy for each database had to be modified and shortened. Modifications to each search strategy were informed by the results of pre-scoping in order to ensure that relevant documents were still captured during the systematic search (Appendix A). The full search strategy can be seen in Table 2.1.

Table 2.1 Search strategies for NTRS, LSDA and TDL

Search number	Term	Key words in Boolean search format	Reason
NASA Technical Report Server Search Strategy:			
1	Orion MPCV	“MPCV” OR “Orion MPCV”.	Locate studies which consider the Orion MPCV.
2	Exercise	“Exercise*” OR “Physical Exercise”.	To find studies that are related to astronaut exercise and fitness.
3	Technical Constraints	“squat” OR “biomechanical” OR “modelling” OR “hybrid” OR “lifting kit” OR "grey water" OR "gray water" OR "humidity" OR "oxygen" OR "O2" OR "Straps" OR "fire risk" OR "friction" OR "respiration" OR "volume" OR "energy consumption" OR "stabilization" OR "sweat" OR “technical constraint”.	Limiting search to technical constraints.
4	Combined/ Increased sensitivity search	1 AND 2 AND 3.	Combined Search.
NASA Life Science Data Archive Search Strategy:			
1	MPCV	Orion OR MPCV OR Exploration vehicle.	Locate studies which consider the Orion MPCV.
2	Exercise	Exercise OR Exercise area OR Exercise test OR test OR Training.	To find studies that are related to astronaut exercise and fitness.
3	Technical Constraints	Technical constraint OR Sweat OR straps OR Volume.	Limiting search to technical constraints.
4	Combined/ Increased sensitivity search	1 AND 2 AND 3.	Combined Search.
Texas Digital Library Search Strategy:			
1	MPCV	“MPCV”.	Locate studies which consider the Orion MPCV.
2	Exercise	“Exercise*”.	To find studies that are related to astronaut exercise and fitness.
3	Technical Constraints	“lifting kit” OR “gaseous composition” OR “physical constraints” OR “isolation” OR “volume” OR “crew time” OR “vibration” OR “sweat” OR "technical constraint*" OR “habitation module”.	Limiting search to technical constraints.
4	Combined/ Increased sensitivity search	1 AND 2 AND 3.	Combined Search.

2.2.2. Inclusion Criteria

Any studies that did not meet the inclusion criteria were excluded. No restrictions on language, publication date or status were applied. As the Orion MPCV is a very new vehicle and its full technical limitations are likely classified within NASA databases (as indicated by pre-scoping of the literature) the inclusion criteria is expanded to consider grey literature sources, such as technical reports and presentations. The full inclusion criteria are presented in Table 2.2.

Table 2.2 Inclusion Criteria

Participants/Populations	**Intervention/Interest**	**Control/Comparison**	**Outcome Measures**	**Study Types**
Orion MPCV or transferable spacecraft. The criteria for vehicles transferable to the Orion MPCV are all human capsular exploration class mission vehicles (Faget et al., 1963). As such, the following spacecraft are considered transferable: Soyuz; Shenzhou; Vostok; Voskhod; Mercury; Gemini; Apollo; SpaceX Dragon V2; Boeing CST-100 Starliner; Federatsiya/Federation; Gaganyaan/ISRO Orbital Vehicle; and Crew Exploration Vehicle (Faget et al., 1963).	Physiological or technical constraints of spacecraft.	No control/comparison as this is not an intervention review.	Prevent or reduce the capability of astronauts to exercise effectively during spaceflight.	All relevant literature of interest to the topic was included in the review.

2.2.3. Study Selection and Data Extraction

The initial screening of documents, using abstracts and titles, was carried out by the lead author (JL) and an academic colleague (CM) using the Rayyan systematic review online application (Ouzzani, Hammady, Fedorowicz, & Elmagarmid, 2016). was blinded to the inclusion or exclusion of documents by the other. If it was unclear from the initial screening whether a study met the inclusion criteria, the full text of the document was obtained. Any conflict or uncertainty in study inclusion was discussed once blinded screening had been completed and agreed upon with a member of the supervision team (AW). NVivo 12 (QSR NVivo 12, 2014) was used to extract data from each paper by the lead author (JL) and a sample of this extracted data was assessed by a colleague (BW) to increase reliability. An additional colleague (CB) advised and assisted with the extraction of data from NVivo. Any disagreements were discussed until a consensus was reached.

2.2.4. Quality Assessment

All relevant documents included in the review consisted of grey literature and technical documents. There is no universally accepted model or method in use for assessing the validity and quality of integrative review data, such as grey literature and technical documents (Russell, 2005). Accordingly, a tool developed by the Aerospace Medicine Systematic Review Group at Northumbria University (Laws & Winnard, 2019b) was used to assess the overall quality and rank of evidence compared to other sources of evidence, and to assess the reported content in comparison to an "ideal design" (Laws et al., 2019b). The design of the developed tool was based upon a pre-existing evidence levelling system (Cuenca & Crawford, 2011); as well as guidance provided on the quality scoring of integrative literature (Whittemore & Knafl, 2005). It is important to consider here that the method is yet to be validated.

The quality scoring tool is split into two sections: 'Evidence Level' and 'Clarity and Consistency'. The evidence level section works on a point scale of 1–7, wherein documents are given a score depending on the corresponding evidence level of the document. For example, documents that are meta-analyses receive the highest score of 7, whilst documents that are laws and regulations receive the lowest score of 1. The criteria for the evidence level section, as reproduced from Cuenca et al. (2011), are as follows:

- Meta-analysis of multiple large sample or small sample randomised controlled studies, or meta-synthesis of qualitative studies with results that consistently support a specific action, intervention or treatment receive a score of 7.
- Well-designed controlled studies, both randomized and nonrandomized, prospective or retrospective studies, and integrative reviews with results that consistently support a specific action, intervention, or treatment receive a score of 6.

- Qualitative studies, descriptive or correlational studies, integrative reviews, systematic reviews, or randomized controlled trials with inconsistent results receive a score of 5.
- Peer-reviewed professional organizational standards, with clinical studies to support recommendations receive a score of 4.
- Theory-based evidence from expert opinion or multiple case reports, case studies, consensus of experts, and literature reviews receive a score of 3.
- Manufacturer's recommendation; anecdotes receive a score of 2.
- Laws and regulations (local, state, federal; licensing boards, accreditation bodies, etc) receive a score of 1.

Section 2, clarity and consistency, involves rating documents on four individual criteria for which a score of 1 is awarded for each criterion met (resulting in a maximum possible score of 4). The criteria assess whether:

- The factual information of the document is clearly sourced.
- The methodological information is clearly stated and/or sourced.
- The information is clearly explained/of clear information value.
- The information is representative of all available primary sources.

The scores for sections 1 and 2 of the quality scoring tool are totalled for a final quality score where a higher score indicates a higher quality document. Two academic colleagues (JL and BW) independently quality assessed each included study by means of the quality assessment tool; any disagreements were discussed to reach consensus. If consensus was not possible, a member of the supervision team (AW) was consulted.

2.2.5. Data Analysis

As all of the data included in this review were qualitative in nature, qualitative analysis of the systematic review data followed the Braun and Clarke thematic analysis method (Braun et al., 2006; Braun et al., 2019). Thematic analysis is a data-driven approach that involves a six step processing of qualitative data through systematic identification and organisation to offer insight into themes (patterns of meaning) within a data set (Braun et al., 2019). Analysis further employed methods from thematic synthesis, a shortened three-step version of thematic analysis to the integration of qualitative data in systematic reviews (Thomas et al., 2008). While thematic synthesis uses the principles of thematic analysis, it also includes the use of computer software to aid the analysis of qualitative data (Thomas et al., 2008), such as NVivo 12 (QSR NVivo 12, 2014). Thematic synthesis has been implemented in a number of previous qualitative systematic reviews (Harden et al., 2006; Harden et al., 2004; Thomas et al., 2007; Thomas et al., 2003) and is a method that allows qualitative synthesis

of primary data without compromising the key principles of systematic review research (Barnett-Page & Thomas, 2009; Thomas et al., 2008). While this review has used the full six-stage thematic analysis (Braun et al., 2006), it integrates a thematic synthesis approach to analysis through the use of qualitative data analysis software (QSR NVivo 12, 2014).

The first stage of thematic analysis involves familiarisation with the included literature, namely: reading and re-reading of the data; highlighting of relevant information; noting of ideas; and becoming familiar with the overall content of the data set (Braun et al., 2019). Documents included in the review are uploaded into a qualitative data management software (QSR NVivo 12, 2014)) (Thomas et al., 2008).

The second stage involves generating initial codes. Codes are labels for identifying features within the data sets relevant to the research question (Braun et al., 2019). Within this review, for example, individual technical constraints of the Orion MPCV (such as power constraints) would be identified as codes. Using NVivo 12 (QSR NVivo 12, 2014) text is selected from the included documents and coded.

The third stage involves searching for themes. Themes describe important concepts within the dataset that are relevant to the research question and are constructed based upon similarities; overlap, and broad topics within the codes identified during the second stage. Codes are assigned to different themes based upon patterned responses within the data that are relevant to the research question (Braun et al., 2019). For example, the codes "CO_2 removal constraints" and "O_2 consumption constraints" may be grouped into a theme based upon respiratory or environmental constraints. This stage further involves the consideration of how different themes may relate to one another and how they tell an overarching story about the data set in preparation for the fourth stage (Braun et al., 2019).

The fourth stage involves reviewing the potential themes. This stage involves the quality checking of potential themes against the extracts taken from the dataset to ensure that the theme logically describes the data. This stage involves asking a number of questions: is the theme a theme and not just a code? Does the theme provide useful information about the dataset? What does the theme include and exclude? Is there enough data to support the theme? Is the theme too wide-ranging or diverse? Themes may have to be expanded or split into separate themes during this stage to better fit the dataset (Braun et al., 2019).

The fifth stage involves the defining and naming of the identified themes. This involves the development of clearly independent themes which are specific and unique. Final themes should have a singular focus and may be related, but do not overlap, with other themes, and each theme should directly address the research question. Some themes may have sub-themes that emerge within them (Braun et al., 2019; Côté, Salmela, Baria, & Russell, 1993). Themes may be grouped into dimensions (major themes), higher order themes (sub themes), and lower order themes (codes) (Nowell, Norris,

White, & Moules, 2017). For example, while it was clear that within this dataset the lower order themes CO_2 removal constraints, O_2 consumption constraints, heat generation and cooling constraints, and humidity and moisture removal constraints were all aspects of metabolic management, a more suitable theme to group these under in relation to the research question was the higher order theme "environmental control and life support constraints" as each constraint is managed by environmental control and life support systems of the spacecraft. To enhance the trustworthiness of the results, analyst triangulation can be used in which a second researcher (in this review an academic colleague, CB) analyses a sample of the themed data independently and any disagreements are agreed between the two researchers (Nowell et al., 2017).

The sixth and final stage involves producing the report. The aim of the report writing stage is to produce a compelling narrative, based upon the themes and codes, in answer to the research question. Themes should connect logically and may build upon previous themes to produce a narrative (Braun et al., 2019).

2.3. Results

A total of 877 documents were identified, including 1 document from the screening of reference lists, which were reduced to 352 after duplicates were removed. 331 documents were excluded after screening of the title and abstracts of the documents were completed. The full text was obtained for the remaining 21 documents, and 2 exclusions were made. The final number of documents included in the review was 19 (Figure 2.1).

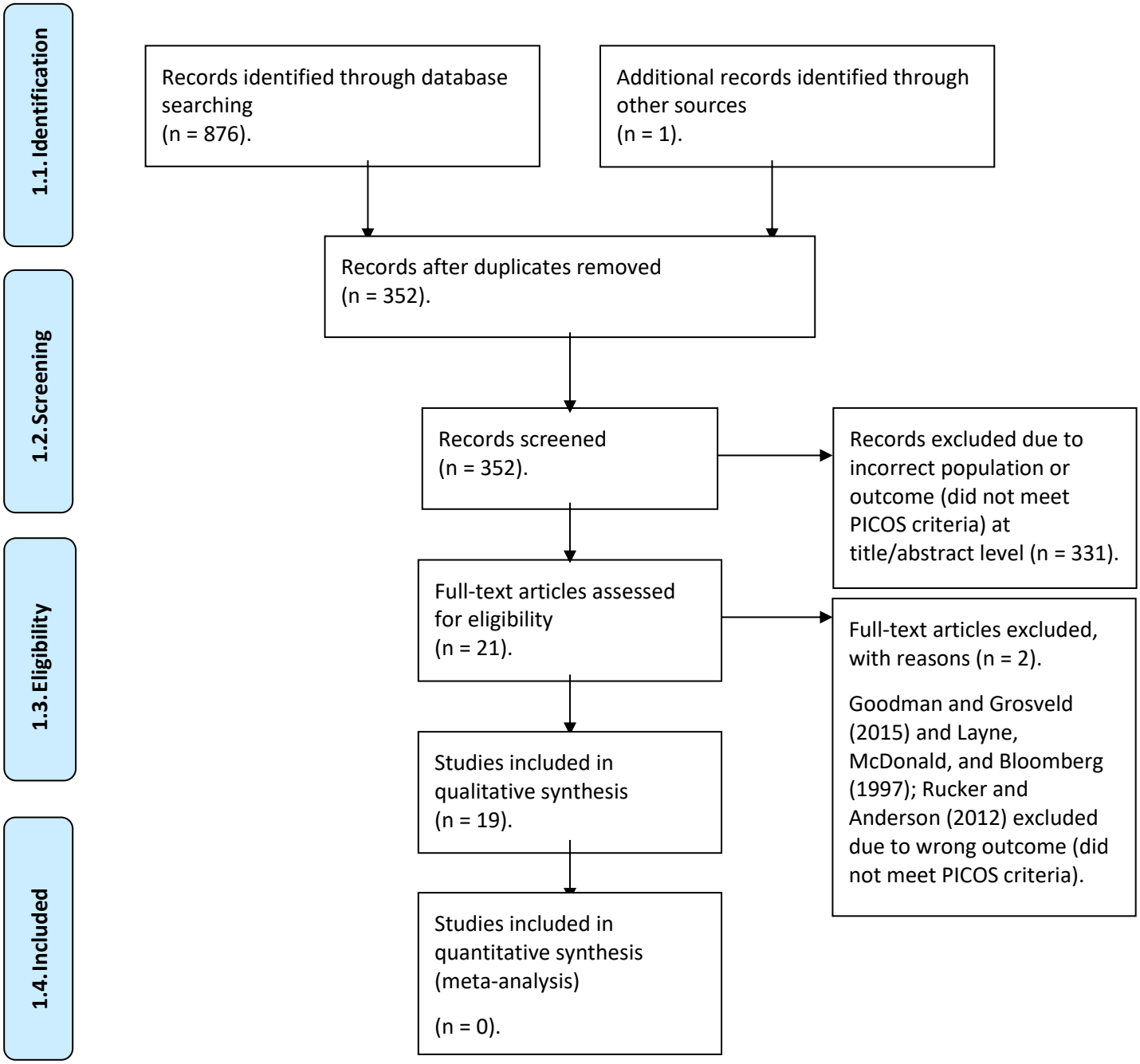

Figure 2.1 PRISMA flow diagram displaying search and screening results

2.3.1. Characteristics of Included Documents

The characteristics of the included documents are summarised in Table 2.3. All of the included documents were in English. Of the documents included two were academic/scientific posters, three were conference papers, one was a lab report abstract, one was a conference paper abstract, one was a lab report (cohort study), eight were PowerPoint presentations and three were technical report documents. All 19 of the documents from which data could be extracted were included for thematic analysis. For documents that included no date, or were only abstracts, requests were made for the full paper and/or date, but no responses were received from the authors, with the exception of one. Personal communication with a NASA representative (N. Raimondi, Personal Communication, August 23, 2019) has indicated that for the Ryder et al. (2016) paper, only an abstract was submitted and as such no full paper exists. The information contained within the abstract was still included for thematic analysis.

Table 2.3 Characteristics of the Included Studies

Author(s)	Document type	Technical constraint(s) reported
Steinberg (2015)	Technical Report	Limited Mass of Spacecraft, Limited Volume of Spacecraft
Funk et al. (n.d)	Conference paper	Limited Mass of Spacecraft, Limited Volume of Spacecraft, Limited Power Usage/Access
Sheehan et al. (2016)	PowerPoint presentation	Limited Mass of Spacecraft, Limited Volume of Spacecraft, Limited Power Usage/Access
Thompson et al. (2015)	Technical report	Limited Mass of Spacecraft, Limited Volume of Spacecraft, Limited Power Usage/Access
De Witt, Caldwell, Fincke, Newby, and Scott- Pandorf (n.d)	Lab report (Cohort Study)	Limited Mass of Spacecraft, Limited Volume of Spacecraft
Downs, Hanson, and Newby (2015)	Technical Report	Limited Mass of Spacecraft, Limited Volume of Spacecraft
Moore, Howard, and Mendeck (2014)	Conference paper	Limited Mass of Spacecraft, Limited Volume of Spacecraft, CO2 Removal Limitations, Heat Generation and Cooling, Humidity and Moisture Control
Perusek et al. (2015)	PowerPoint presentation	Limited Mass of Spacecraft, Limited Volume of Spacecraft, Limited Power Usage/Access
Downs et al. (2017)	PowerPoint presentation	Limited Mass of Spacecraft, Limited Volume of Spacecraft, Limited Power Usage/Access
Thompson et al. (2014)	Conference paper	Limited Mass of Spacecraft, Limited Volume of Spacecraft, Limited Power Usage/Access
Witt (2016)	PowerPoint presentation	Limited Volume of Spacecraft, Limited Power Usage/Access, Heat Generation and Cooling
Godfrey, Humphreys, Funk, Perusek, and Lewandowski (2017)	PowerPoint presentation	Limited Volume of Spacecraft
Downs (2017)	Academic/Scientific Poster	Limited Volume of Spacecraft, Limited Power Usage/Access
Moore (2016)	PowerPoint Presentation	Limited Volume of Spacecraft, Limited Power Usage/Access, Limited Mass of Spacecraft, Limited Volume of Spacecraft, Limited Power Usage/Access, CO2 Removal Limitations, O2 Consumption Limitations, Heat Generation and Cooling, Humidity and Moisture Control, Noise Generation Limitations, Spacecraft Structural Integrity, Vibration of Exercise Device, Exercise Device Structural Integrity, Isolation of Exercise Device, Stabilisation of Exercise Device
Gallo, Thompson, Lewandowski, and Jagodnik (2016)	PowerPoint presentation	Limited Volume of Spacecraft
Lewandowski et al. (2016)	PowerPoint presentation	Limited Mass of Spacecraft, Limited Volume of Spacecraft, Limited Power Usage/Access
Ryder et al. (2016)	Conference paper (Abstract only)	Limited Volume of Spacecraft, Humidity and Moisture Control, Data Transmission Limitations
Colosky (n.d)	Lab report (Abstract only)	Limited Mass of Spacecraft, Limited Volume of Spacecraft, Limited Power Usage/Access
Buxton, Kalogera, and Hanson (2017)	Academic/Scientific Poster	Limited Volume of Spacecraft

2.3.2. Quality Scoring

For section 1 (evidence level criteria) all 19 documents included for analysis were ranked as theory based evidence, resulting in a quality score of 3. This indicates that all of the studies included were theory-based evidence from expert opinion or multiple case reports, case studies, consensus of experts, and literature reviews.

For section 2 (clarity and consistency) only two documents received the highest possible score of 4. Six documents received a score of 2 and the remaining documents received a score of 1.

The sum of section 1 (evidence level) and section 2 (clarity and consistency) scores resulted in a total overall quality score for each document; the higher the score, the higher the overall quality of the document. The lowest score of 4 was met by 11 documents. The highest score was 7 was met by two documents, with the remaining 6 documents receiving a total score of 5. A summary of the overall quality scores for all documents can be seen in Table 2.4.

Table 2.4 Quality scoring results across all studies, ticks indicate a condition was met, crosses indicate a condition was not met.

	Steinberg (2015)	Funk et al. (n.d)	Sheehan et al. (2016)	Thompson et al. (2015)	De Witt et al. (n.d)	(Downs et al., 2015)	Moore et al. (2014)	Perusek et al. (2015)	Downs et al. (2017)	Thompson et al. (2014)	Witt (2016)	Godfrey et al. (2017)	Downs (2017)	Moore (2016)	Gallo et al. (2016)	Lewandowski et al. (2016)	Ryder et al. (2016)	Colosky (n.d)	Buxton et al. (2017)
Evidence Level																			
Meta-Analysis	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Controlled Studies	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Qualitative Studies	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Organisational Standards	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Theory-Based Evidence	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Manufacturer's Recommendation	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Laws & Regulations	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Total Score (Part 1)	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Clarity & Consistency																			
Clearly sourced factual information	✗	✗	✗	✓	✗	✗	✗	✗	✗	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗
Clearly sourced methodological information	✗	✗	✗	✓	✗	✗	✗	✗	✗	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗
Clearly explained information	✓	✓	✗	✓	✓	✓	✓	✗	✗	✓	✗	✗	✗	✗	✗	✗	✓	✗	✗
Representative of primary sources	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Total Score (Part 2)	2	2	1	4	2	2	2	1	1	4	1	1	1	1	1	1	2	1	1
OVERALL TOTAL SCORE	**5**	**5**	**4**	**7**	**5**	**5**	**5**	**4**	**4**	**7**	**4**	**4**	**4**	**4**	**4**	**4**	**5**	**4**	**4**

For Section 1 (evidence level) a score of: 7 is given for meta-analysis; 6 is given for controlled studies; 5 is given for qualitative studies; 4 is given for organisational standards; 3 is given for theory based evidence; 2 is given for manufacturer's recommendations; and 1 is given for laws and regulations. For section 2 (clarity and consistency) a score of 1 is given for each criteria met, for a maximum score of 4. Overall total score is the sum of section 1 and section 2 scores.

2.3.3. Technical Constraints Assessed

A summary of the technical constraints that were reported in each of the documents included in this review is shown in Table 2.5.

Table 2.5 Technical Constraints identified in the systematic search

	Steinberg (2015)	Funk et al. (n.d)	Sheehan et al. (2016)	Thompson et al. (2015)	De Witt et al. (n.d)	Downs et al. (2017)	Moore et al. (2014)	Perusek et al. (2015)	Downs et al. (2017)	Thompson et al. (2014)	Witt (2016)	Godfrey et al. (2017)	Downs (2017)	Moore (2016)	Gallo et al. (2016)	Lewandowski et al. (2016)	Ryder et al. (2016)	Colosky (n.d)	Buxton et al. (2017)
Technical Constraints Identified																			
Limited Mass of Spacecraft	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗	✗	✗	✓	✗	✓	✗	✓	✗
Limited Volume of Spacecraft	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Limited Power Usage/Access	✗	✓	✓	✓	✗	✗	✗	✓	✓	✓	✓	✗	✓	✓	✗	✓	✗	✓	✗
CO_2 Removal Limitations	✗	✗	✗	✗	✗	✗	✓	✗	✗	✗	✗	✗	✗	✓	✗	✗	✗	✗	✗
O_2 Consumption Limitations	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✓	✗	✗	✗	✗	✗
Heat Generation and Cooling	✗	✗	✗	✗	✗	✗	✓	✗	✗	✗	✓	✗	✗	✓	✗	✗	✗	✗	✗
Humidity and Moisture Control	✗	✗	✗	✗	✗	✗	✓	✗	✗	✗	✗	✗	✗	✓	✗	✗	✓	✗	✗
Noise Generation Limitations	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✓	✗	✗	✗	✗	✗
Data Transmission Limitations	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✓	✗	✗
Spacecraft Structural Integrity	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✓	✗	✗	✗	✗	✗
Vibration of Exercise Device	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✓	✗	✗	✗	✗	✗
Exercise Device Structural Integrity	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✓	✗	✗	✗	✗	✗
Isolation of Exercise Device	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✓	✗	✗	✗	✗	✗
Stabilisation of Exercise Device	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✓	✗	✗	✗	✗	✗

Thematic analysis of the included documents indicated two major themes thought to impact the capability of astronauts to exercise effectively during spaceflight on-board the MPCV: limited volume of spacecraft; limited mass of spacecraft. Underpinning these two major themes were 10 lower order themes: heat generation and cooling; humidity and moisture control; CO_2 removal limitations; O_2 consumption limitations; volume restrictions on exercise device; exercise device structural integrity; limited power usage/access; noise generation; mass restrictions on exercise device; and spacecraft structural integrity.

The 10 lower order themes were organised between two higher order themes: limitations of environmental control and life support systems (ECLSS); constraints upon exercise device/program. A characteristic was identified that described a relationship between some lower order themes. The characteristic "exacerbated by distance from Earth" was identified as impacting four constraints: data transmission limitations; O_2 consumption limitations; exercise device structural integrity; and spacecraft structural integrity. Data transmission limitations was the only lower order theme that was not linked to the two major themes, and was instead solely related to distance from Earth.

The thematic map demonstrating the relationship between each technical constraint can be seen in Figure 2.2. Dotted lines indicate a relationship with "Limited Volume of Spacecraft". Dashed lines indicate a relationship with "Limited Mass of Spacecraft". "Exacerbated by distance from Earth" is a characteristic which describes links between some technical constraints, but is not linked to the mass and volume of the spacecraft. Most of the included documents reported only qualitative data. Any quantitative data that was reported within the included documents is presented in Table 2.6.

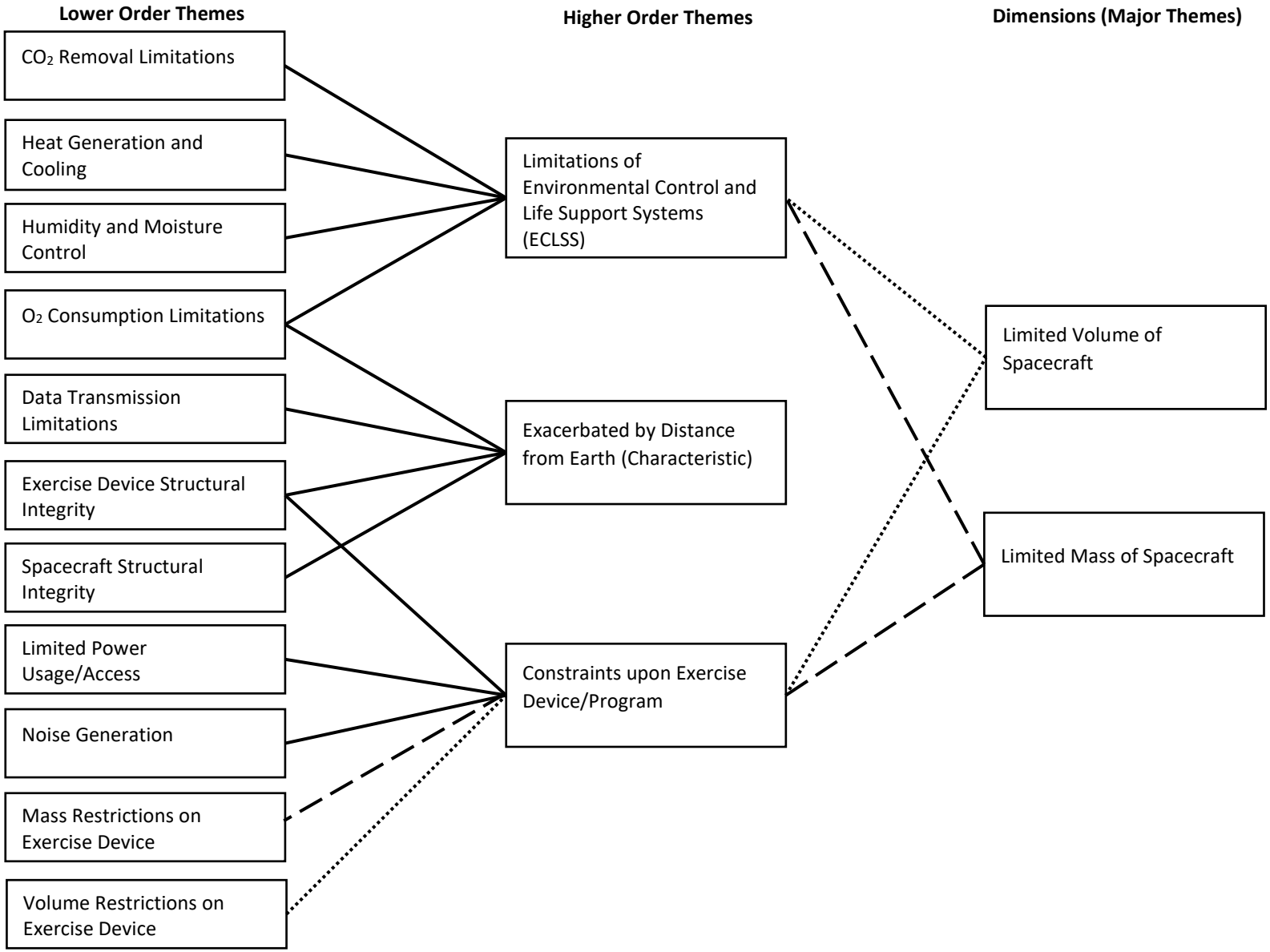

Figure 2.2 Thematic Map. Dotted lines indicate a relationship with "Limited Volume of Spacecraft". Dashed lines indicate a relationship with "Limited Mass of Spacecraft". "Exacerbated by distance from Earth" is a characteristic which describes links between some technical constraints, but is not linked to the mass and volume of the spacecraft

Table 2.6 Quantitative information relating to exercise constraints identified within the included documents

Extracted Technical Constraints	**Extracted Quantitative Information**
Volume Constraints	• $5m^3$/54% (of $9m^3$ available) habitable volume required for exercise (Moore et al., 2014). • Maximum exercise device dimensions: 34.29cm–53.34cm width x 34.29cm height x 19.05cm depth (Sheehan et al., 2016).
Mass Constraints	• Maximum weight of exercise device must not exceed 10.6kg (Sheehan et al., 2016).
Exercise device structural integrity	• Exercise device must be capable of producing a resistive load of up to 181.437kg without breaking, buckling or bending, while still meeting the mass and volume restrictions (Sheehan et al., 2016). • For comparison, the resistive exercise device on-board the ISS, ARED, is capable of providing a resistive load of 272kg (Scott et al., 2019).
CO_2 removal limitations, humidity and moisture control, heat generation and cooling	• Exercise is limited to 30 minutes for every 90 minute period in order to be able to effectively filter the by-products of exercise (Moore et al., 2014). • Moisture is contributed to the MPCV's environment due to increased sweating and respiratory rate (exhaling of air at 100% relative humidity) of astronauts during exercise.
Data Transmission Constraints	• A spacecraft in Martian orbit would take up to 25 minutes to receive a one-way communication from ground control on Earth, depending on the current location in space of the two planets (Kanas, 2013; Kanas et al., 2009)

2.4. Discussion

2.4.1. Summary of Evidence

The main finding of this review was that all constraints, other than data transmission limitations, are ultimately a result of spacecraft volume and upload mass constraints. Thematic analysis of the included documents identified the following 11 technical constraints: heat generation and cooling; humidity and moisture control; CO_2 removal limitations; O_2 consumption limitations; volume restrictions; exercise device structural integrity; limited power usage/access; noise generation; mass restrictions; data transmission constraints; and spacecraft structural integrity.

2.4.2. Limitations of Environmental Control and Life Support Systems (ECLSS)

The Environmental Control and Life Support Systems (ECLSS) refers to the technology aboard spacecraft that provides a suitable habitat in which astronauts can survive (Wieland, 1994). ECLSS manages atmosphere composition, temperature, distribution of water, pressure, processing of waste matter, detection and suppression of fires, and any other functions necessary to ensure astronaut survival in outer-space (Wieland, 1994). Thematic analysis of the included documents suggested that technical constraints related to limitations of ECLSS included: limitations to CO_2 removal; O_2 consumption; heat generation and cooling; and humidity and moisture control. Four of the included documents (Moore, 2016; Moore et al., 2014; Ryder et al., 2016; Witt, 2016) indicate that the limitations to ECLSS may create limitations for the exercise capability of astronauts.

As a countermeasure to musculoskeletal deconditioning, astronauts must exercise for up to 2.5 h a day, six days per week (seven days per week for ESA astronauts (Petersen et al., 2016)) including preparation time of 60 minutes (Richter et al., 2017). The current US ISS exercise countermeasures program consists of two sessions per day, including one 30-45 minute aerobic session and one 45 minute resistance session, 6 days per week (Scott et al., 2019). These exercise countermeasures produce CO_2 and heat as by-products (Moore et al., 2014), as well as moisture within the spacecraft due to a raised respiratory rate, exhaled at 100% relative humidity, and the production of sweat (Ryder et al., 2016).

Aboard larger spacecraft, like the ISS, ECLSS can effectively filter these by-products of exercise (Moore et al., 2014). On the MPCV and transferable capsular spacecraft, by-products of exercise cannot be effectively filtered fast enough to allow more than 30 minutes of exercise every 90 minutes (Moore et al., 2014). This would mean the current US ISS exercise countermeasures program would have to be split into 3 sessions per astronaut each day. For an astronaut to meet the current US exercise quota of 90 minutes (2 x 45 minutes) (Scott et al., 2019) on-board the MPCV, where astronauts can only exercise for 30 minutes within a 90 minute period, would take a single astronaut 4.5 hours (270 minutes) in total (i.e 3 x 90 minutes) Assuming the MPCV was carrying its maximum

number of astronauts (4 astronauts), it would take 18 hours in total per day (4.5 hours x 4 astronauts) for all astronauts to complete their required amount of exercise. During 6 of those 18 hours ((90 x 4)/60 = 6), 5m^3 of the 9m^3 available habitable space would be taken up by exercise (Moore et al., 2014); although this exercise would be discontinuous (30 minutes non-stop, broken up by 60 minute breaks). It is unclear from the included documents how this may impact other mission procedures and tasks, and it may be the case that the limitations of the ECLSS could result in a change in exercise regime on the MPCV compared to the current regime on the ISS. For example, as CO_2 production increases as a result of metabolic demands of the exercising muscles (Phillipson, Bowes, Townsend, Duffin, & Cooper, 1981), intense exercises that produce more CO_2 than the ECLSS can effectively filter may not be possible on-board the MPCV, and so new exercise strategies may have to be developed.

The consumption of O_2 during exercise may also present challenges to the ECLSS (Moore, 2016). However, it is difficult to determine exactly how this will occur as none of the documents included in this review provided specific or detailed information as to how O_2 consumption could challenge exercise capabilities. There is evidence that O_2 consumption is higher than at rest, both during and post exercise (Excess Post-exercise O_2 Consumption (EPOC)) for up to 12 h, the magnitude of which is proportional to the length of the exercise undertaken (Bahr, Ingnes, Vaage, Sejersted, & Newsholme, 1987). The intensity of the exercise undertaken further increases the duration and the magnitude of EPOC (Bahr & Sejersted, 1991). However, the relationship of these variables in relation to resistance exercise remains unclear due to the limited number of studies and difficulties with the quantification of exercise work intensity (Laforgia, Withers, & Gore, 2006). As EPOC comprises at least 6-15% of the net total oxygen cost of an exercise (Laforgia et al., 2006), the length and intensity of any exercise countermeasure will need to be taken into account to ensure that O_2 supplies are capable of supporting not only increased O_2 consumption during exercise but also post-exercise. It may be possible to split exercise up into shorter duration but higher intensity sessions to overcome this limitation, as higher intensity exercises have been shown to be equally or even more effective at building and maintaining aerobic capacity than longer duration exercises (Ryder et al., 2016). However, exercise by-products produced by these exercises must not exceed the limitations of the MPCV's ECLSS.

While the included documents have identified that exercise will be limited to 30 minutes of exercise per every 90 minutes in order to effectively filter the by-products of exercise (Moore et al., 2014), they did not indicated any other specific figures as to what the upper limits are for temperature control, humidity and sweat production, or O_2 consumption.

2.4.3. Constraints upon exercise device/program

A number of the constraints identified in this review relate to the exercise device and exercise programme necessary to accomplish exercise during spaceflight. Spacecraft exercise devices are adapted for use in microgravity, such as the Advanced Resistive Exercise Device (ARED) (Loehr et al., 2015; Petersen et al., 2016) to maintain musculoskeletal health (Convertino & Sandler, 1995). Exercise devices use a restraint system, such as a harness or bungee that provides a force to keep astronauts attached to the exercise device (De Witt et al., 2014). Constraints related to the higher order theme Exercise Device and Program include: Limited power usage/access (e.g. to power an exercise device (Sheehan et al., 2016)); exercise device structural integrity; volume constraints upon the exercise device; mass constraints upon the exercise device; noise generation constraints; and spacecraft structural integrity.

The volume and upload mass constraints of the MPCV provide challenges for the development of effective exercise countermeasures that need to be as effective as pre-existing countermeasures currently used on-board much larger spacecraft such as the ISS (Perusek et al., 2015). The ARED currently stands as the resistive exercise device for use in the space environment to minimise musculoskeletal deconditioning (Downs, 2017). The volume and upload mass constraints of the MPCV mean that ARED (and similar devices) are too large and heavy for use on-board the MPCV (Perusek et al., 2015). The functional requirements of an Orion MPCV exercise device require dimensions of 10.6kg, 34.29cm - 53.34cm width x 34.29cm height x 19.05cm depth (Sheehan et al., 2016) and the astronauts will need a space of $5m^3$ (out of $9m^3$, 54% of the habitable volume) to accommodate the movements needed for exercise (Moore et al., 2014; Scott et al., 2019). Exercise devices that fit this criteria are under development (Lewandowski et al., 2016). However, there is concern that these devices will be incapable of protecting against musculoskeletal deconditioning to the same extent as current countermeasures (Lewandowski et al., 2016), as they may not be able to provide sufficient load during the performance of resistance and aerobic/anaerobic exercises while meeting the MPCV's mass, volume and power requirements (Thompson et al., 2015).

Upload mass constraints of the MPCV place limitations on the structure and design of exercise devices, which is problematic as the exercise device must be capable of providing sufficient load (181.437kg resistive peak load capability (Sheehan et al., 2016)) during exercises while meeting these mass constraints (Thompson et al., 2015). Current exercise countermeasures, such as ARED, that are not limited by these constraints and are capable of providing greater resistive load (272kg (Scott et al., 2019)) are unable to achieve complete musculoskeletal protection (Thompson et al., 2014). For example, current evidence-based countermeasures are unable to provide complete protection for the lumbopelvic system (Winnard et al., 2017). As of yet there have been no exercise devices identified that are capable of both meeting the volume and mass requirements of the MPCV, and also being able to meet physiological performance parameters (Moore et al., 2014).

The limitations to mass and volume become more concerning when it is considered that current countermeasures, including ARED, are incapable of fully protecting against physiological deconditioning during spaceflight (Moore et al., 2014; Winnard et al., 2017). For example, if the musculoskeletal system is too heavily atrophied then it is possible an astronaut on a Lunar or Mars landing mission, or upon returning to Earth, would lack the strength to open the spacecraft hatch to exit the vehicle (Gernand, 2004). Musculoskeletal deconditioning may further prevent astronauts from completing nominal or emergency activities, and the risk of this occurring increases with longer duration missions (Gernand, 2004). As such, the volume and mass constraints of the MPCV present a major challenge to mission success if a suitable exercise countermeasure cannot be developed that works effectively within the spacecraft's volume and mass constraints.

Noise production from training devices is another challenge for exercising effectively on the MPCV (Moore, 2016). Astronauts on-board spacecraft experience chronic exposure to noise and vibration (Morphew, 2001). Chronic exposure to noise can cause disruption, interfere with communication, cause damage and pain to the inner ear and, in a worst case scenario, result in hearing loss (Barber, Crooks, & Fristrup, 2010; Connors, Harrison, & Akins, 1985). Noise is of particular concern during spaceflight as noise is amplified within enclosed spaces (Gershon, Qureshi, Barrera, Erwin, & Goldsmith, 2005). While Moore (2016) indicates that noise is a technical constraint that will interfere with astronaut exercise on the MPCV (due to the production of noise in an enclosed space), they do not provide any explicit figures on noise limitations. Previous literature on noise in the space environment indicates that noise during spaceflight should be limited to a maximum of 45 dB (Connors et al., 1985), although it is not clear if this will also apply to the MPCV. On this basis it may be a requirement that exercise device countermeasures intended for use in the MPCV do not result in noise levels above 45 dB.

From a psychological perspective, loss or reduction of hearing could result in negative emotional reactions, difficulties in communication (Monzani, Galeazzi, Genovese, Marrara, & Martini, 2008), social isolation, and potentially stigmatisation of affected crew members, resulting in a reduction in crew cohesion, well-being and self-esteem, and an increase in symptoms of anxiety and depression (Tambs, 2004) in crew members with hearing loss. These psychosocial elements of spaceflight can have a range of impacts upon mission success, ranging from decreases in individual performance to the possibility of mission failure (Palinkas, 2007). Therefore, ensuring the auditory health of the crew is of the utmost importance.

Power availability is another technical constraint for MPCV exercise devices (Thompson et al., 2015). The most common method of generating electrical power during spaceflight is through the use of solar arrays (Jones & Spence, 2011). The ISS hosts eight solar arrays (Reddy et al., 2008) with the largest, the ISS alpha solar array, being capable of generating 75,000 watts (Jones et al., 2011). Given

the much smaller size of the MPCV in comparison to the ISS (Perusek et al., 2015), it is likely that the MPCV is not able to generate as much electrical power as the ISS (Rehman, Bader, & Al-Moallem, 2007). The lack of power available to the MPCV will, alongside other constraints such as volume and upload mass, prevent the use of currently available exercise countermeasures such as ARED (Downs, 2017). While a number of exercise devices are under consideration and designed for use on-board the MPCV (Sheehan et al., 2016) the limited availability of power may impact exercise device capabilities, such as the provision of biofeedback (Winnard, Debuse, et al., 2019). While 11 of the included documents indicate that power limitations will impact astronaut exercise, the amount of power available to run exercise devices has not been quantified in any of the sources analysed in this review. However, the limited availability of a power supply would seem to imply design ramifications for an exercise device and programme and raises concerns that exercise devices and programmes developed for the MPCV will not be as effective as previous exercise countermeasures such as the ARED (Lewandowski et al., 2016).

One further challenge is the structural integrity of the exercise device and spacecraft (Moore, 2016). The exercise device used on board the MPCV must be mounted on an isolation and stabilisation structure that protects the spacecraft, and possibly microgravity research, from vibration while maintaining the necessary stability for exercise (Moore, 2016). The mass restrictions, combined with volume constraints, make it difficult to isolate, stabilise, prevent vibration and keep the spacecraft structurally intact, as such a structure requires more volume and adds more weight to the spacecraft (Moore, 2016). While Moore (2016) identified that such an isolation structure would be needed, they do not give any specific detail on how much volume such a structure would take up, or the mass of such a structure. It is also unclear based upon the included documents if the volume allocated to the exercise device (34.29cm - 53.34cm width x 34.29cm height x 19.05cm depth (Sheehan et al., 2016)) includes space for an isolation structure. Moore et al. (2014) reported that structural assessments of the MPCV indicated that while the use of an exercise device may not damage spacecraft structure (such as solar arrays), it may distort spacecraft attitude (orientation). Therefore, the infrequent use of thruster responses may be necessary to maintain course.

2.4.4. Exacerbated by distance from Earth

Data transmission is the only constraint which is limited solely by the ‘exacerbated by distance from Earth’ characteristic, unlike the constraints discussed previously which are also influenced by the spacecraft upload mass and volume. Data transmission refers to the communication of data (Petersen et al., 2016). In the context of astronaut physiological outcomes, it may refer to data communication such as ground crew providing exercise prescription changes, feedback, and coaching (Petersen et al., 2016). The further a spacecraft travels from Earth, the longer it takes for a one-way communication to

occur (Kanas, 2013; Kanas et al., 2009). For example, a spacecraft in Martian orbit would take up to 25 minutes to receive a one-way communication from ground control on Earth, depending on the current location in space of the two planets (Kanas, 2013; Kanas et al., 2009). This presents problems for exercise on-board the MPCV during future exploration missions as astronauts will have to act in an autonomous manner during periods in which there is a lack of effective communication with ground control (McGregor, 2013). Data transmission problems, due to a longer distance from Earth, will impact the ability of ground control to real-time monitor (e.g. via video conference) the health and wellbeing of astronauts or to prescribe changes to the exercise programmes (McGregor, 2013). A way to address this may be to provide daily or weekly changes (if needed) to exercise prescriptions as opposed to instant feedback.

The ECLSS constraint, O_2 consumption, is also exacerbated as a result of increased distance from Earth due to the inability to re-supply critical resources during a long-distance/duration mission beyond the Earth-Moon system (Jones, Hodgson, & Kliss, 2014; Schaezler & Cook, 2015). It could be argued that this constraint is ultimately a result of volume constraints: the small volume available for the MPCV means that more O_2 cannot be taken during a long-distance mission, limiting the ECLSS in its capacity to support exercise requiring higher O_2 consumption (Moore et al., 2014).

The structural integrity of the exercise device itself may also be an exacerbated constraint due to the distance from Earth. Due to volume limitations, there is limited space available for an exercise device (Moore et al., 2014). Furthermore, the device must have strong structural integrity in order to prevent it buckling, bending, or breaking entirely (Moore, 2016) and to minimise any damage and the necessity of repairs. The latter is important, because as communication delays will also exist on board the MPCV during far-from-Earth voyages, astronauts may lack ground support at times, and being unable to exercise may, in a worst case scenario, result in mission failure (Kanas, 2013; Kanas et al., 2009). The distance from Earth will also impact the structural integrity of the exercise device in so far as it will need to be extremely robust, as if it breaks or needs new parts and cannot be fixed it may not be possible to resupply the spacecraft with a new device from Earth, potentially leading to mission failure (Jones et al., 2014).

The limited volume of the spacecraft, at longer distances from Earth, may also have knock-on effects for other spacecraft supplies such as food and water storage (Scott et al., 2019). The limited volume of the vehicles lowers their storage capabilities, while the increased distance from Earth limits or prevents entirely the capacity for resupply (Jones et al., 2014; Scott et al., 2019). As intense exercise requires food to maintain energy balance and water to maintain hydration, the exercise program on-board exploration spacecraft will create a challenge for consumables storage (Scott et al., 2019). Therefore, all of the food and water needed for astronauts to exercise on an exploration mission would need to fit within the limitations of the vehicle's volume requirements. No quantitative details are

given within the included literature as to how much volume such storage would take up or how long an exploration mission could occur with the maximum number of food and water supplies, or the rate at which astronauts would consume these supplies.

A single astronaut on the ISS consumes 2.49kg of food per day (0.83kg per meal) (Allen & Dubar, 2007), and NASA recommends they consume at least 2 litres of fluid per day (Lane & Feeback, 2002). On the MPCV, assuming a crew of four astronauts that were eating three meals per day and following the same exercise countermeasures as the ISS, 209.16kg of food and 168 litres of fluid would be needed for a 21 day mission. A three year mission to Mars, although such a mission is likely to involve additional space (such as a Deep Space Habitat (DSH) (Curley, Stambaugh, Swickrath, Anderson, & Rotter, 2012)), would require 10886kg of food (Allen et al., 2007) and and 8760 L of fluid for a crew of four (Lane et al., 2002).

There is potential for the use of selective androgen receptor modulators as a countermeasure method that could reduce the need for exercise. As mentioned above, current exercise protocols on-board the ISS are effective, but they require mission hardware with significant mass and volume, in addition to significant crew time. It would be sensible to employ the same countermeasure strategy used to ensure mission bone health, namely develop a pharmaceutical countermeasure that can be used either as an alternative to exercise or as a supplement. It is known that testosterone therapy encourages the growth of muscle tissue (Bhasin et al., 1996) and has been used in men to prevent muscle atrophy associated with cancer, other wasting diseases, and even aging (Hardee & Lynch, 2019). NASA has conducted a promising preliminary study in a bedrest analog to determine the utility of low-dose testosterone for men on space missions (Dillon et al., 2018). However, testosterone is an endogenously produced hormone with multiple targets throughout the body, and carries the risk of significant unwanted side effects in men and women. New selective androgen receptor modulators (SARMs) are being developed to specifically target the type of testosterone receptor expressed by muscle cells (Solomon et al., 2019). Several SARMs have been shown to increase muscle mass in various pre-clinical models. Of particular interest is the result of both anabolic and anti-catabolic activity associated with use of SARM S42 in rats and cell culture (Muta et al., 2019). Enobosarm (S22) was shown to increase lean body mass in elderly women, but did not meet desired efficacy goals in trials regarding pelvic floor muscle (Crawford, 2016; Crawford et al., 2016). SARM GSK2881078 has been shown to increase lean body mass in a dose-dependent fashion in both men and women (Neil et al., 2018). With continuing mechanistic studies and clinical trials, the data may show that one or more SARMs may be excellent countermeasure candidates for the muscle loss associated with long duration spaceflight, providing a potential solution to the volume and mass constraints of the Orion MPCV.

2.4.5. Summary of predicted quantified constraints

Not all constraints were quantified in the included documents. All available extracted constraints were reported in the results. Where constraints were not quantified in the included documents, predictions have been made based upon the interpretation and discussion of the thematic analysis. Table 2.6 in the results section summarised the quantitative data extracted from the included documents. Table 2.7 presents the predicted additional constraints based on the available information.

Table 2.7 Additional predicted constraints based upon the available information

Additional predicted Technical Constraints	**Predicted Quantitative Information**
Volume and Environmental Control and Life Support Constraints	• On the MPCV by-products of exercise cannot be effectively filtered fast enough to allow more than 30 minutes of exercise every 90 minutes (Moore et al., 2014). • The US ISS exercise countermeasures program would have to be split into 3 sessions per astronaut each day to be implemented on-board the MPCV. • Meeting the current US exercise quota of 90 minutes (2 x 45 minutes) (Scott et al., 2019) under this regimen would take a single astronaut 4.5 hours in total. • Assuming the MPCV was carrying its maximum number of astronauts (4 astronauts), it would take 18 hours in total per day for each astronaut to complete their required amount of exercise. • During 6 of those 18 hours, $5m^3$ of the $9m^3$ available habitable space would be taken up by exercise (Moore et al., 2014). • On the MPCV (assuming a crew of four astronauts that were eating three meals per day and following the same exercise countermeasures as the ISS) 209.16kg of food and 924 litres of water would be needed for a 21 day mission. • A three year mission to Mars on the MPCV would require 10886kg of food (Allen et al., 2007) and 48180 litres of water for a crew of 4.
O_2 Consumption Constraints	• O_2 consumption is higher than at rest, post exercise (Excess Post-exercise O_2 Consumption (EPOC)) for up to 12 hours, the magnitude of which is proportional to the length of the exercise undertaken (Bahr et al., 1987). • EPOC comprises at least 6-15% of the net total oxygen cost of an exercise (Laforgia et al., 2006).
Noise Constraints	• Noise during spaceflight, including exercise, should be limited to a maximum of 45 dB (Connors et al., 1985) to reduce risk of hearing loss (Connors et al., 1985; Morphew, 2001).

2.4.6. Space Agency Operational Insights

The discussion of this review has been based upon evidence from publicly available grey literature and technical documents, however, personal communications with space agencies suggest that they may be considering additional approaches or changes to an MPCV mission. On-board the ISS exercise occurs 6 days per week (seven days per week for ESA astronauts (Petersen et al., 2016)), lasting approximately 2.5 hours per astronaut (2 x 45 minutes, including preparation time) (Richter et al., 2017). Personal communications with the European Space Agency indicate that MPCV missions, being up to 21 days in length, may implement exercise for 3 days per week rather than 6 days per week (A. Frechette, personal communication, August 07, 2019). As such, the previous estimate that 6 hours per day $5m^3$ of the $9m^3$ available habitable space would be taken up by exercise (Moore et al., 2014) could be reduced to 90-180 minutes per day (as some days will require more than one astronaut to exercise on the same day, if there is a crew of four astronauts), assuming that the exercise schedule still consisted of 90 minutes of exercise per astronaut.

Personal communications further indicated that mission to Mars or asteroids are likely to have significantly more power and volume available (A. Frechette, personal communication, August 07, 2019). One way that this may be accomplished is if the MPCV were to be attached to a Deep-Space Habitat (DSH) (Curley et al., 2012). During these missions the crew would live within a DSH which would minimise the volume and power constraints of the MPCV in relation to exercise, as the MPCV would only be used to leave/return to Earth, emergency escape, and for exploration excursions for up to seven days (Curley et al., 2012).

The European Space Agency's current policy for exercise in the outer-space environment is that it is not necessary for short-duration missions of nine days or less (A. Frechette, personal communication, August 07, 2019). As the MPCV, without a DSH, is designed for missions of up to 21 days (Burns et al., 2013) it is the case that currently only the final 12 days out of 21 will require exercise countermeasures. A recent systematic review (Winnard, Scott, Waters, Vance, & Caplan, 2019) has found that, based upon bed-rest simulations of microgravity, moderate effects of muscle deterioration were observed after seven days when undertaking no exercise countermeasures. As such it is recommended that the European Space Agency amends policy to necessitate exercise for missions of seven days or more, rather than nine, and that the MPCV is not used for missions longer than seven days unless exercise countermeasures are available in order to reduce risk of injury to the crew involved. As current ISS countermeasures are not useable within the constraints of the MPCV identified within this review (Thompson et al., 2014), new exercise countermeasures will need to be developed that work within these constraints, or the MPCV will need to be used in conjunction with a DSH (Curley et al., 2012) with enough space to allow the use of current ISS countermeasures.

2.4.7. Limitations of the systematic review

The lack of detailed studies and lack of consistency in specifying spacecraft in the literature all limit the conclusions of this review. The evidence base that met the inclusion criteria consisted almost entirely of expert testimony and anecdotal evidence, including NASA PowerPoint learning materials, as opposed to detailed controlled trials, detailed technical specifications, engineering manuals, space-agency specified exercise constraints and experimental studies. This means that the technical constraints identified often lacked clear and detailed information as to how they impacted exercise or they lacked a clear empirical source, as demonstrated through quality assessment. Only two of the included documents (Moore et al., 2014; Sheehan et al., 2016) in this review contained quantified information on the technical constraints, and whilst quantitative information has been listed on the mass and volume constraints, load requirements of an exercise device and exercise program duration (Table 2.5), clear quantitative information is still missing for all remaining technical constraints. In order for the research community to provide informed recommendations about exercise countermeasures, space agencies should ensure that information on relevant spacecraft constraints is clearly available. This information should be made accessible in an official published document as opposed to disparate and grey literature, and include quantitative information rather than qualitative summaries. While it is possible that data exists within internal and classified space agency documents that are not yet publicly available, the present review presents the most comprehensive, state of the art synthesis of the publicly available data and identifies both gaps within this literature and barriers to existing research goals. The repeatable methods provided in this review provide a means by which the review can be updated should data that is not currently publicly available become declassified. Most of the literature on future exploration missions and their constraints do not refer to specific spacecraft (e.g. MPCV), but instead use variations of the term “future exploration vehicles”. This was problematic for the systematic search as such terminology made it impossible to distinguish between larger spacecraft (such as the ISS) and smaller spacecraft (such as the MPCV). To ensure that all literature included was relevant, it was necessary to exclude any sources that did not specifically state the spacecraft it referred to (and as such did not match the inclusion criteria). Unfortunately, this means that it is possible some relevant documents were missed. It is, therefore, recommended that future documents ensure they refer to a specific spacecraft when discussing future exploration spacecraft and/or missions. Gap analysis provides a means by which both the gaps in a research area and the reasons for their existence can be identified and research then designed to fill them (Robinson et al., 2011). The limitations identified in this review provide two of the most present obstacles in developing a more clear understanding of the technical constraints that impact exercise on-board the MPCV.

2.4.8. Conclusions

This review identified the following technical and physiological constraints of the exploration mission spacecraft: constraints of the environmental control and life support systems (heat generation and cooling, humidity and moisture control, CO_2 removal limitations, O_2 consumption limitations (limiting exercise to 30 minutes in every 90 minute period), constraints upon the exercise device and program (volume restrictions ($5m^3$ /54% (of $9m^3$) habitable volume for exercise space, with maximum dimensions for an exercise device of 34.29cm – 53.34cm width x 34.29cm height x 19.05cm depth), exercise device structural integrity, limited power usage/access, noise generation, mass restrictions on exercise device of 10.6kg maximum mass, while providing 181.437kg load, and spacecraft structural integrity) and data transmission limitations. The most frequently reported technical constraint was volume (size/ space) constraints (reported by every document), followed by upload mass constraints and power constraints. Thematic analysis of the documents suggest that all constraints, other than data transmission limitations, are ultimately a result of the volume and upload mass constraints, which may explain why volume and mass constraints were the most widely reported constraints throughout the included documents. The findings of this review suggest that the limited volume and upload mass of these spacecraft present the most important challenges to the capability of astronauts to exercise effectively during spaceflight, with almost all other identified technical constraints resulting from the upload mass and volume constraints. While upload mass and volume constraints have been widely reported, the impact they have had on additional factors such as noise generation and the supply of consumables has not. This review has compiled each of these constraints into a single document and highlighted any quantitative information available, as seen in Table 6, in order to aid the development of future research questions and development of exercise countermeasures for exploration spaceflight. The review has further predicted a number of potential constraints based upon the quantitative information available, such as the maximum level of noise the exercise devices can safely produce and the weight of consumables required for a Mars mission, as seen in Table 2.7. Some constraints (data transmission limitations, O_2 consumption limitations, exercise device structural integrity, and spacecraft structural integrity) were also found to be exacerbated by distance from Earth, indicating that longer distance missions (such as to the Moon) may require further considerations for exercise countermeasures that differ from short distance missions (such as to low Earth orbit). The identification of these technical constraints is an important step for the future recommendation of exercise countermeasures for use on-board the MPCV or transferable exploration class spacecraft and the method given within this review provide a means by which to update this document in the event additional data becomes available. Future research to identify suitable countermeasures should consider if they will work within the context of the constraints identified within this review.

3. Chapter Three: Musculoskeletal and cardiovascular outcomes of relevance to astronaut health and operational success

This chapter forms part of three publications, currently under peer-review, which have received funding from the Aerospace Medical Association Foundation to cover the costs of publication with Aerospace Medicine and Human Performance.

3.1. Introduction

3.1.1. Rationale

Chapter 2 identified that the technical constraints of the Orion MPCV that would present challenges to the use of current ISS countermeasures were primarily a result of the spacecraft's maximum volume and upload mass requirements. To make useful exercise recommendations for use within these constraints, relevant musculoskeletal and cardiovascular health outcomes also need to be identified.

A number of published studies concerning musculoskeletal and cardiovascular deconditioning exist (either via simulation or operational spaceflight), but there is no complete synthesis of this information. In order to assist in the evaluation of new countermeasures, the musculoskeletal and cardiovascular outcomes impacted by microgravity exposure should be identified, grouped by common theme, and ranked in order of their relevance to astronaut health and operational spaceflight success. By identifying and ranking these musculoskeletal and cardiovascular outcomes, potential exercise countermeasures can be more thoroughly assessed for future spaceflight suitability. The grouping of these outcomes by common theme will also assist in the preparation for quantitative meta-analysis to be undertaken in Chapter 4 when evaluating existing countermeasure suitability. From an operational perspective, a failure to perform high-quality evidence synthesis could also lead to operational medical guidelines not fully reflecting the true findings across the evidence base. A lack of high quality synthesis could also create a risk of impaired operational decision making, the wastage of both time and funding, or the implementation of less-effective exercise interventions for musculoskeletal and cardiovascular deconditioning. As such, the next step to determining the most effective exercise countermeasures, direct future research goals and to understand spaceflight musculoskeletal and cardiovascular deconditioning more fully is to collect and synthesise all available information within this field.

While this chapter is primarily concerned with exposure to microgravity during spaceflight, several spaceflight simulations exist which aim to replicate the effects of spaceflight as closely as possible to the outer-space environment (Richter et al., 2017). These include: vertical body weight support systems; lower body positive pressure treadmill; titled body weight support systems; supine suspension systems; centrifugation; head up tilt (bed-rest); and parabolic flight (Richter et al., 2017). While these simulations exist, they may be limited in their capability to successfully replicate the full effects of spaceflight (Richter et al., 2017) which may impact the safety of transferring their results directly to operational spaceflight medical guidelines. For example, while parabolic flights are the only analog capable of providing complete weightlessness via freefall, it is only capable of producing these effects for a very short period of time (usually around 25 seconds) (Shelhamer, 2016). As such a parabolic flight is not suitable for studying the effects of longer-duration spaceflight deconditioning (Shelhamer, 2016). Pre-scoping during this chapter indicated that there is a substantial number of operational spaceflight publications on this topic, providing an opportunity for results that are

comprehensive and representative of astronauts in microgravity without the need to risk introducing any of the limitations resulting from inclusion of simulation studies. To ensure that the results of this chapter are completely representative of the effects of operational microgravity exposure upon the musculoskeletal and cardiovascular systems, microgravity simulations will not be included.

3.1.2. Aim and Objectives

The aim of this systematic review was to provide an over-arching guide to the musculoskeletal and cardiovascular-related space medicine outcomes used during operational spaceflight missions, as informed by the publicly available literature. This includes the identification of the outcomes of greatest relevance to astronaut health and operational success, gaps or barriers to complete and transparent synthesis of the data, and recommendations for common study protocols to improve the quality of the overall evidence-base.

3.2. Methods and Materials

This systematic review was conducted following the protocols set out in the Aerospace Medicine Systematic Review Group (AMSRG) methods guides (Winnard et al., 2021), which adapt the gold standard terrestrial medical systematic review Cochrane Collaboration guidelines (Higgins et al., 2019), thematic analysis (Braun et al., 2006; Braun et al., 2019), and thematic synthesis (Thomas et al., 2008) to space medicine reviews. The PRISMA standards (Preferred Reporting Items for Systematic reviews and Meta Analyses) (Moher et al., 2015) checklist was followed to ensure gold standard, transparent and complete reporting of results.

3.2.1. Search Strategy

A range of terms (Table 3.1) were used in combinations to search the Cochrane Central Library Database (which also integrates records from MEDLINE/PubMed, CINAHL, ClinicalTrials.gov, and WHO's ICTRP RCTs and CTs, Embase RCTs, and KoreaMed RTs (Cochrane, 2020)), PubMed/MEDLINE, Web of Science, and the NASA technical report server (NTRS) in August 2019. The initial databases searched were chosen based upon guidance presented in the Aerospace Medicine Systematic Review Group (AMSRG) list of potential data sources tool (Winnard et al., 2021). The range of search terms were decided by a pre-scoping search of the literature to ensure that each search would capture the most relevant results possible (Appendix B).

Table 3.1 Systematic Review Search Strategy

Search number	Search Term	Key words in Boolean search format	Reason	Search Mask
1	Spaceflight/Astronaut	"spaceflight" OR "space flight" OR "astronaut*" OR "microgravity" OR "micro gravity" OR "weightless*" OR "Space Flight" [Mesh] OR "Weightlessness" [Mesh] OR "Astronauts" [Mesh]	Locate studies with astronaut populations.	Title/Abstract
2	Musculoskeletal	"musc*" OR "strength*" OR "bone*" OR "skeletal" OR "Musculoskeletal" OR "neuromusculoskeletal" OR "Musculoskeletal System" [Mesh]	Limiting search to musculoskeletal area.	All Fields
3	Cardiovascular/Pulmonary	"Cardiovascular" OR "vascular*" OR "heart*" OR "Cardiopulmonary" OR "Pulmonary" OR Cardio-pulmonary" OR "Cardiovascular System" [Mesh] OR "lung" [Mesh]	Limiting search to cardiovascular/pulmonary outcomes.	All Fields
4	Combined search	1 AND (2 OR 3)	Musculoskeletal and/or cardiopulmonary outcomes within astronaut studies.	All Fields

3.2.2. Inclusion Criteria

Any studies that did not meet the inclusion criteria were excluded. No restrictions on publication date or status were applied. Only full-text, peer-reviewed documents in English language were included. If only the abstract or citation of a manuscript were available, and the manuscript could not be accessed via other means (e.g. through Research Gate), the author was contacted to obtain the full-text. If the author could not be contacted, did not respond to the request for the full-text, or were unable to provide the full-text of the manuscript, then the manuscript was excluded. The full inclusion criteria are presented in Table 3.2.

Table 3.2 PICOS Eligibility criteria

Participants/**P**opulations	**I**nterventions/**I**nterest	**C**ontrols/**C**omparisons	**O**utcome Measures	**S**tudies
Astronauts or equivalent (e.g. cosmonauts).	Exposure to spaceflight/microgravity.	Comparison to each other, no intervention, or placebo/sham.	Only documents that consider musculoskeletal or cardiovascular health will be included.	RCT, CT, interrupted time series or before-after studies from peer-reviewed literature. Full-text manuscripts only.

RCT = randomised control trail, CT = clinical control trial.

3.2.3. Study Selection and Data Extraction

The initial screening of documents, using abstracts and titles, was carried out by the lead author (JL) and an academic colleague (BW) using the Rayyan systematic review web app software (Ouzzani et al., 2016). Each author was blinded to the inclusion or exclusion of documents by the other. If it was unclear from the initial screening whether a study met the inclusion criteria, the full text of the document was obtained. Any conflict or uncertainty in study inclusion was discussed once blinded screening had been completed to come to a decision and agreed upon with a member of the supervision team (AW). Following guidance from the AMSRG NVivo user guide (Laws, Bruce-Martin, & Winnard, 2020b), NVivo 12 qualitative data analysis software (QSR NVivo 12, 2014) was used to extract qualitative data from each paper by the lead author (JL) and a sample of this extracted data were assessed by academic colleagues (EDM, AW, CBM) to increase reliability. An academic colleague (CBM) advised and assisted with the extraction of data from NVivo. Any disagreements were discussed until a consensus was reached. Quantitative data were extracted using the AMSRG study information and data extraction spreadsheet (Winnard & Waters, 2018), following guidance from the AMSRG quantitative systematic review guide (Winnard, Bruce-Martin, & Laws, 2020) by the lead author (JL) and an academic colleague (AL), and disagreements were discussed to reach consensus.

3.2.4. Quality Assessment

The quality of included studies was assessed using the Risk of Bias Assessment Tool for Nonrandomised Studies (RoBANS) (Kim et al., 2013). While the gold standard tool for quality scoring in systematic reviews is the Cochrane Risk of Bias 2 (RoB2) (Higgins et al., 2019), this is designed specifically for randomised controlled trials and as such is not appropriate for assessing non-randomised studies (Kim et al., 2013) which were found during the systematic search. A systematic review (Deeks et al., 2003) of quality scoring tools for non-randomised studies found only one tool that had been formally validated, the Methodological Index for Non-Randomised Studies (MINORS) (Slim et al., 2003). MINORS was unsuitable for this systematic review as it is unable to assess before-and-after research designs (Kim et al., 2013), which were common among the included studies. RoBANS has been externally validated for use in non-randomised studies during systematic reviews and has been shown to be both reliable and feasible for assessing the quality of before and after studies (Kim et al., 2013). As such RoBANS was chosen to assess the quality of literature in the systematic reviews.

RoBANS assesses the quality of non-randomised literature across six domains: the selection of participants; confounding variables; measurement of exposure; blinding of outcome assessments; incomplete outcome data; and selective outcome reporting, with each study ranking either low,

unclear or high risk (Kim et al., 2013). The six domains assess: if selection bias is caused by the inadequate selection of participants; if selection bias is caused by the inadequate confirmation and consideration of confounding variables; if performance bias is caused by the inadequate measurement of exposure; if detection bias is caused by the inadequate blinding of outcome assessments; if attrition bias is caused by the inadequate handling of incomplete data; and if reporting bias is caused by the selective reporting of outcomes (Kim et al., 2013). For each domain, the study is rated as either low, unclear or high risk of bias according to the RoBANS scoring advice criteria accessed from the supplementary materials of Kim et al. (2013). The lead author (JL) and an academic colleague (PS) independently quality assessed each of the included documents. Any disagreements were discussed to reach consensus with a third academic colleague (BW) to reach a majority if required.

3.2.5. Data Analysis

This review has implemented a multi-nodal, integrative, and holistic analysis strategy to extract and analyse both quantitative and qualitative data. Meta-analysis could not be implemented as it assumes that there is independence of observations in the data, creating difficulty for human spaceflight studies which often use repeated measures designs (Cheung, 2019; "The negative effect of unloading exceeds the bone-sparing effect of alkaline supplementation: a bed rest study," 2018; Peters & Mengersen, 2008). Quantitative data were instead analysed by calculating effect sizes for each physiological outcome between pre- and post- spaceflight when the data were available (mean, standard deviation and number of participants were required). Where a study reported results from multiple time points, the data immediately prior (for baseline scores) and following (for post-experimental scores) the microgravity exposure were used to ensure the greatest consistency across all studies. The calculated effect sizes were bias corrected using the Hedge's *g* method to account for sample size by using weighted pooled standard deviations (Ellis, 2010). Hedge's *g* effect sizes are more suitable to space medicine reviews than traditional Cohen's *d* effect sizes as astronaut and bedrest study sample sizes are often small in comparison to traditional medicine reviews (Winnard, Bruce-Martin, et al., 2020). Thresholds were defined as small (0.2), medium (0.5), large (0.8), and very large (1.3) (Rosenthal, 1996) between pre and post spaceflight scores, as recommended by the AMSRG quantitative systematic review guide (Winnard, Bruce-Martin, et al., 2020). It should be noted that Rosenthal (1996) emphasised that these effect size cut offs are generic and not specific to any one review area. Where the data to calculate effect size scores were not available, statistically significant increase, decrease or no change were instead extracted and reported. It should be noted that significance reporting is not a common method for comparing results during a systematic review and it is only reported in this review to provide an indication of changes across individual outcomes pre- to post-spaceflight and as such, caution should be used if comparing these outcomes.

For qualitative data, thematic analysis (Braun et al., 2006; Braun et al., 2019) and thematic synthesis (Thomas et al., 2008), following the AMSRG qualitative review guides (Laws, Bruce-Martin, & Winnard, 2020a; Laws & Winnard, 2019a), was used. The full procedure for thematic analysis is discussed in detail in Chapter 2. The data were coded using NVivo 12 (QSR NVivo 12, 2014). Outcomes were grouped by common theme and presented as thematic maps. The themes were then ranked in order of importance to astronaut health and mission success by a medical doctor (EDM) who was blinded to all other aspects of the study. A second medical doctor with a space medicine research background (VW) independently validated the rankings and disagreements were discussed to reach consensus. To supplement these rankings, the number of times each outcome was reported within the evidence base was also recorded.

3.3. Results

A total of 1149 documents were identified, including 11 documents identified through additional sources (e.g. reference list searching), which were reduced to 1040 documents after duplicates were removed. 944 documents were excluded after screening of the title and abstracts of the documents were completed. For documents that were only abstracts, if access to the full paper could not be gained, then the document was excluded. The full text was obtained for the remaining 96 documents, and 12 exclusions were made (Figure 3.1). The final number of documents concerning astronaut musculoskeletal and cardiovascular health were 84. Twenty-four documents were concerned with muscular health, 21 documents were related to skeletal health and 42 documents were linked to cardiovascular health, with three of the documents examining both muscle and skeletal outcomes (Figure 3.1).

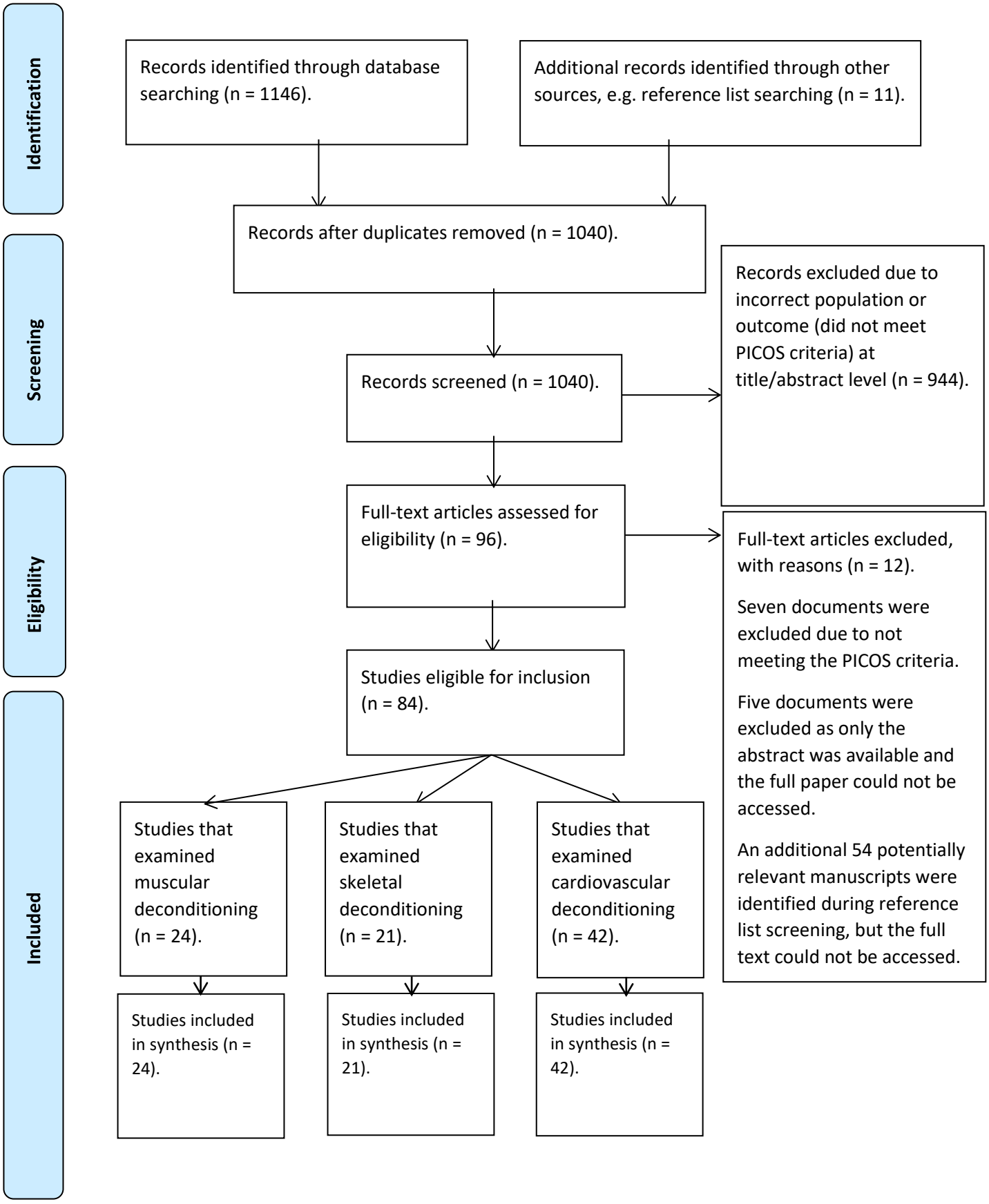

Figure 3.1 PRISMA flow diagram. Some documents examined multiple areas (e.g. muscular and skeletal deconditioning) and as such the documents eligible for inclusion does not equal the total of the documents split into each group.

3.3.1. Characteristics of Included Studies

The characteristics of the included studies are summarised in Table 3.3. Across all 84 studies, 28 were before and after studies while 56 were interrupted time series. 79 studies used repeated measure designs, one used independent groups, and four used both repeated measures and independent groups.

For muscle outcomes only, 13 were before and after studies, while 11 were interrupted time series studies. Except for two studies, which used both independent and repeated measure designs, all muscle studies used repeated measure designs.

For skeletal outcomes only, eight were before and after studies, while 13 were interrupted time-series studies. Except for a single study, which used both independent and repeated measure designs, all studies used repeated measure designs.

For cardiovascular outcomes only, seven were before and after studies, while 35 were interrupted time series studies. All studies used repeated measure designs, except for one study which used both independent and repeated measures, and one study that used just independent measures.

Table 3.3 Characteristics of the included studies

Article (author cross reference number)	Study Design	Outcome(s)	Number of Participants	Days of Spaceflight
Arbeille, Fomina, Achaibou, Pottier, and Kotovskaya (1995) [4]	RM, ITS	C	2	14
Arzeno, Stenger, Bloomberg, and Plats (2013) [5]	RM, ITS	C	7*	10-15
Baevsky et al. (2007) [6]	RM, ITS	C	8*	162-196
Baevsky, Chernikova, Funtova, and Tank (2011) [7]	RM, ITS	C	48*	152-182
Baisch et al. (2000) [8]	RM, BA	C	6*	38
Beckers, Verheyden, Couckuyt, and Aubert (2007) [9]	RM, BA	C	5*	10-30
Beckers, Verheyden, Liu, and Aubert (2009) [10]	RM, ITS	C	5*	10-30
Buckey, Gaffney, et al. (1996) [12]	RM, BA	C	14*	9-14
Buckey, Lane, et al. (1996) [11]	RM, BA	C	3*	N/A
Bungo, Charles, and Johnson Jr (1985) [82]	IG, ITS	C	26 (24, 2 flew twice)*	54-192 hours
Cooke et al. (2000) [81]	RM, ITS	C	3*	274
Di Rienzo et al. (2007) [19]	RM, ITS	C	4	16
Fu et al. (2002) [22]	RM, ITS	C	5	16
Fu et al. (2019) [83]	RM, ITS	C	13*	Aprox. 183
Grigoriev, Kotovskaya, and Fomina (2011) [24]	RM, ITS	C	26*	8-438
Hughson et al. (2011) [25]	RM, BA	C	6*	153, 120, 52, 175, 199, and 180.
Iellamo et al. (2006) [26]	RM, BA	C	4	16
Karlsson, Montmerle, Rohdin, and Linnarsson (2009) [27]	RM, BA	C	4	16
Khine et al. (2018) [84]	RM, ITS	C	13*	Aprox. 183
Levine et al. (2002) [35]	RM, ITS	C	6	16

Article (author cross reference number)	Study Design	Outcome(s)	Number of Participants	Days of Spaceflight
Liu et al. (2015) (36)	RM, ITS	C	3	15
Migeotte, Prisk, and Paiva (2003) (39)	RM, ITS	C	4	16
Morita, Abe, and Tanaka (2016) (41)	RM, ITS	C	6*	127-188
Otsuka et al. (2015) (42)	RM, ITS	C	7*	172.6 ± 14.6
Otsuka et al. (2016) (43)	RM, ITS	C	10*	171.8 ± 14.4
Pastushkova et al. (2019) (44)	RM and IG, ITS	C	10*	169-199
Prisk, Elliott, Guy, Kosonen, and West (1995) (45)	RM, ITS	C	8*	9-14
Prisk, Fine, Cooper, and West (2006) (46)	RM, ITS	C	10	130-196
Prisk, Guy, Elliott, and West (1994) (47)	RM, ITS	C	4	9
Prisk, Guy, Elliott, Deutschman 3rd, and West (1993) (48)	RM, ITS	C	4	9
Prisk, Guy, Elliott, Paiva, and West (1995) (49)	RM, ITS	C	4	9
Rossum, Ziegler, and Meck (2001a) (53)	RM, ITS	C	21*	N/A
Rossum, Ziegler, and Meck (2001b) (54)	RM, ITS	C	21*	N/A
Shiraishi et al. (2004) (55)	RM, ITS	C	4	183
Shykoff et al. (1996) (56)	RM, ITS	C	6*	9 and 15 (3 astronauts in each)
Vandeput, Widjaja, Aubert, and Van Huffel (2013) (64)	RM, ITS	C	8*	183 (five astronauts) and 10 (three astronauts)
Verbanck et al. (1997) (65)	RM, ITS	C	4	10
Verheyden, Beckers, Couckuyt, Liu, and Aubert (2007) (66)	RM, ITS	C	5*	10-11
Wantier, Estenne, Verbanck, Prisk, and Paiva (1998) (68)	RM, ITS	C	3	10
Waters, Ziegler, and Meck (2002) (69)	RM, ITS	C	36*	5-16
Xu et al. (2013) (72)	RM, ITS	C	7*	52-199

Article (author cross reference number)	Study Design	Outcome(s)	Number of Participants	Days of Spaceflight
Yamamoto et al. (2015) [73]	RM, ITS	C	19-25*	163-199
Akima, Kawakami, et al. (2000) [1]	RM, BA	M	3*	9-16
Antonutto, Capelli, Giradis, Zamparo, and diPrampero (1995) [2]	RM, ITS	M	4*	31
Antonutto, Capelli, Girardis, Zamparo, and di Prampero (1999) [3]	RM, BA	M	4*	31-180
Burkhart, Allaire, and Bouxsein (2019) [13]	RM, ITS	M	17*	121-213
Capri et al. (2019) [16]	IG and RM, ITS	M	2	183
Edgerton et al. (2001) [76]	RM, ITS	M	4	N/A
English et al. (2015) [20]	RM, BA	M	37*	N/A
Fitts et al. (2010) [21]	RM, BA	M	10*	161-192
Koryak (2018) [29]	RM, BA	M	8*	115-380
Lambertz, Goubel, Kaspranski, and Perot (2003) [30]	RM, ITS	M	3* (*EuroMir '95, '98-E space missions*); 12* (*Mir missions EO 19-24*).	90-180
Lambertz, Perot, Kaspranski, and Goubel (2001) [31]	RM, BA	M	4* (EuroMir '94, '95 and '98-E space missions); 14* (Mir Missions EO 19-24).	90-180
McNamara, Greene, Moore, Lenchik, and Weaver (2019) [38]	RM, BA	M	16*	121-183
Narici, Kayser, Barattini, and Cerretelli (2003) [75]	RM, ITS	M	4	17
Riley et al. (2000) [50]	RM, BA	M	4	17
Riley et al. (2002) [51]	RM, BA	M	4	17
Rittweger et al. (2018) [52]	RM, BA	M	2	183
Tesch, Berg, Bring, Evans, and LeBlanc (2005) [63]	IG and RM, BA	M	4	16
Trappe et al. (2009) [77]	RM, ITS	M	9*	161-192
Widrick et al. (1999) [70]	RM, ITS	M	4	17

Article (author cross reference number)	Study Design	Outcome(s)	Number of Participants	Days of Spaceflight
Widrick et al. (2001) [71]	RM, BA	M	4	17
Zange et al. (1997) [78]	RM, BA	M	4*	30-183
Chang et al. (2016) [17]	RM, ITS	M, S	6*	117-213
LeBlanc et al. (2000) [34]	RM, BA	M, S	4 (SpaceLab mission); 16* (Shuttle/Mir missions)	17 (SpaceLab mission); 112-196 (Shuttle/Mir missions)
Miyamoto et al. (1998) [40]	RM, ITS	M, S	2	8.9-14.7
Caillot-Augusseau et al. (1998) [14]	RM, ITS	S	4	180
Caillot-Augusseau et al. (2000) [15]	RM, ITS	S	2	21
Collet et al. (1997) [18]	RM, BA	S	2*	28-183
Goodship et al. (1998) [23]	RM, BA	S	1	152
Keyak, Koyama, LeBlanc, Lu, and Lang (2009) [28]	RM, BA	S	13*	131-198
Lang et al. (2004) [32]	RM, BA	S	14*	131-198
Lang, Leblanc, Evans, and Lu (2006) [80]	RM, ITS	S	16*	136-183
LeBlanc et al. (1999) [33]	IG and RM, ITS	S	4	17
Leblanc et al. (2013) [79]	RM, BA	S	7*	136-189
McCarthy et al. (2000) [37]	RM, ITS	S	3*	20-180
Sibonga et al. (2007) [59]	RM, ITS	S	29* (Mir mission); 17* (ISS mission)	126-438
Sibonga, Evans, Spector, et al. (2006) [58]	RM, ITS	S	12* (ISS mission); 22* (Mir mission); 5* (ISS mission)	121-183
Sibonga, Evans, Sung, et al. (2006) [57]	RM, BA	S	45*	121-183
Smith et al. (2005) [60]	RM, ITS	S	13* (Study 1); 6* (Study 2)	121-183
Smith et al. (2012) [61]	RM, ITS	S	13*	48-215
Smith et al. (2014) [62]	RM, BA	S	42*	49-215

Article (author cross reference number)	Study Design	Outcome(s)	Number of Participants	Days of Spaceflight
Vico et al. (2000) [67]	RM, ITS	S	22*	30-183
Zwart, Morgan, and Smith (2013) [74]	RM, ITS	S	23*	50-247

*Indicates that data collected from participants was split across multiple spaceflights, or it was unclear if the data was collected across multiple flights. N/A indicates that the total days of spaceflight was not reported or unclear. Where the specific number of days were not given (e.g the paper only reported spaceflight duration in months) the number of days were calculated if possible. RM = Repeated measures; ITS = Interrupted Time Series; BA = Before and After study; IG = Independent groups, M = Muscle outcomes, S = Skeletal outcomes, C = Cardiovascular outcomes.

3.3.2. Quality Scoring

Full reporting of RoBANS risk of bias scores for each of the included studies can be seen in Table 3.4. Across all outcomes, 18 studies were scored as high risk of bias in relation to selection of participants (11 for muscle, four for skeletal, and four for cardiovascular), one study was scored as low risk of bias (one muscle), and the remaining studies were scored as unclear risk of bias. All studies were scored as unclear risk of bias for confounding variables and low risk of bias for measurement of exposure and selective outcome reporting. Four studies were scored low risk of bias for blinding of outcome assessments (four muscle), while the remaining were scored unclear. All studies scored low risk of bias for incomplete outcome data, with the exception of one (one cardiovascular) which scored high.

Table 3.4 RoBANS Risk of Bias

Article (author cross reference number)	RoBANS Risk of Bias Domains					
	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcome assessments	Incomplete outcome data	Selective outcome reporting
Akima, Kawakami, et al. (2000) [1]	–	–	↓	↓	↓	↓
Antonutto et al. (1995) [2]	–	–	↓	↓	↓	↓
Antonutto et al. (1999) [3]	–	–	↓	–	↓	↓
Burkhart et al. (2019) [13]	↑	–	↓	↓	↓	↓
Capri et al. (2019) [16]	↑	–	↓	↓	↓	↓
Chang et al. (2016) [17]	–	–	↓	–	↓	↓
English et al. (2015) [20]	–	–	↓	–	↓	↓
Fitts et al. (2010) [21]	–	–	↓	–	↓	↓
Koryak (2018) [29]	–	–	↓	–	↓	↓
Lambertz et al. (2003) [30]	↑	–	↓	–	↓	↓
Lambertz et al. (2001) [31]	↑	–	↓	–	↓	↓
LeBlanc et al. (2000) [34]	↑	–	↓	–	↓	↓
McNamara et al. (2019) [38]	↑	–	↓	–	↓	↓
Riley et al. (2000) [50]	↑	–	↓	–	↓	↓
Riley et al. (2002) [51]	↑	–	↓	–	↓	↓
Rittweger et al. (2018) [52]	↑	–	↓	–	↓	↓
Tesch et al. (2005) [63]	↓	–	↓	–	↓	↓
Widrick et al. (1999) [70]	–	–	↓	–	–	↓
Widrick et al. (2001) [71]	–	–	↓	–	–	↓
Narici et al. (2003) [75]	–	–	↓	–	↓	↓
Edgerton et al. (2001) [76]	–	–	↓	–	↓	↓
Trappe et al. (2009) [77]	–	–	↓	–	↓	↓
Zange et al. (1997) [78]	↑	–	↓	–	↓	↓
Caillot-Augusseau et al. (1998) [14]	–	–	↓	–	↓	↓
Caillot-Augusseau et al. (2000) [15]	–	–	↓	–	↓	↓
Collet et al. (1997) [18]	–	–	↓	–	↓	↓

Article (author cross reference number)	RoBANS Risk of Bias Domains					
	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcome assessments	Incomplete outcome data	Selective outcome reporting
Goodship et al. (1998) [23]	–	–	↓	–	↓	↓
Keyak et al. (2009) [28]	–	–	↓	–	↓	↓
Lang et al. (2004) [32]	–	–	↓	–	↓	↓
LeBlanc et al. (1999) [33]	–	–	↓	–	↓	↓
McCarthy et al. (2000) [37]	–	–	↓	–	↓	↓
Miyamoto et al. (1998) [40]	–	–	↓	–	↓	↓
Sibonga, Evans, Sung, et al. (2006) [57]	↑	–	↓	–	↓	↓
Sibonga, Evans, Spector, et al. (2006) [58]	↑	–	↓	–	↓	↓
Sibonga et al. (2007) [59]	↑	–	↓	–	↓	↓
Smith et al. (2005) [60]	–	–	↓	–	↓	↓
Smith et al. (2012) [61]	–	–	↓	–	↓	↓
Smith et al. (2014) [62]	↑	–	↓	–	↓	↓
Vico et al. (2000) [67]	–	–	↓	–	↓	↓
Zwart et al. (2013) [74]	–	–	↓	–	↓	↓
Leblanc et al. (2013) [79]	–	–	↓	–	↓	↓
Lang et al. (2006) [80]	–	–	↓	–	↓	↓
Arbeille et al. (1995) [4]	–	–	↓	–	↓	↓
Arzeno et al. (2013) [5]	–	–	↓	–	↓	↓
Baevsky et al. (2007) [6]	–	–	↓	–	↓	↓
Baevsky et al. (2011) [7]	–	–	↓	–	↓	↓
Baisch et al. (2000) [8]	–	–	↓	–	↓	↓
Beckers et al. (2007) [9]	–	–	↓	–	↓	↓
Beckers et al. (2009) [10]	–	–	↓	–	↓	↓
Buckey, Lane, et al. (1996) [11]	–	–	↓	–	↓	↓
Buckey Jr et al. (1996) [12]	–	–	↓	–	↓	↓
Di Rienzo et al. (2007) [19]	–	–	↓	–	↓	↓

Article (author cross reference number)	RoBANS Risk of Bias Domains					
	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcome assessments	Incomplete outcome data	Selective outcome reporting
Fu et al. (2002) [22]	–	–	↓	–	↓	↓
Grigoriev et al. (2011) [24]	↑	–	↓	–	↓	↓
Hughson et al. (2011) [25]	–	–	↓	–	↓	↓
Iellamo et al. (2006) [26]	–	–	↓	–	↓	↓
Karlsson et al. (2009) [27]	–	–	↓	–	↓	↓
Levine et al. (2002) [35]	–	–	↓	–	↓	↓
Liu et al. (2015) [36]	–	–	↓	–	↓	↓
Migeotte et al. (2003) [39]	–	–	↓	–	↓	↓
Morita et al. (2016) [41]	–	–	↓	–	↓	↓
Otsuka et al. (2015) [42]	–	–	↓	–	↓	↓
Otsuka et al. (2016) [43]	–	–	↓	–	↓	↓
Pastushkova et al. (2019) [44]	–	–	↓	–	↓	↓
Prisk, Elliott, et al. (1995) [45]	–	–	↓	–	↓	↓
Prisk et al. (2006) [46]	–	–	↓	–	↓	↓
Prisk et al. (1994) [47]	–	–	↓	–	↓	↓
Prisk et al. (1993) [48]	–	–	↓	–	↓	↓
Prisk, Guy, et al. (1995) [49]	–	–	↓	–	↓	↓
Rossum et al. (2001a) [53]	↑	–	↓	–	↓	↓
Rossum et al. (2001b) [54]	↑	–	↓	–	↓	↓
Shiraishi et al. (2004) [55]	–	–	↓	–	↓	↓
Shykoff et al. (1996) [56]	–	–	↓	–	↓	↓
Vandeput et al. (2013) [64]	–	–	↓	–	↓	↓
Verbanck et al. (1997) [65]	–	–	↓	–	↓	↓
Verheyden et al. (2007) [66]	–	–	↓	–	↓	↓
Wantier et al. (1998) [68]	–	–	↓	–	↓	↓
Waters et al. (2002) [69]	↑	–	↓	–	↓	↓

Article (author cross reference number)	RoBANS Risk of Bias Domains					
	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcome assessments	Incomplete outcome data	Selective outcome reporting
Xu et al. (2013) [72]	–	–	↓	–	↓	↓
Yamamoto et al. (2015) [73]	–	–	↓	–	↓	↓
Cooke et al. (2000) [81]	–	–	↓	–	↑	↓
Bungo et al. (1985) [82]	–	–	↓	–	↓	↓
Fu et al. (2019) [83]	–	–	↓	–	↓	↓
Khine et al. (2018) [84]	–	–	↓	–	↓	↓

↑ Indicates a high risk of bias, ↓ indicates a low risk of bias, and – indicates an unclear risk of bias.

3.3.3. Outcomes Assessed

The review identified a total of 616 (301 muscle, 149 skeletal, and 166 cardiovascular) individual physiological outcome measures that had been examined during operational human spaceflight missions. Only 63 of the 616 unique outcome measures (five for muscle, 32 for skeletal, and 26 for cardiovascular) were reported in more than one study. A table of these physiological outcome measures, including any quantitative data that was extracted and the categorisation of each physiological outcome using qualitative thematic analysis can be found in Appendix C.

3.3.3.1. Muscular deconditioning

Thematic analysis indicated that the outcomes can be categorised into three major themes: architectural and structural properties of the muscles; functional and mechanical properties of the muscles; and biomarkers of muscular deconditioning. These major themes are underpinned by 12 higher order themes and their 11 additional sub-themes: muscle volume; muscle cross-sectional area; muscle attenuation; muscle fibre architectural and structural properties (which is further divided into the sub-themes of gastrocnemius muscle fibre architectural and structural properties, and soleus muscle fibre architectural and structural properties); muscle strength and power (which is further divided into isokinetic strength, isometric strength, and muscle maximal power); functional and mechanical properties of the triceps surae (which is further divided into gastrocnemius muscle functional and mechanical properties, and soleus muscle functional and mechanical properties); functional and mechanical properties of the triceps surae muscle fibres (which is further divided into functional and mechanical properties of the gastrocnemius muscle fibres, and functional and mechanical properties of the soleus muscle fibres); protein biomarkers (which is further divided into skeletal muscle anaerobic metabolism protein alterations, skeletal muscle contractile protein alterations, and protein biomarkers of muscular deconditioning); enzyme biomarkers; plasma metabolic alterations; and blood c-markers.

Within each of the higher order themes, individual physiological outcomes related to muscular deconditioning were categorised. For example, sartorius muscle volume would be categorised under the higher order theme muscle volume which is itself categorised under the major theme architectural and structural properties. While higher-order themes and sub-themes provide additional clarity by grouping similar outcome measures, it should be noted that each sub-theme is ultimately a function of the major theme under which they have been grouped. The thematic map displaying the relationship between the major and higher order themes can be seen in Figure 3.2.

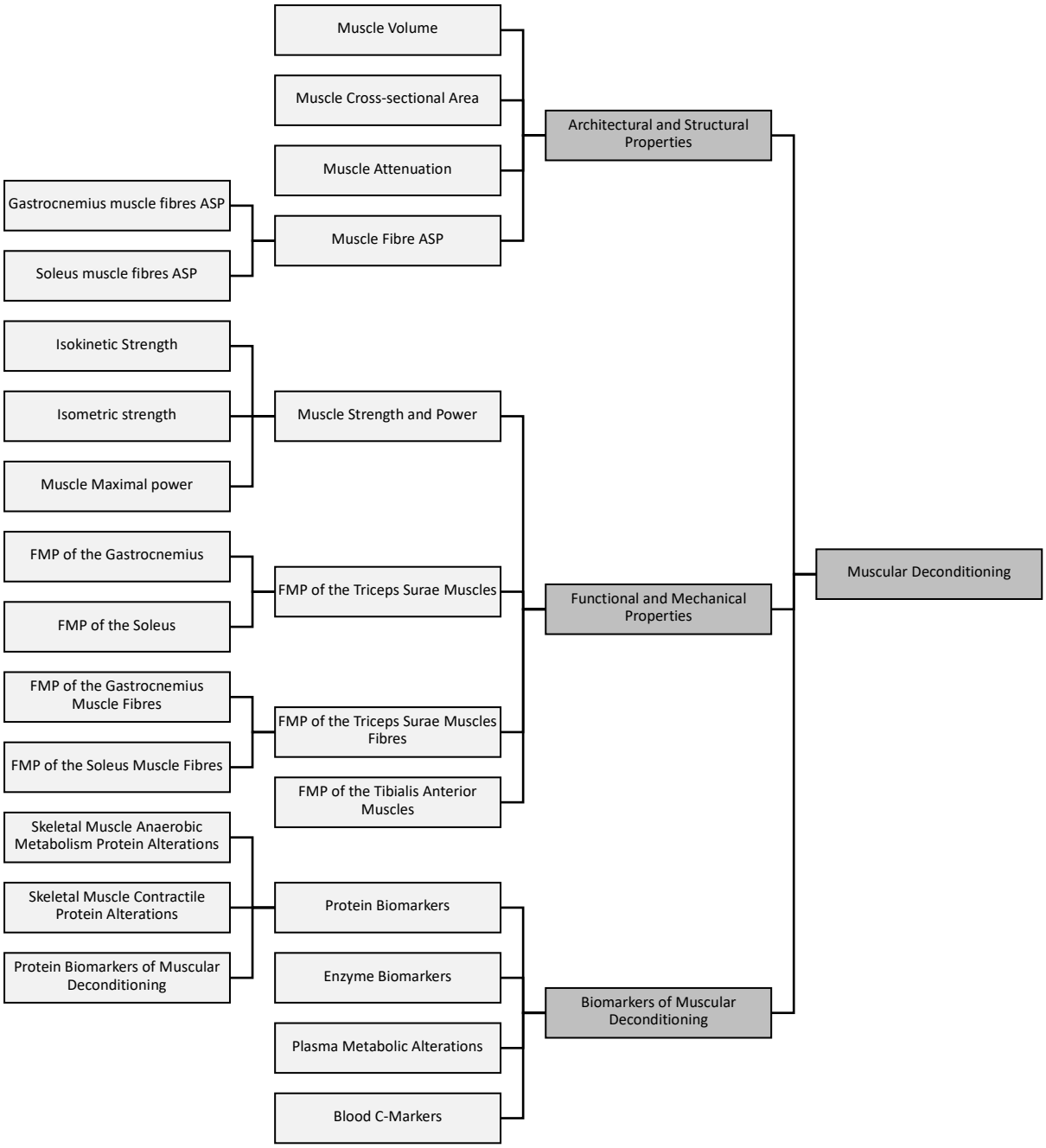

Figure 3.2 Thematic map of the major and higher order themes of muscular deconditioning. Major themes are shown in dark grey while higher order themes are shown in light grey. The thematic maps presented throughout the results branch off from this thematic map, exploring the individual outcomes reported within each of these themes. As such, the thematic maps can be used to trace the relationship of each individual outcome. *ASP = Architectrual and Structural Properties, FMP = Funtional and Mechanical Properties.*

The major themes were ranked from 1-3 based upon the medical risk each theme presents to astronaut health and operational mission success (evidence-based justifications for these rankings are provided in Table 3.5). The order of medical ranking in descending importance was outcomes related to: the functional and mechanical properties; the architectural and structural properties; and the biomarkers of muscular deconditioning.

Table 3.5 Ranking of major themes, based on impact on mission success and the number of times individual outcomes within each theme were reported

Major theme	Higher order themes	Major theme medical ranking	Number of times outcomes in this major theme were reported (ranking)	Justification for medical ranking
Functional and Mechanical Properties	Muscle strength and power Functional and mechanical properties of the triceps surae fibres Functional and mechanical properties of the triceps surae Functional and mechanical properties of the tibialis anterior muscle	1	122 (1)	Maximal strength/power deficits represent both an operational and medical risk to the individual crewmembers (English et al., 2015). For example, deficits in maximal strength and power may prevent successful spacewalks or emergency egress (Moore, Lee, Stenger, & Platts, 2010; Wang et al., 2019). As such, these aspects of functional and mechanical properties are the most relevant to astronaut health and mission success during spaceflight. The functional and mechanical properties of the soleus muscle are particularly susceptible to microgravity deconditioning (Akima et al., 2002; Alkner et al., 2004). This is because the soleus is typically characterised by a high proportion of type I (oxidative) muscle fibres that tend to express more glycolytic characteristics during exposure to microgravity (Widrick et al., 2001). The functional and mechanical properties of the gastrocnemius muscle is also susceptible to microgravity-induced deterioration (Akima et al., 2002; Alkner et al., 2004). However, gastrocnemius has a higher proportion of type IIa fibres compared to the soleus (Widrick et al., 2001). Therefore, it is less affected compared with the soleus during exposure to microgravity.
Architectural and Structural Properties	Muscle fibre architectural and structural properties Muscle volume Muscle cross-sectional area Muscle attenuation	2	81 (2)	While architectural and structural outcomes indicate structural changes, it is unclear to what extent they are informative relative to the direct measures of functional and mechanical changes which may alter astronaut performance (Koryak, 2018). As such, priority is given to the functional and mechanical properties over the architectural and structural (morphology) properties.
Biomarkers of Muscular Deconditioning	Protein biomarkers Blood c-markers Plasma metabolic alterations Enzyme biomarkers	3	78 (3)	Biomarkers are indirect outcomes of muscle functional and mechanical properties and structural and architectural properties (Capri et al., 2019). While these outcomes may indicate changes to the architectural, structural, functional or mechanical properties of a muscle they are not in themselves very informative about how or to what extent specific aspects of astronaut health or performance has been altered, when compared to the higher ranked outcomes (Calder et al., 2017; Capri et al., 2019).

The column “medical ranking” was rank scored from 1-3, with one being most impactful on astronaut health and mission success and three being least impactful, as determined by a medical doctor with a space medicine research background and supported by data extracted during thematic analysis. The column “number of times outcomes in this group were reported” was rank scored from 1-3, with one being most reported and three being least reported during studies included in this systematic review.

The medical rankings were also directly reflected in the number of times these outcomes were reported. Outcomes related to functional and mechanical properties were reported 122 times, those related to architectural and structural properties were reported 81 times, and biomarkers of muscular deconditioning 78 times.

3.3.3.1.1. Muscle Functional and Mechanical Properties

Outcome groups identified in this review that fall into the theme of functional and mechanical properties include: the strength and power of muscles (Figure 3.3, 3.4 and 3.5) the functional and mechanical properties of the triceps surae muscles (Figure 3.6 and 3.7), the functional and mechanical properties of the triceps surae muscle fibres (Figure 3.8 and 3.9) and the functional and mechanical properties of the tibialis anterior muscle (Figure 3.10). Each of these thematic maps branch off the major thematic map presented in Figure 3.2. As such, the thematic maps can be used to trace the relationship of each individual outcome measure to its common theme. Outcomes identified in this review that were related to the functional and mechanical properties of muscles were reported to primarily decrease between pre- and post-spaceflight. Appendix C provides the quantitative effect size or significant change findings depending on data availability, shown as pre- to post-spaceflight changes.

3.3.3.1.1.1. Isokinetic Strength

There was insufficient data on isokinetic strength reported to calculate effect sizes. Where significant changes were reported the trend was to decreases pre-post spaceflight, except for dorsiflexor torque which showed no change.

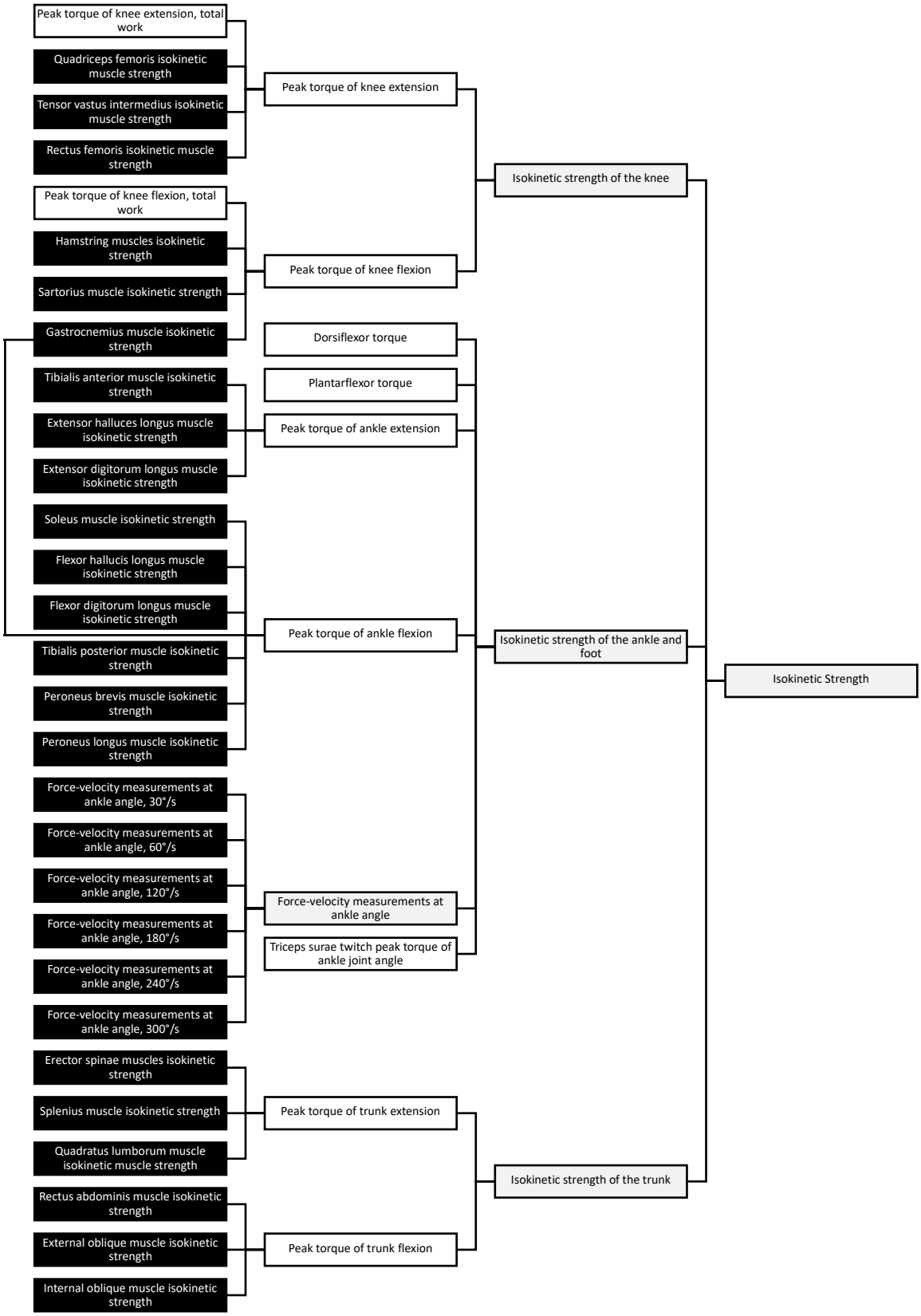

Figure 3.3 Thematic map of isokinetic muscle strength outcomes. Higher order themes are shown in light grey while individual outcomes are shown in white. Black with white text is used to display outcomes that are a breakdown of the reported muscle outcomes (e.g. The individual hamstring muscles).

3.3.3.1.1.2. Isometric Strength

All measurements of isometric strength decreased between pre- and post-spaceflight. A medium effect size decrease was reported for maximal voluntary isometric knee extensor force and small effect size decreases were reported for concentric and eccentric knee extensor force.

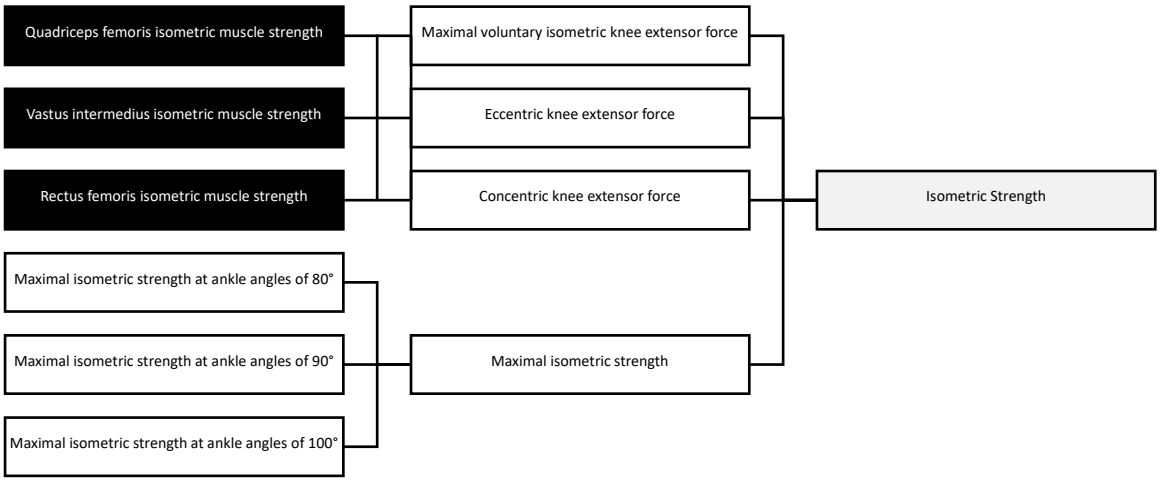

Figure 3.4 Thematic map of isometric strength outcomes. Higher order themes are shown in light grey while individual outcomes are shown in white. Black with white text is used to display outcomes that are a breakdown of the reported muscle outcomes (e.g. The individual hamstring muscles).

3.3.3.1.1.3. Muscle Maximal Power

All measurements of muscle maximal power decreased between pre- and post-spaceflight. Very large effect size decreases were reported for mean force, mean maximal power, peak maximal power, maximal acceleration, and overall mechanical work of the lower limbs. For all remaining outcomes that did not report enough data to calculate effect size changes but did report significance testing, there were significant decreases between pre- and post-spaceflight.

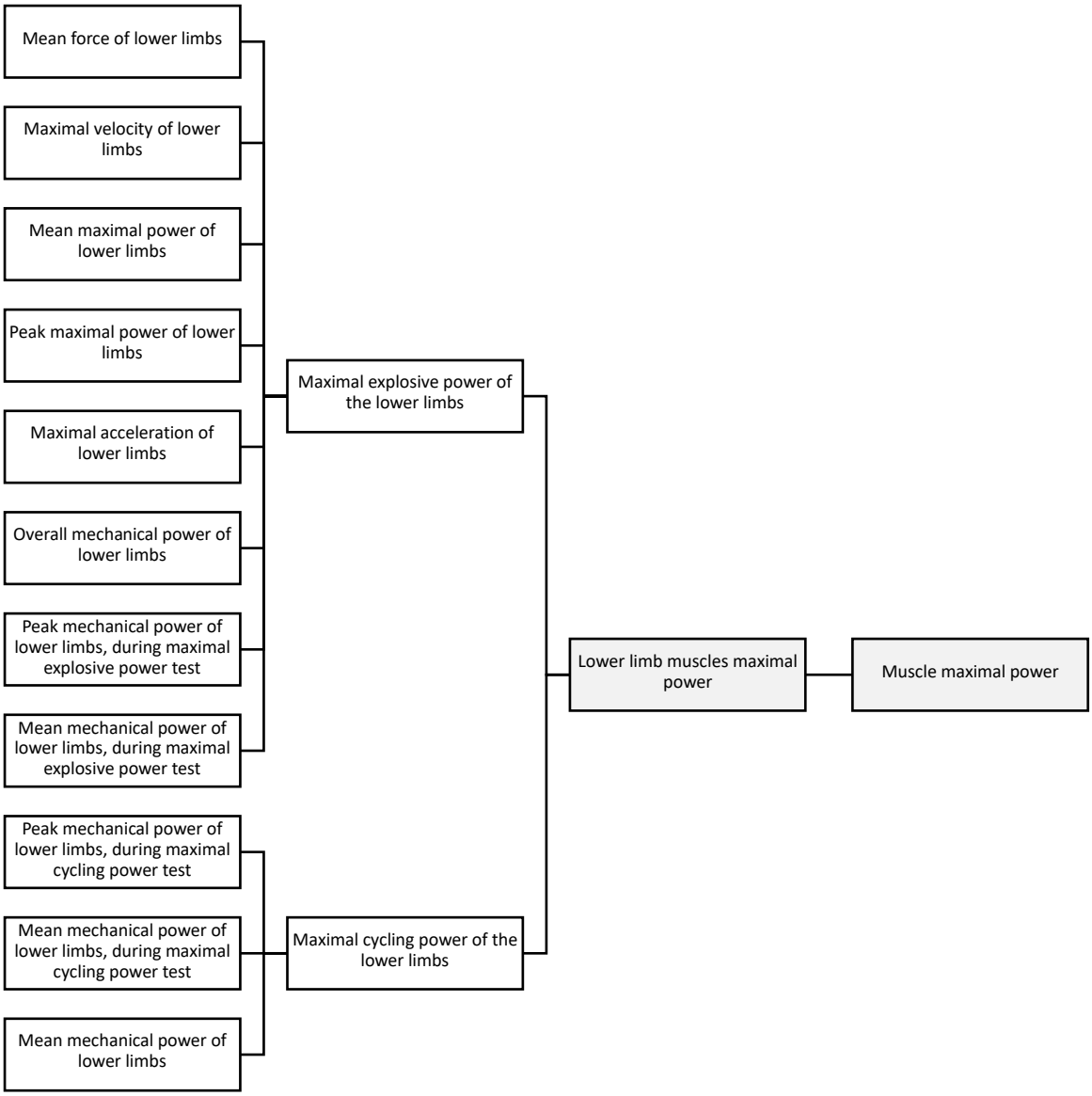

Figure 3.5 Thematic map of muscle maximal power outcomes. Higher order themes are shown in light grey while individual outcomes are shown in white.

3.3.3.1.1.4. Functional and Mechanical Properties of the Gastrocnemius Muscle

Data for all outcomes related to functional and mechanical properties of the gastrocnemius muscle were not reported in enough detail to standardize changes into effect sizes or to determine if changes between pre- and post-spaceflight were statistically significant.

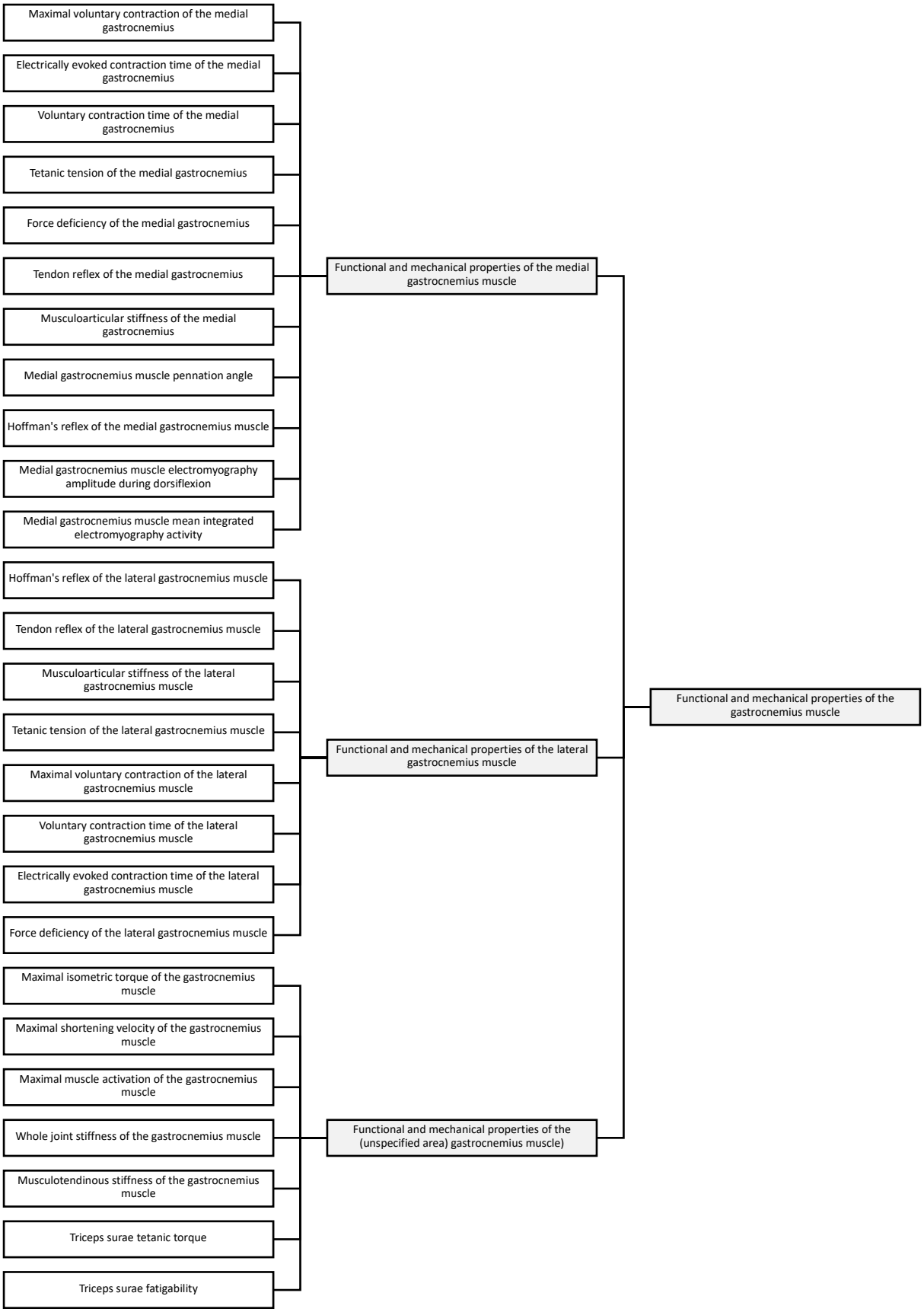

Figure 3.6 Thematic map of the functional and mechanical properties of the gastrocnemius muscle. Higher order themes are shown in light grey while individual outcomes are shown in white.

3.3.3.1.1.5. Functional and Mechanical Properties of the Soleus Muscle

Data for all outcomes related to functional and mechanical properties of the soleus muscle were not reported in enough detail to standardize changes into effect sizes or to determine if changes between pre- and post-spaceflight were statistically significant, with the exception of mean integrated electromyography activity of the soleus muscle, which decreased significantly between pre-post spaceflight.

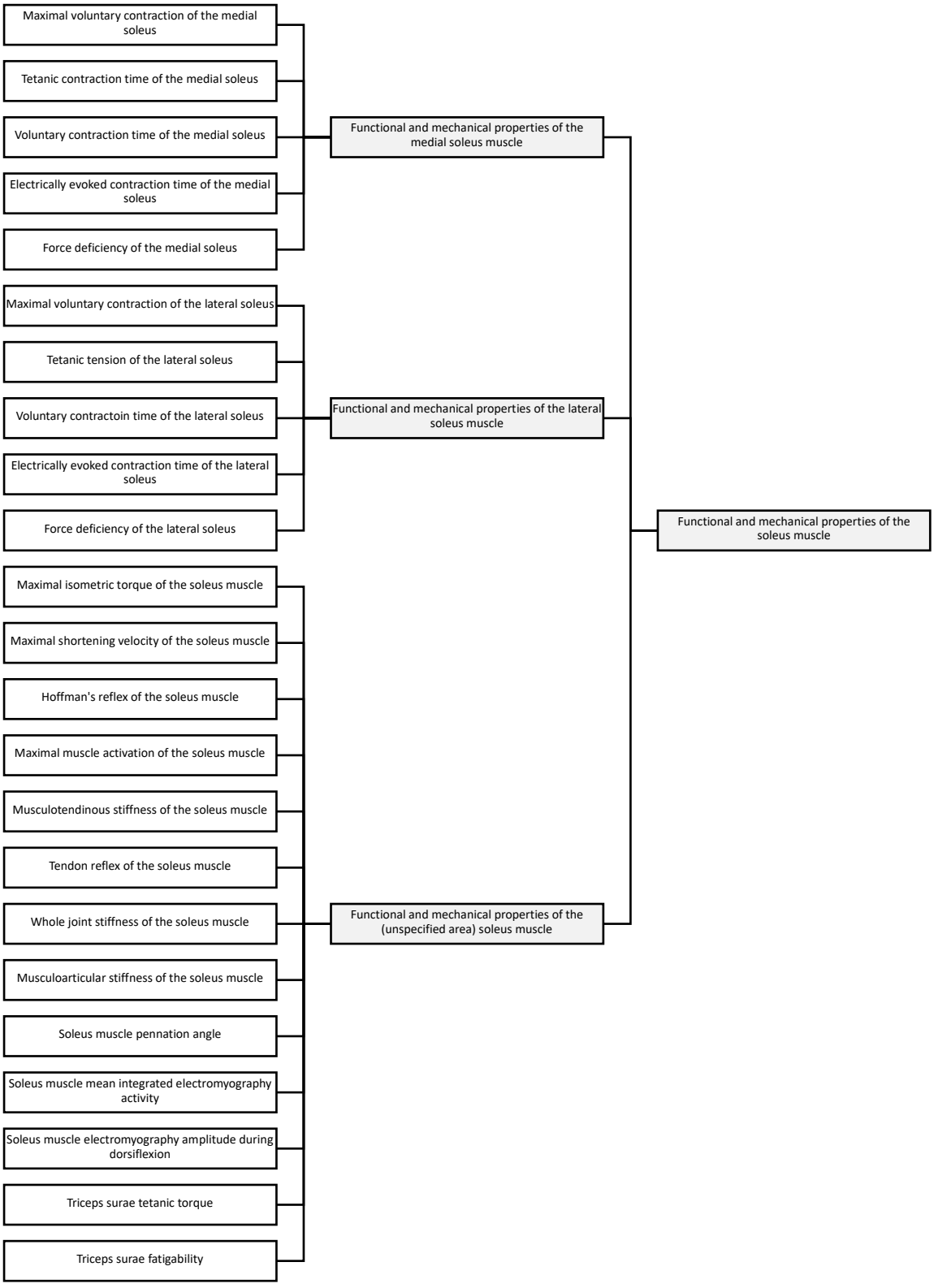

Figure 3.7 Thematic map of the functional and mechanical properties of the soleus muscle. Higher order themes are shown in light grey while individual outcomes are shown in white.

3.3.3.1.1.6. Functional and Mechanical Properties of the Gastrocnemius Muscle Fibres

There were mixed findings for outcomes related to the functional and mechanical properties of the gastrocnemius muscle fibres. Muscle fibre types can be classified by myosin heavy chain (MHC) protein isoform, metabolic enzyme activity, and/or contractile speed. Human skeletal muscle is comprised of pure fibres (MHC I, IIa, and IIx), as well as "hybrid" fibre types. They can also be more generally classified as type I (includes MHC I) and type II (includes MHC IIa and IIx) (Schiaffino & Reggiani, 2011).

In regards to type I fibres, there were a small effect size decrease in type I force constant, a medium decrease for type I peak activated force, and a large decrease for type I peak stiffness/peak force ratio. Studies reported a very large decrease in type I rate constant of tension redevelopment and type I peak stifffness. There were also a large effect size increase in type I peak stiffness ratio and unloaded shortening velocity. Other findings tended to vary: type I peak power showed a very large effect size decrease in one study and a small effect size decrease in another. One study reported a very large decrease for type I peak force while another reported a medium decrease. Type I maximum shortening velocity was reported by one study to show a very large decrease while in the other there was a large increase.

In regards to type II and hybrid fibres there was a small effect size decrease for IIa/IIx peak power, a medium effect size decrease for type II peak force, IIa peak force, IIa peak stiffness, IIa peak stiffness/peak force ratio, and IIa peak power. There was also a large decrease for type IIa/IIx peak activated force and a very large decrease in type II maximal shortening velocity and type IIa peak activated force. Small effect size increases were reported for type IIa/IIx unloaded shortening velocity and IIa/IIx force constant, and a medium effect size increase for IIa/IIx peak stiffness and IIa maximum shortening velocity. There was a large increase in type IIa unloaded shortening velocity. Type IIa/IIx showed an increase in muscle fibre peak force and force constant, but the effect size was not large enough to meet the criteria for a small change. There was no change in IIa/IIx maximum shortening velocity.

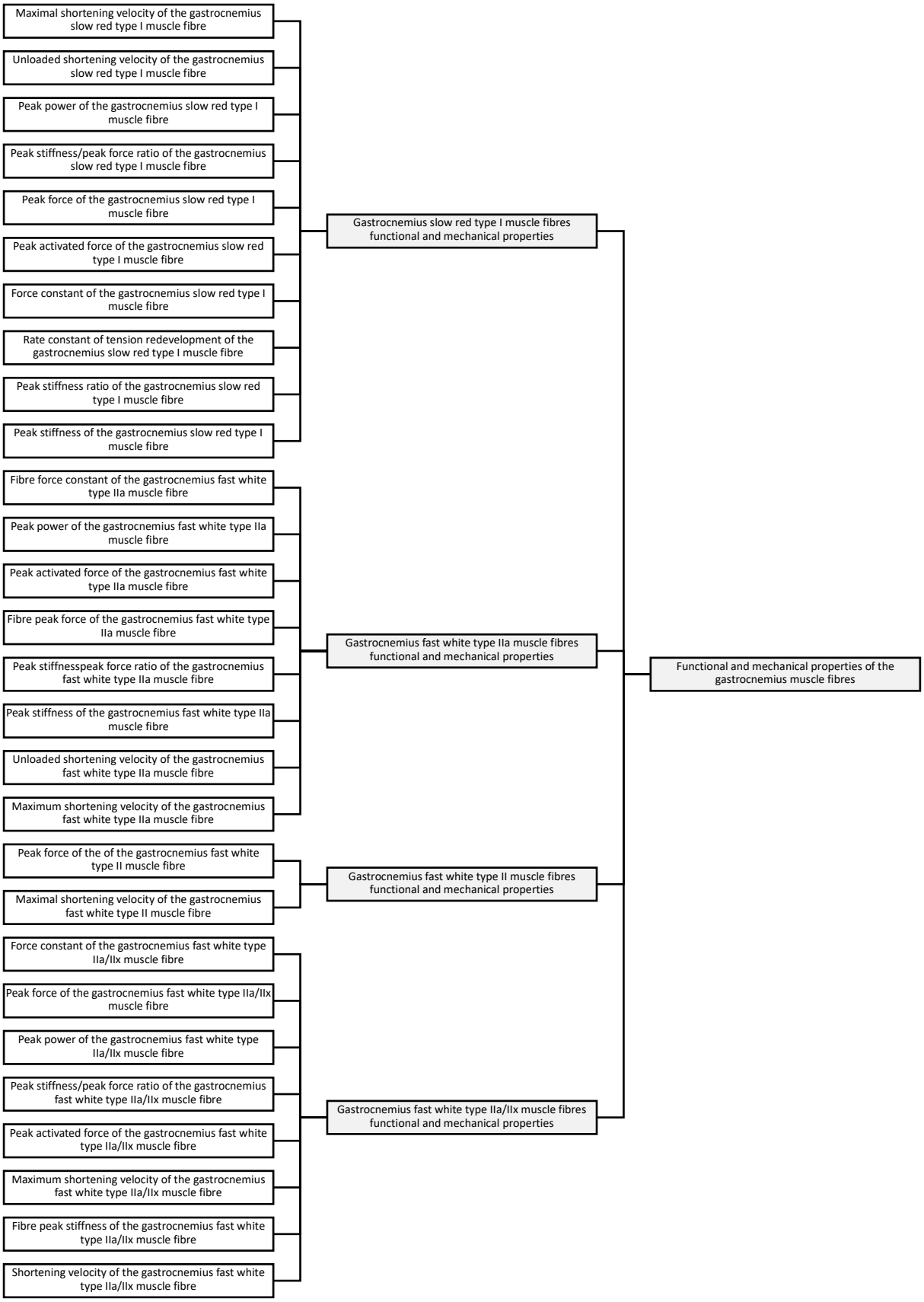

Figure 3.8 Thematic map of the functional and mechanical properties of the gastrocnemius muscle fibres. Higher order themes are shown in light grey while individual outcomes are shown in white.

3.3.3.1.1.7. Functional and Mechanical Properties of the Soleus Muscle Fibres

In relation to the functional and mechanical properties of the soleus muscle fibres, there was a very large effect size decrease in type I peak force, type I maximal shortening velocity, type I rate constant of tension redevelopment, and type I peak activated force. There was also a very large increase in type I peak stiffness ratio. In regards to soleus type II fibres, there was a very large decrease in peak force and a medium decrease in maximal shortening velocity.

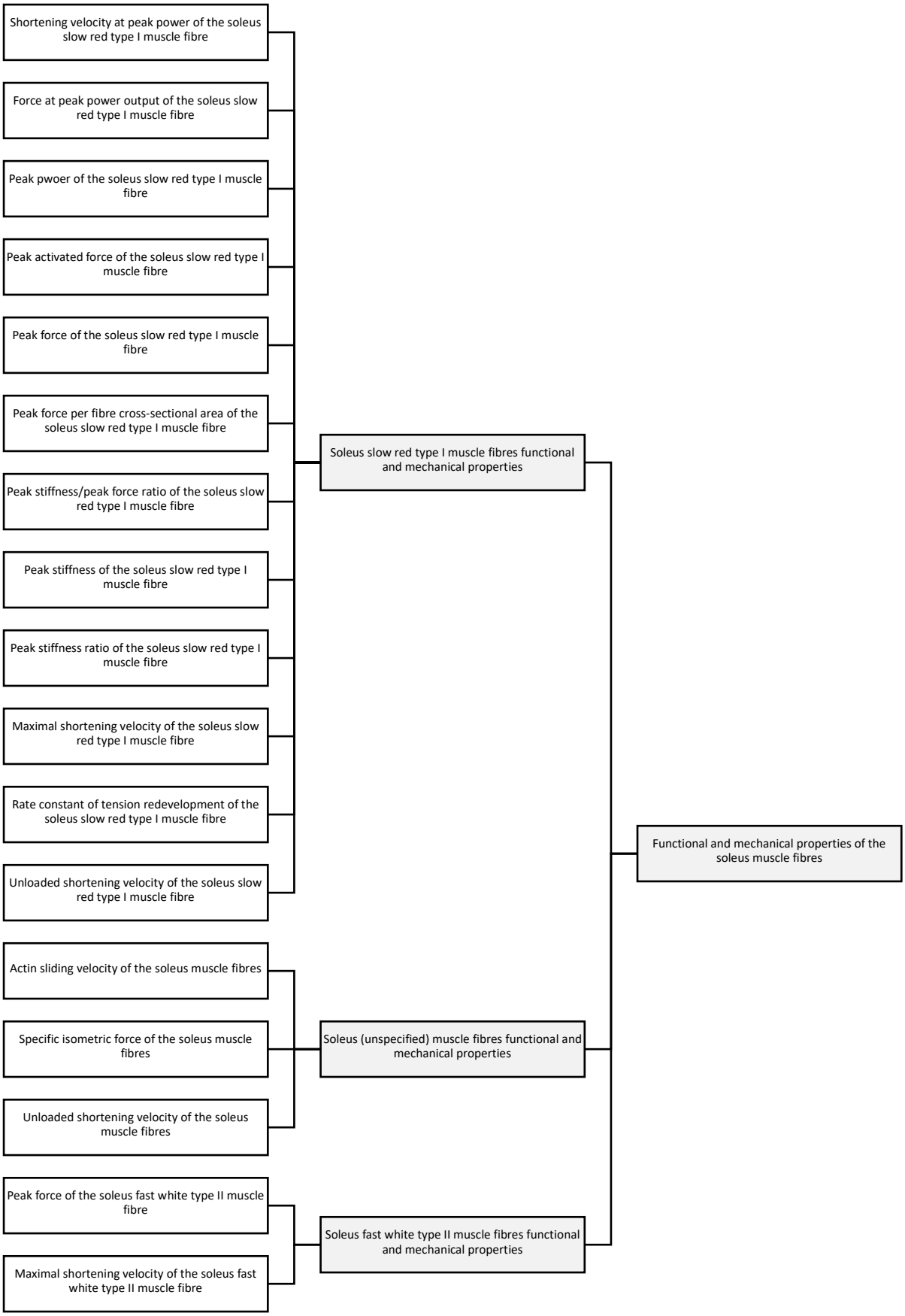

Figure 3.9 Thematic map of the functional and mechanical properties of the soleus muscle fibres. Higher order themes are shown in light grey while individual outcomes are shown in white.

3.3.3.1.1.8. Functional and Mechanical Properties of the Tibialis Anterior

All measurements of the functional and mechanical properties of the tibialis anterior were not reported in enough detail to calculate effect size changes. Mean integrated electromyographic activity significantly increased; electromyography amplitude during plantarflexion significantly decreased; and electromyography amplitude during dorsiflexion experienced no change.

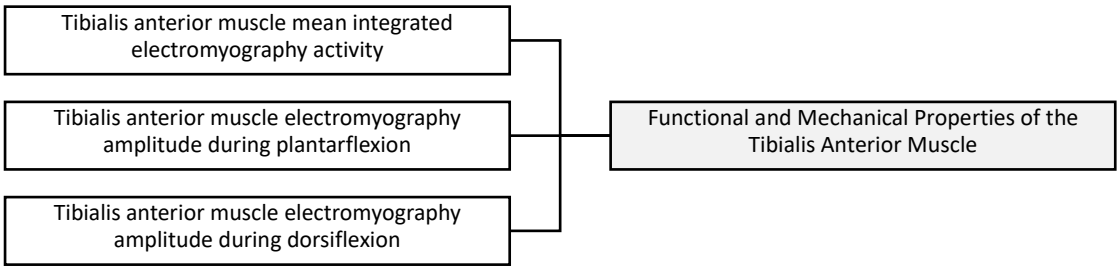

Figure 3.10 Thematic map of the functional and mechanical properties of the tibialis anterior muscle. Higher order themes are shown in light grey while individual outcomes are shown in white.

3.3.3.1.2. Muscle Architectural and Structural Properties

Outcome groups identified in this review that fall into the theme of architectural and structural properties include: muscle volume (Figure 3.11); muscle cross-sectional area (Figure 3.12); muscle attenuation (Figure 3.13); and fibre type compositions (Figure 3.14 and Figure 3.15). Summaries of effect size changes are presented below (based upon the information presented in Appendix C) for outcomes which reported enough information to generate effect sizes or reported if changes were statistically significant. Outcomes related to the architectural and structural properties of the muscles primarily decreased between pre- and post-spaceflight.

3.3.3.1.2.1. Muscle Volume

While there was not enough data reported for effect sizes to be calculated, there was a significant decrease in all measures of muscle volume between pre- and post-spaceflight, except for psoas muscle volume where one paper reported no change and another reported a significant decrease.

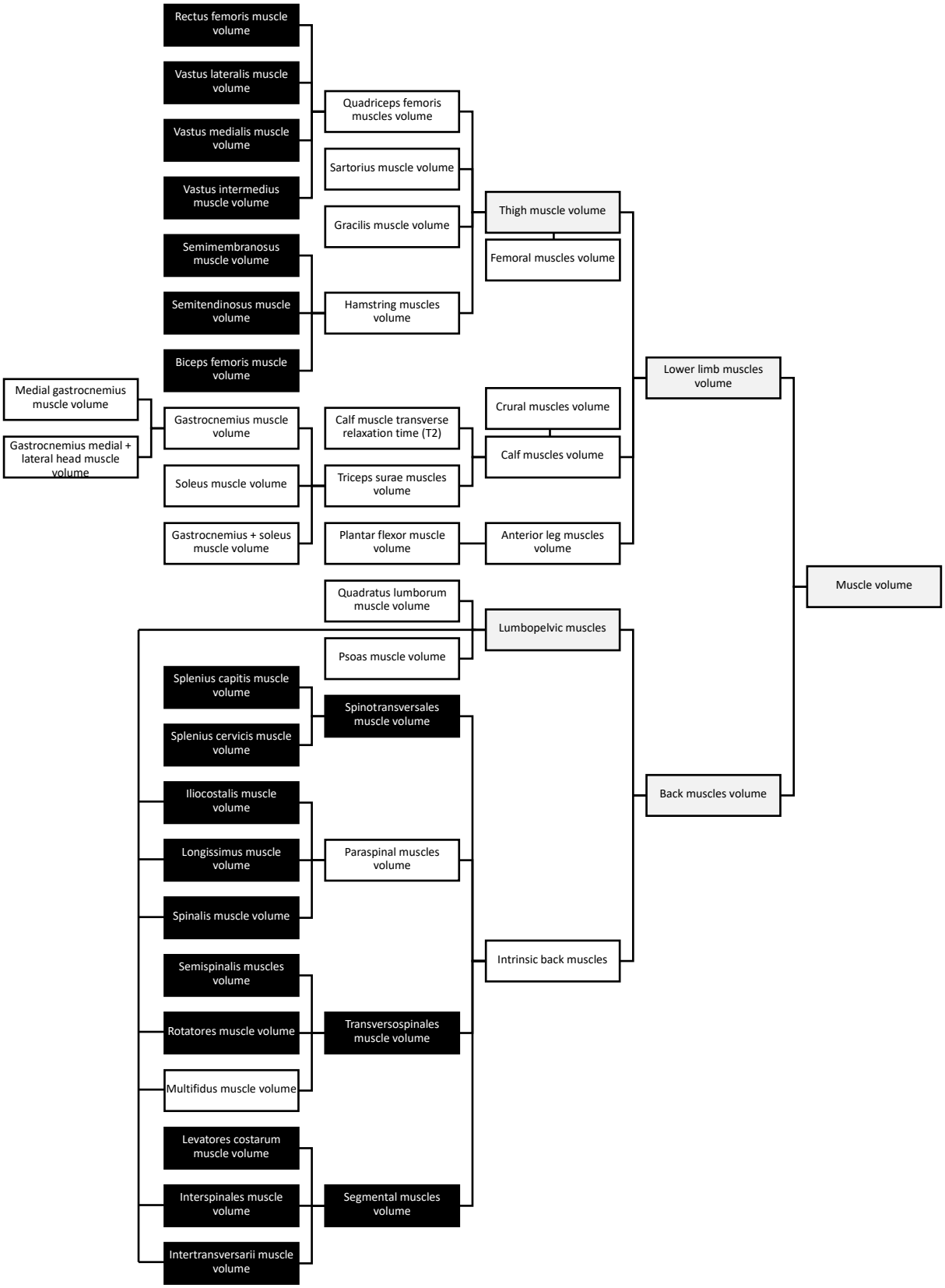

Figure 3.11 Thematic map of muscle volume outcomes. Higher order themes are shown in light grey while individual outcomes are shown in white. Black with white text is used to display outcomes that are a breakdown of the reported muscle outcomes (e.g. The individual hamstring muscles).

3.3.3.1.2.2. Muscle Cross-Sectional Area

Where data were reported, muscle cross-sectional area (CSA) decreased across all measures between pre- and post-spaceflight. A large effect size decrease was reported for the gluteal muscles CSA and a medium effect size decrease was reported for the quadriceps muscles CSA. Small effect size decreases were reported for psoas, quadratus lumborum, and the multifidus. Lumbar paraspinal muscle and hamstring muscles CSA were reported to decrease, but this did not reach the cut off for a small effect size change.

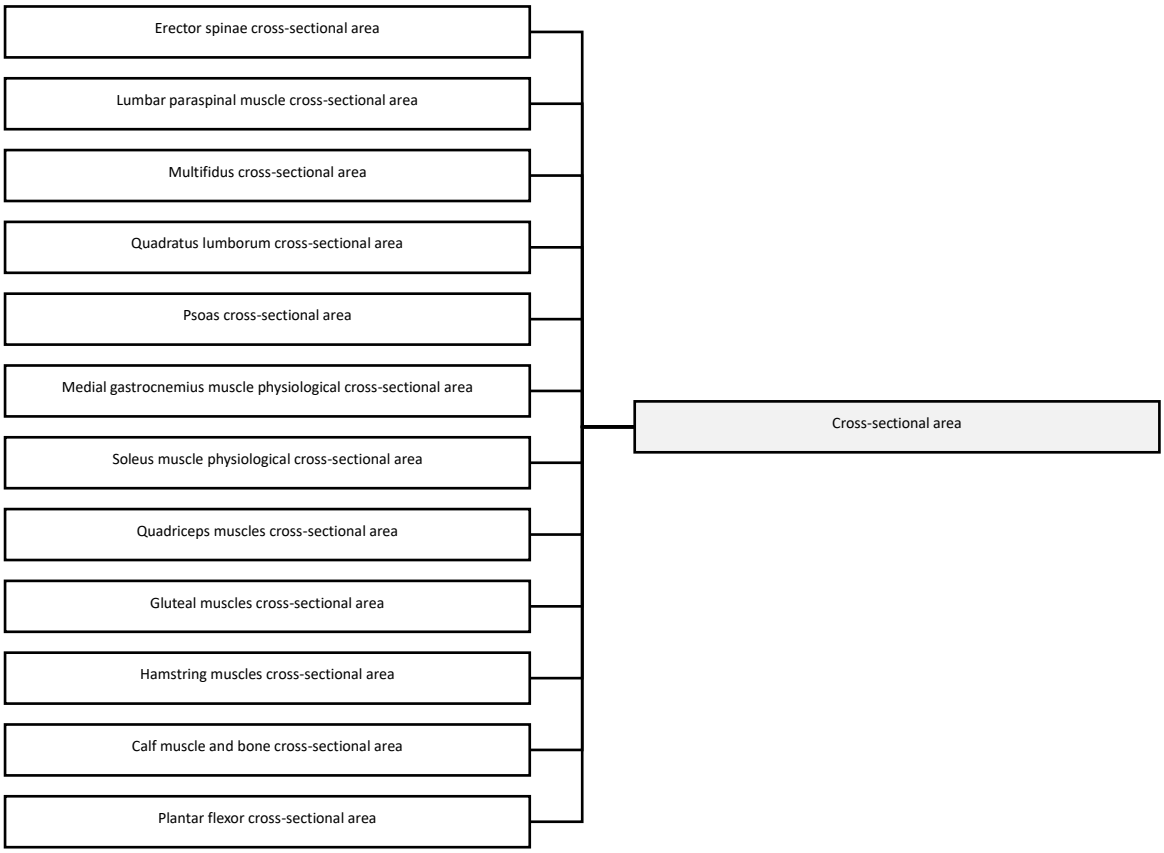

Figure 3.12 Thematic map of cross-sectional area outcomes. Higher order themes are shown in light grey while individual outcomes are shown in white.

3.3.3.1.2.3. Muscle Attenuation

All muscle attenuation outcomes were reported to experience a medium effect size decrease except for erector spinae attenuation which experienced a large effect size decrease.

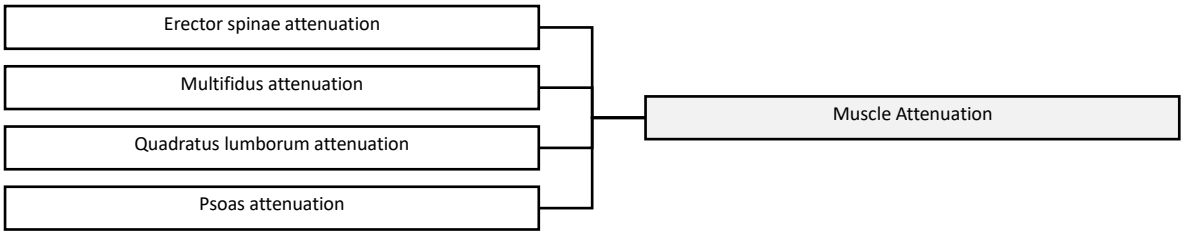

Figure 3.13 Thematic map of muscle attenuation. Higher order themes are shown in light grey while individual outcomes are shown in white.

3.3.3.1.2.4. Architectural and Structural Properties of the Gastrocnemius Muscle Fibres

There were mixed findings for outcomes related to the architectural and structural properties of the gastrocnemius muscle fibres. Of the slow red type I muscle fibres there was a large and very large effect size decrease in diameter, a large decrease in CSA, and a small decrease in thin filament density. While there was a decrease in thick filament density this did not reach the cut-off for a small effect size change. Despite these changes, there was a medium effect size increase in the percentage of short thin filaments and a very large effect size increase in the distribution of slow red type I muscle fibres.

Regarding type II muscle fibres, there were small effect size decreases in type II CSA and the percentage of type IIa/IIx fibres. Decreases were also reported for IIa/IIx thin filament density, IIa thin filament density, IIa/IIx thick filament density, IIa/IIx diameter, and type II diameter, but these outcomes did not reach the threshold for a small effect size change. A large increase was reported for IIa/IIx distribution, and very large increases were reported for I/IIa distribution, IIa distribution, IIx distribution, and hybrid distribution. Increases were also reported for IIa thick filament density, IIa/IIx percentage of short thin filaments, and IIa percentage of short thin filaments, but these outcomes did not meet the threshold for a small effect size increase. There was no change in the diameter of type IIa muscle fibres, and I/IIa/IIx distribution.

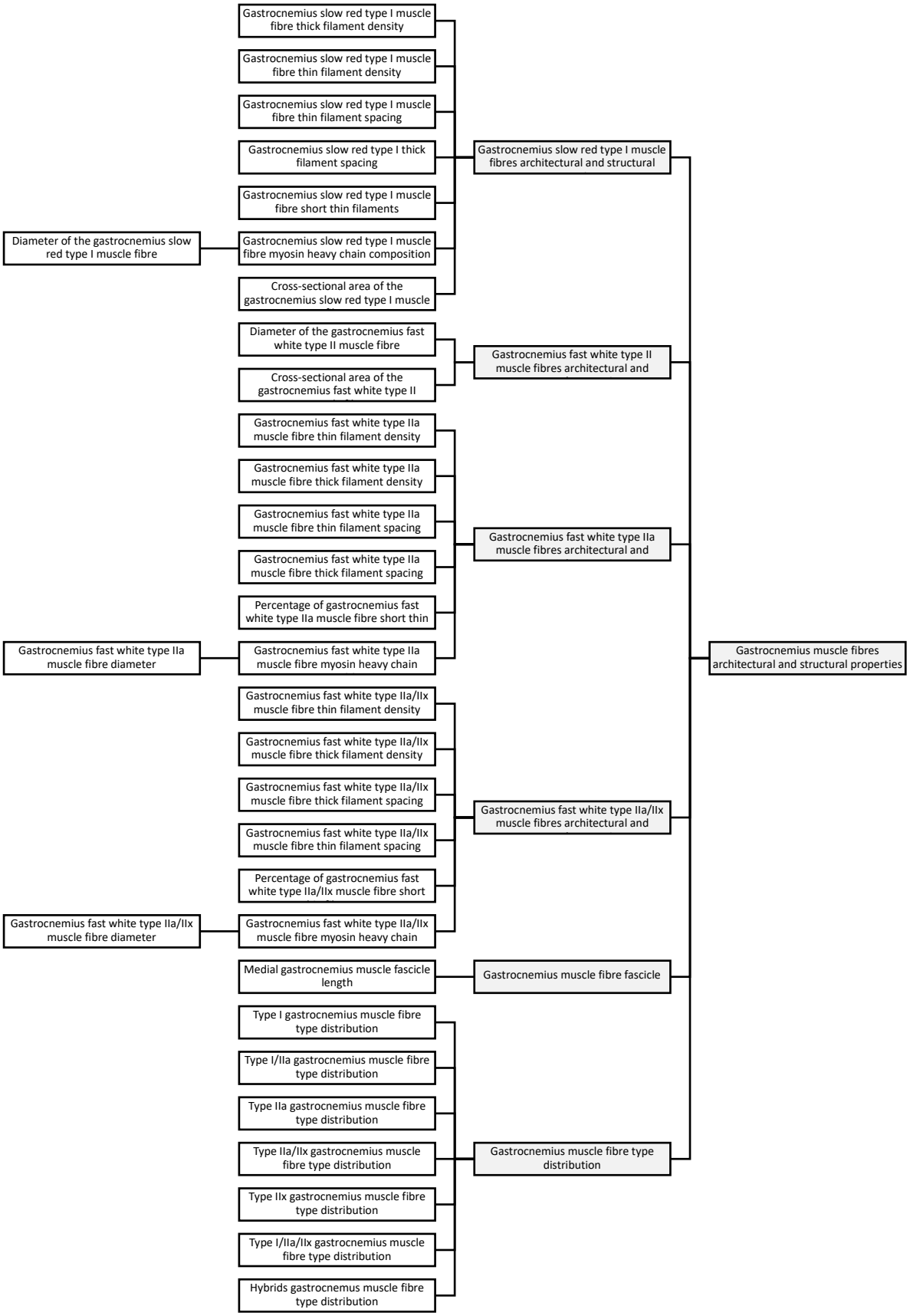

Figure 3.14 Thematic map of gastrocnemius muscle fibres architectural and structural properties. Higher order themes are shown in light grey while individual outcomes are shown in white.

3.3.3.1.2.5. Architectural and Structural Properties of the Soleus Muscle Fibres

In relation to the architectural and structural properties of the soleus muscle, for type I fibres there was a large effect size decrease in diameter, a large effect size decrease in thin filament density, and a medium effect size decrease in thick filament density. There was also a large effect size increase in the percentage of short thin filaments and a very large effect size increase in type I fibre distribution.

For the type II and hybrid muscle fibres, there was a large effect size decrease in the diameter and CSA of fibres and a medium effect size decrease in the distribution of type I/IIa fibres. There was a large increase in type IIa distribution, and a medium increase in IIa/IIx distribution. There was no change reported in the distribution of IIx fibres or I/IIa/IIx fibres.

In two papers the specific type of soleus muscle fibres was not always clearly reported. One reported that there were a large effect size decrease in thin filament density, a medium effect size decrease in thick filament density and spacing, and a significant decrease in the percentage of filaments and fibre filament loss. The other paper reported that there was a very large effect size increase in hybrid soleus muscle fibre type distribution.

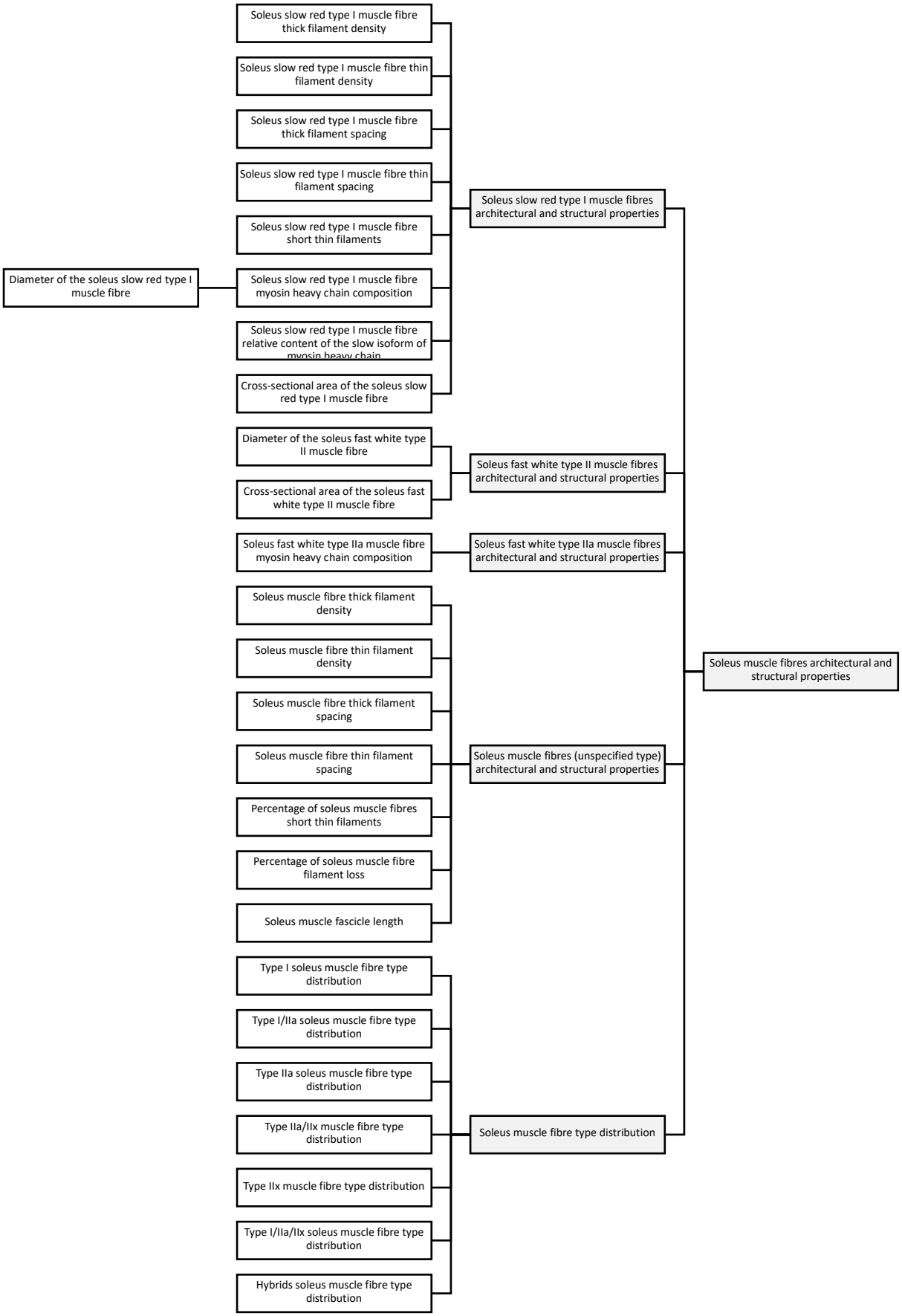

Figure 3.15 Thematic map of soleus muscle fibres architectural and structural properties. Higher order themes are shown in light grey while individual outcomes are shown in white.

3.3.3.1.3. Biomarkers of Muscular Deconditioning

Biomarkers of muscular deconditioning examined in the currently publicly available spaceflight literature include protein (Figure 3.16, 3.17 and 3.18), enzyme (Figure 3.19), plasma metabolic (Figure 3.20), and blood c-marker alterations (Figure 3.21). Data for all outcomes related to biomarkers of muscular deconditioning were not reported in enough detail to standardize changes into effect sizes or to determine if changes between pre- and post-spaceflight were statistically significant (Appendix C).

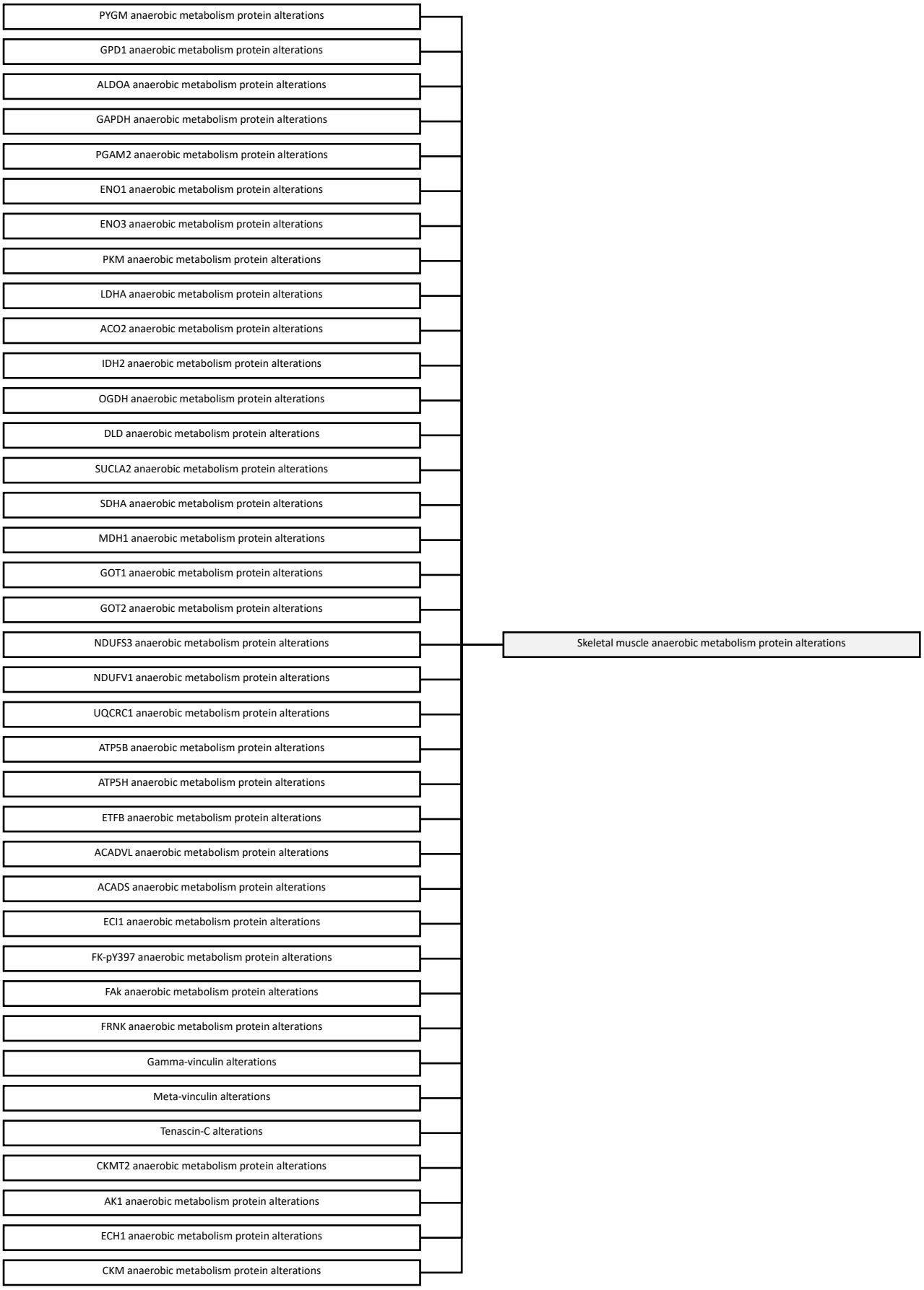

Figure 3.16 Thematic map of skeletal muscle anaerobic metabolism protein alterations. Higher order themes are shown in light grey while individual outcomes are shown in white.

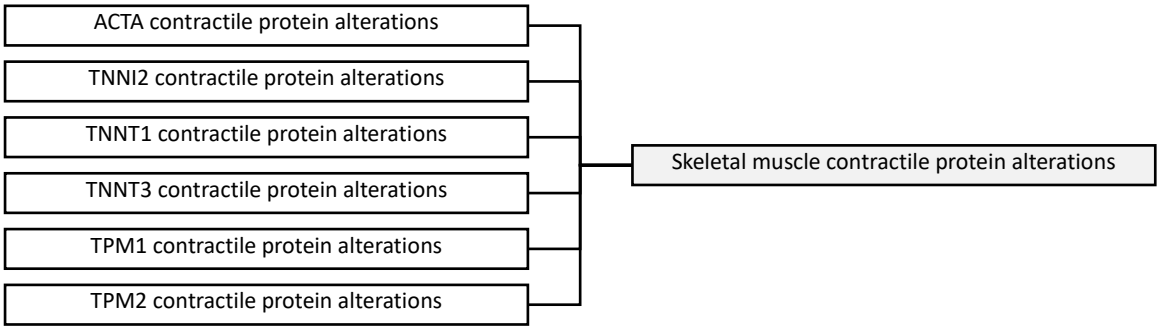

Figure 3.17 Thematic map of skeletal muscle contractile protein alterations. Higher order themes are shown in light grey while individual outcomes are shown in white.

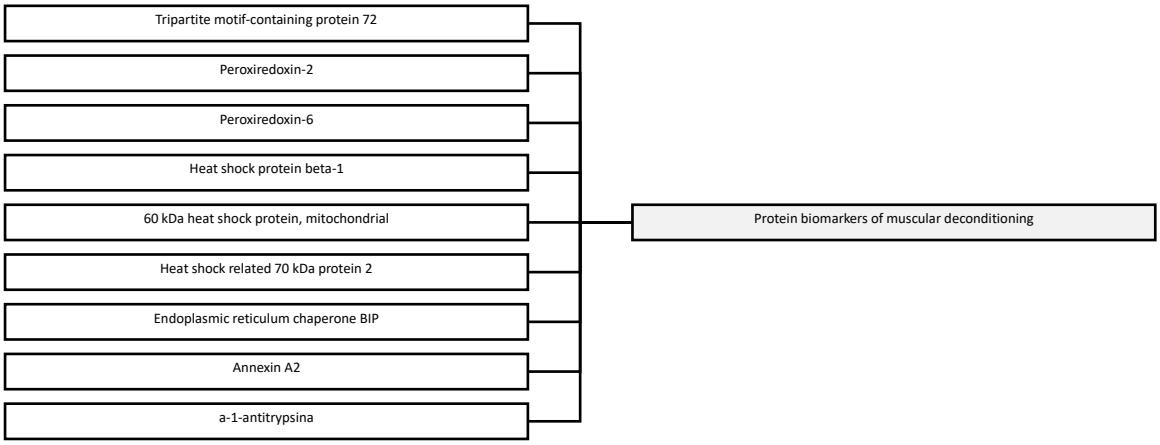

Figure 3.18 Thematic map of protein biomarkers of muscular deconditioning. Higher order themes are shown in light grey while individual outcomes are shown in white.

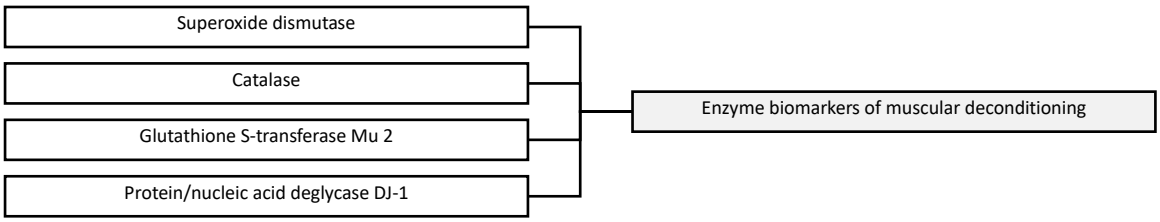

Figure 3.19 Thematic map of enzyme biomarkers of muscular deconditioning. Higher order themes are shown in light grey while individual outcomes are shown in white.

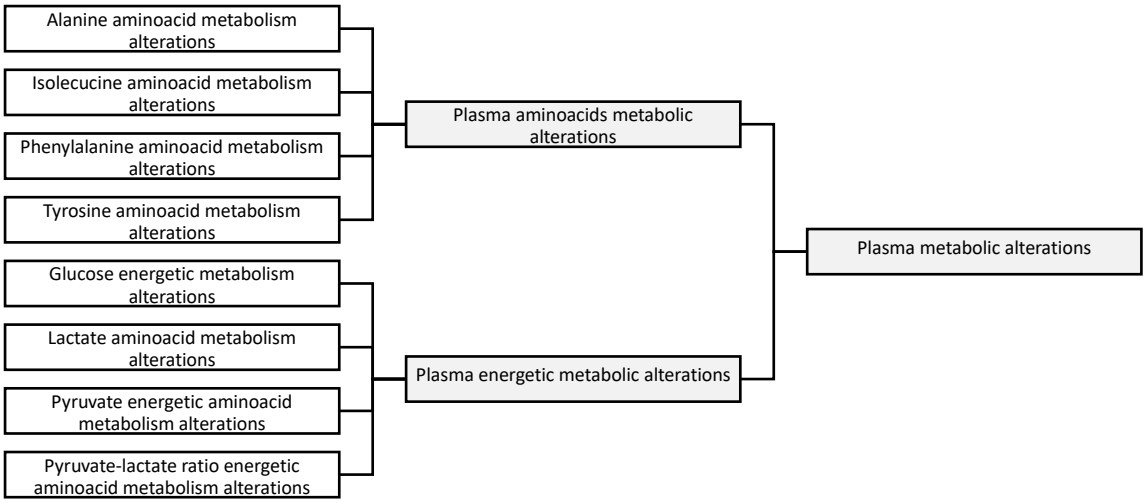

Figure 3.20 Thematic map of plasma metabolic alterations. Higher order themes are shown in light grey while individual outcomes are shown in white.

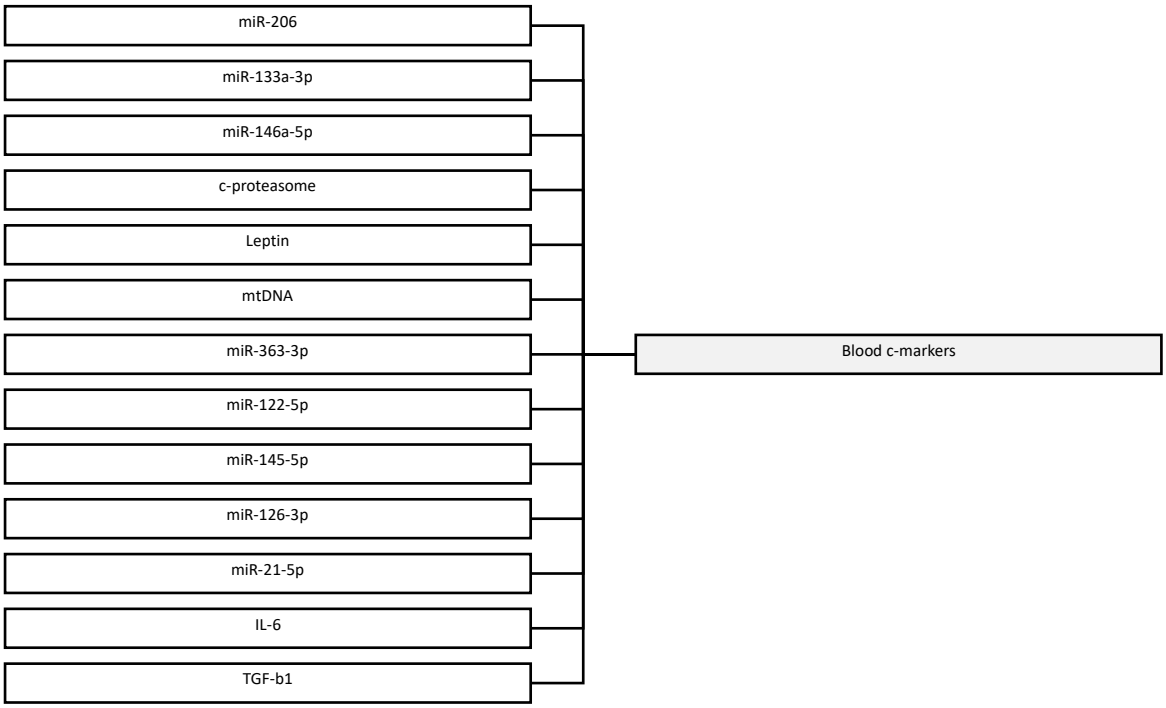

Figure 3.21 Thematic map of blood c-markers. Higher order themes are shown in light grey while individual outcomes are shown in white.

3.3.3.2. Skeletal Deconditioning

Thematic analysis of the included documents suggests that the outcomes can be categorised into five major themes: skeletal functional and mechanical properties; measures of volumetric bone mineral density; biomarkers of bone remodelling; measures of bone mineral density; and skeletal architectural and structural properties. These major themes are underpinned by 12 higher order themes: Bone Mineral Density (BMD); Bone Mineral Content (BMC); areal Bone Mineral Density (aBMD); biomarkers of bone resorption; biomarkers of bone formation; unspecified biomarkers of bone

remodelling; volumetric Bone Mineral Density (vBMD); volumetric Bone Mineral Content (vBMC); bone marrow composition; bone cross-sectional area; bone mass; and bone volume.

Within each of these, higher order themes were categorised by the individual physiological outcomes related to skeletal deconditioning. For example, calcaneus BMD would be categorised under the higher order theme BMD, which is itself categorised under the major theme measures of bone mineral density. The thematic map displaying the relationship between the major and higher order themes can be seen in Figure 3.22.

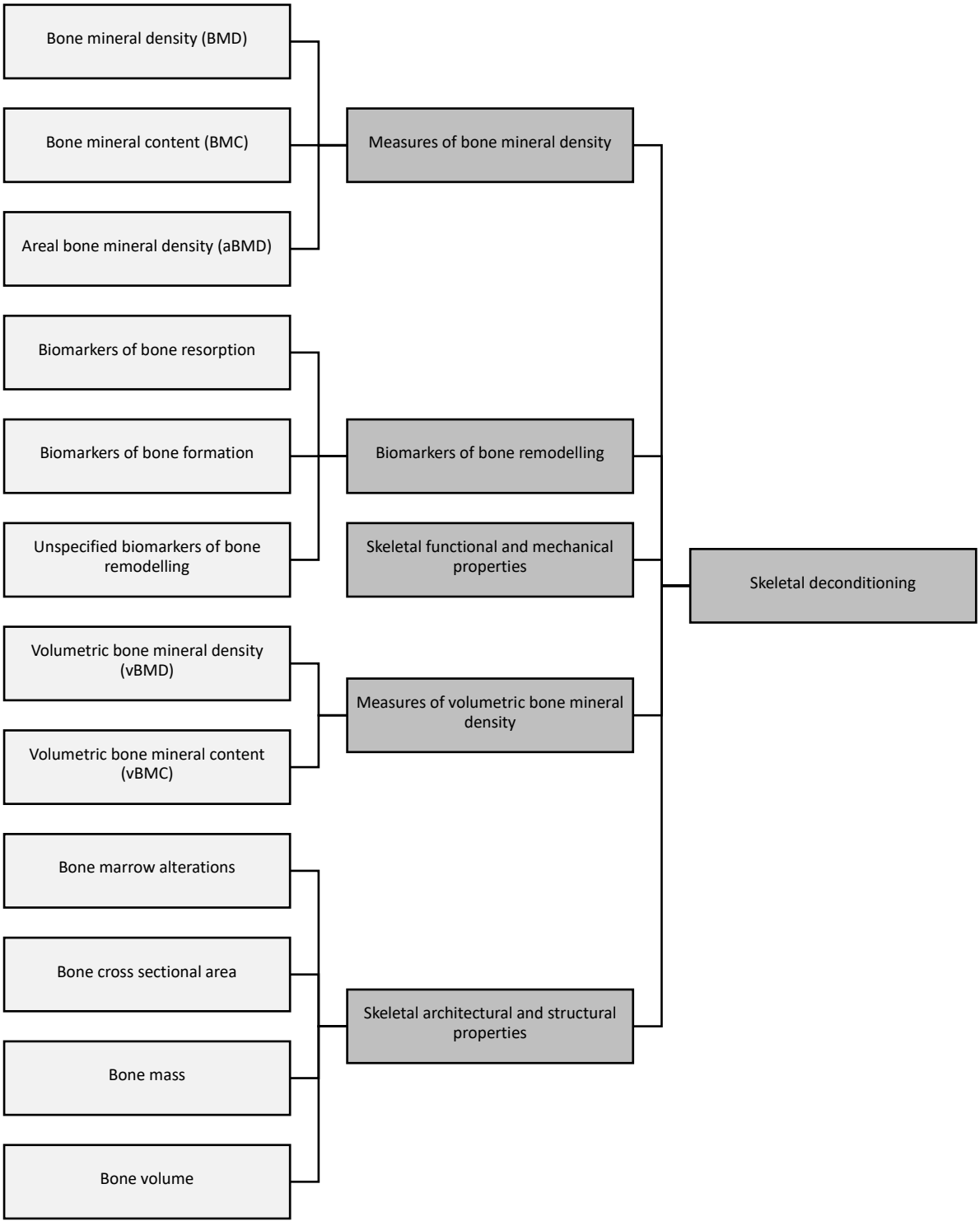

Figure 3.22 Thematic Map of the major and higher order themes of skeletal deconditioning. Major themes are shown in dark grey while higher order themes are shown in light grey. The thematic maps presented throughout the results branch off from this thematic map, exploring the individual outcomes reported within each of these themes. As such, the thematic maps can be used to trace the relationship of each individual outcome.

The major themes were ranked from 1-5 based upon the medical risk each theme presents to astronaut health and mission success (evidence-based justifications for these rankings are provided in Table 3.6). The order of medical rankings in descending order of importance were outcomes related to skeletal functional and mechanical properties; measures of volumetric bone mineral density; biomarkers of bone remodelling; measures of bone mineral density; and skeletal architectural and structural properties.

Table 3.6 Ranking of major themes, based on impact on mission success and the number of times individual outcomes within each theme were reported

Major theme	Higher order themes	Major theme medical ranking	Number of times outcomes in this major theme were reported (ranking)	Justification for medical ranking
Functional and mechanical properties	N/A	1	3 (5)	These outcomes, based on Quantitative Computed Tomography (QCT) and finite element modelling, are very accurate to translate the changes in bone density and geometry to changes in bone strength (Keyak et al., 2009). It is ultimately changes in the functional and mechanical properties, such as bone strength, that present an operational and health risk to astronauts (Keyak et al., 2009) and as such this theme was ranked the most medically relevant to astronaut health and operational mission success.
Measures of volumetric bone mineral density	Volumetric Bone Mineral Density (vBMC) Volumetric Bone Mineral Content (vBMC)	2	32 (3)	Volumetric Bone Mineral Density (vBMD) outcomes is measured using Quantitative Computed Tomography (QCT). Unlike Bone Mineral Density (BMD), vBMD is not a two-dimensional measure (Eapen, Grey, Don-Wauchope, & Atkinson, 2008) and as such can provide an advantage in terms of precision and accuracy over BMD measurements (Bauer et al., 2007). As vBMD provides greater precision in measurement, measures of vBMD are ranked separately and higher in terms of this reviews medical ranking to measures of BMD.
Biomarkers of bone remodelling	Biomarkers of bone resorption Biomarkers of bone formation Unspecified biomarkers of bone remodelling	3	95 (1)	Biomarkers of bone remodelling are indirect measures of skeletal deconditioning which can detect the early stages of bone remodelling (the activity of osteoblasts and osteoclasts) (Eapen et al., 2008). Findings have been inconsistent on if biomarker alterations alone indicate risk of fracture (Dai, Wang, Ang, Yuan, & Koh, 2016), however biomarkers are useful as an independent factor for bone fracture risk assessment (Garnero, 2008; Garnero et al., 1996) and are very sensitive to early detection of undesirable adaptations during microgravity exposure (Eapen et al., 2008).
Measures of bone mineral density	Bone Mineral Density (BMD) Bone Mineral Content (BMC) Areal Bone Mineral Density (aBMD)	4	66 (2)	Dual Energy X-ray Absorptiometry (DEXA) is the gold standard measure used to study the density and strength of bones in terrestrial populations (McCarthy et al., 2000) as it is extensively validated for predicting bone fracture (Koval, Easterling, Pettus, & Mackler, 2005). However, DEXA is not able to accurately detect the early stage of osteopenia (Koval et al., 2005) and BMD is also not the only factor in determining bone strength (and therefore fracture risk) (Black et al., 2008). As such, measures of BMD are ranked lower than the more accurate measures of vBMD (Bauer et al., 2007) and lower than biomarkers which can detect early signs of bone remodelling (Eapen et al., 2008).
Architectural and structural properties	Bone marrow Bone cross-sectional area Bone mass Bone volume	5	25 (4)	Reductions in Bone Mineral Density (BMD) lead to deteriorations of the microarchitecture of bones, as determined by the intensity of bone remodelling (Negredo et al., 2012). Architectural changes can be examined using ultrasound (Collet et al., 1997; McCarthy et al., 2000). The advantage of using ultrasound devices is that it can be brought during a space mission (Sung et al., 2013), as opposed to Dual Energy X-ray Absorptiometry (DEXA) which is too large and heavy to use during spaceflight (McCarthy et al., 2000). However, ultrasound can determine only the superficial cortical bone of a limited area such as the heel and tibia (Syed & Khan, 2002). This is because ultrasound is only able to penetrate fluids and soft tissues, not bones (Law & Macbeth, 2011). Architectural changes are also not widely examined because they are a consequence of other, more well-researched factors such as bone remodelling and BMD alterations (Negredo et al., 2012). As such, the architectural and structural properties were considered the least relevant medically to astronaut health as they are a consequence, not a cause of, of BMD deteriorations.

The column “medical ranking” was rank scored from 1-5, with one being most impactful on astronaut health and mission success and three being least impactful, as determined by two medical doctors with a space medicine research background and supported by data extracted during thematic analysis. The column “number of times outcomes in this group were reported” was rank scored from 1-5, with one being most reported and three being least reported during studies included in this systematic review..

Medical rankings were not reflected directly in the number of times the outcomes were reported. For example, functional and mechanical properties were ranked the highest of all outcomes for its impact on astronaut health and mission success, but it was the least reported set of outcomes. Similar patterns were seen across the remaining rankings. Outcomes related to functional and mechanical properties were reported 3 times, measures of volumetric bone mineral density were reported 32 times, those related to biomarkers of bone remodelling were reported 95 times, measures of bone mineral density were reported 66 times, and those related to architectural and structural properties were reported 25 times.

3.3.3.2.1. Measures of Bone Mineral Density

Outcome groups identified in this review that fall under the category of measures of bone mineral density include: Bone Mineral Density (BMD); Bone Mineral Content (BMC); and areal Bone Mineral Density (aBMD) (Figure 3.23). Summaries of effect size changes are presented below (based upon the information presented in Appendix C) for outcomes which reported enough information to generate effect sizes or reported if changes were statistically significant. All reported results are pre- to post-spaceflight changes. Outcomes related to measures of BMD decreased across almost all outcomes between pre-and post-spaceflight. Where enough data to calculate effect size changes were reported, there were medium effect size decreases in: the BMD of the femoral neck; the integral, cortical and trabecular BMC of the femoral neck and trochanter; and overall proximal femur integral, cortical and trabecular BMC. There were also small effect size decreases in the non-dominant tibia cancellous BMD and lumbar spine BMC. A small effect size decrease was also reported for whole body BMC, however another study reported changes in the same outcome that did not meet the threshold for a small effect size change. A number of outcomes were reported to decrease but did not meet the threshold for a small effect size change, including: calcaneal aBMD; non-dominant radius cancellous BMD; non-dominant tibia cortical BMD; lumbar spine BMD; pelvis BMD; left and right hip BMD; left and right hip trochanter BMD; total left and right hip BMD; and pelvis BMC. While the outcomes trochanter BMD and total hip BMD were not reported in any paper with sufficient data to calculate effect sizes, a significant decrease between pre- and post-spaceflight was found. Mixed results were also reported for the calcaneus BMD. While two studies reported a significant decrease between pre-and post-spaceflight, another study reported no statistically significant change. None of the papers included enough information to calculate effect size changes for calcaneus BMD. The exception to the trend for these outcomes to decrease include: lumbar BMD; distal tibia BMD; proximal femur BMD; ribs BMD; and arms BMD, all of which showed no statistically significant difference between pre- and post-flight scores. Non-dominant radius cortical BMD and whole-body BMD increased, however these changes did not meet the threshold for a small effect size increase. In the case of whole-body BMD, an additional study also reported no statistically significant change

between pre- and post-spaceflight. Skull BMD was also reported to increase significantly between pre- and post-spaceflight however another study found no statistically significant difference in the same outcome.

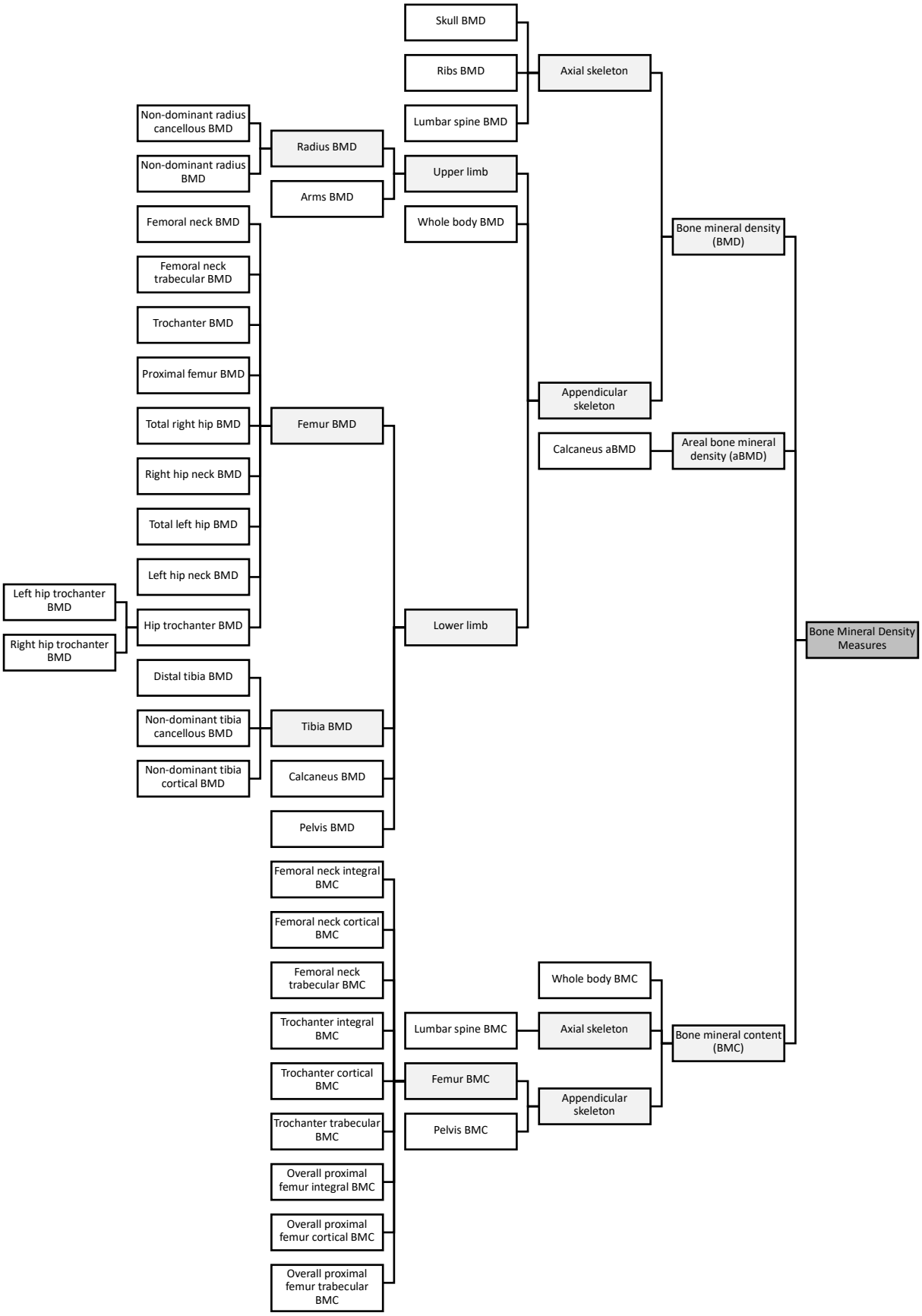

Figure 3.23 Thematic map of measures of bone mineral density outcomes. Major themes are shown in dark grey, while higher order themes are shown in light grey and individual outcomes are shown in white.

3.3.3.2.2. Biomarkers of Bone Remodelling

Outcome groups related to bone remodelling identified in this review include: biomarkers of bone resorption (Figure 3.24); unspecified biomarkers of bone remodelling (Figure 3.25); and biomarkers of bone formation (Figure 3.26).

3.3.3.2.2.1. Biomarkers of Bone Resorption

Most biomarkers related to bone resorption increased between pre-and post-spaceflight. There was a very large effect size increase in pyridinium crosslinks, deoxypyridinoline and N-telopeptide of type 1 collagen, however another study also reported a large effect size increase for N-telopeptide of type 1 collagen. There was a large effect size increase for C-telopeptide and there were medium effect size increases in bone calcium resorption, fecal excretion of calcium and pyridinoline. There was also a small effect size increase in serum ferritin and endogenous excretion of calcium, and a significant increase in fractional excretion of calcium. Four biomarkers of bone resorption also showed decreases. There was a very large effect size decrease in iron, a large effect size decrease in transferrin receptors, and a medium effect size decrease in urinary calcium and transferrin.

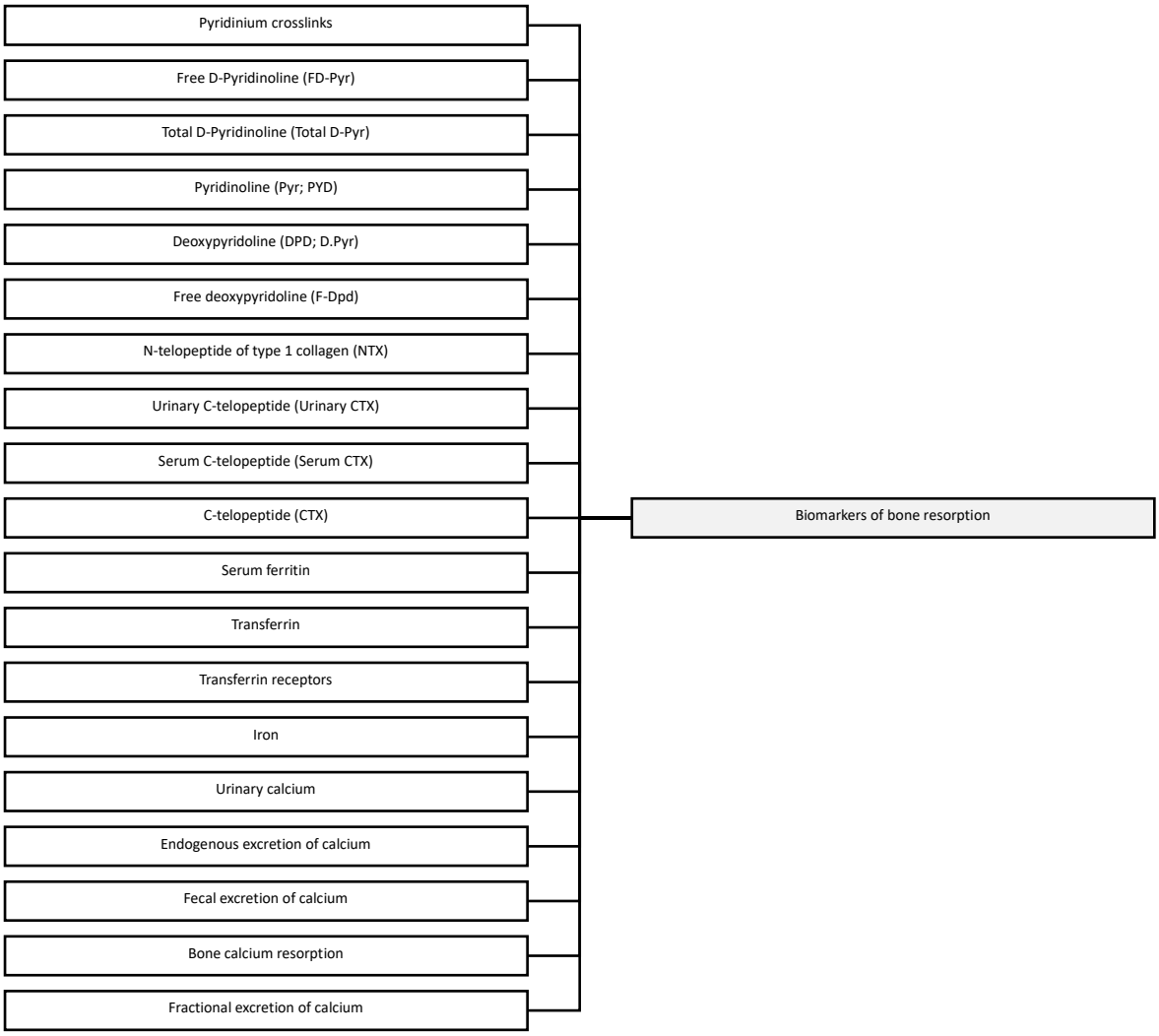

Figure 3.24 Thematic map of the biomarkers of bone resorption. Higher order themes are shown in light grey and individual outcomes are shown in white.

3.3.3.2.2.2. Unspecified Biomarkers of Bone Remodelling

For unspecified biomarkers of bone remodelling, there were very large effect size decreases between pre- and post-spaceflight in fractional calcium absorption, calcium and phosphorus, and a large effect size decrease in haemoglobin. In the case of calcium, one study also reported a small effect size increase. There was a medium effect size decrease in whole-blood haematocrit and ionized calcium, although one study also reported a small effect size decrease for ionized calcium. Small effect size decreases were reported for heme and calcitonin. While calcium absorption and bone calcium balance showed decreases, these did not meet the threshold for a small effect size decrease. A large effect size increase was found for helical peptide and creatinine, although one study reported only a small effect size increase for creatinine. A small effect size increase was found for calcium intake, and there was no change reported in serum calcium.

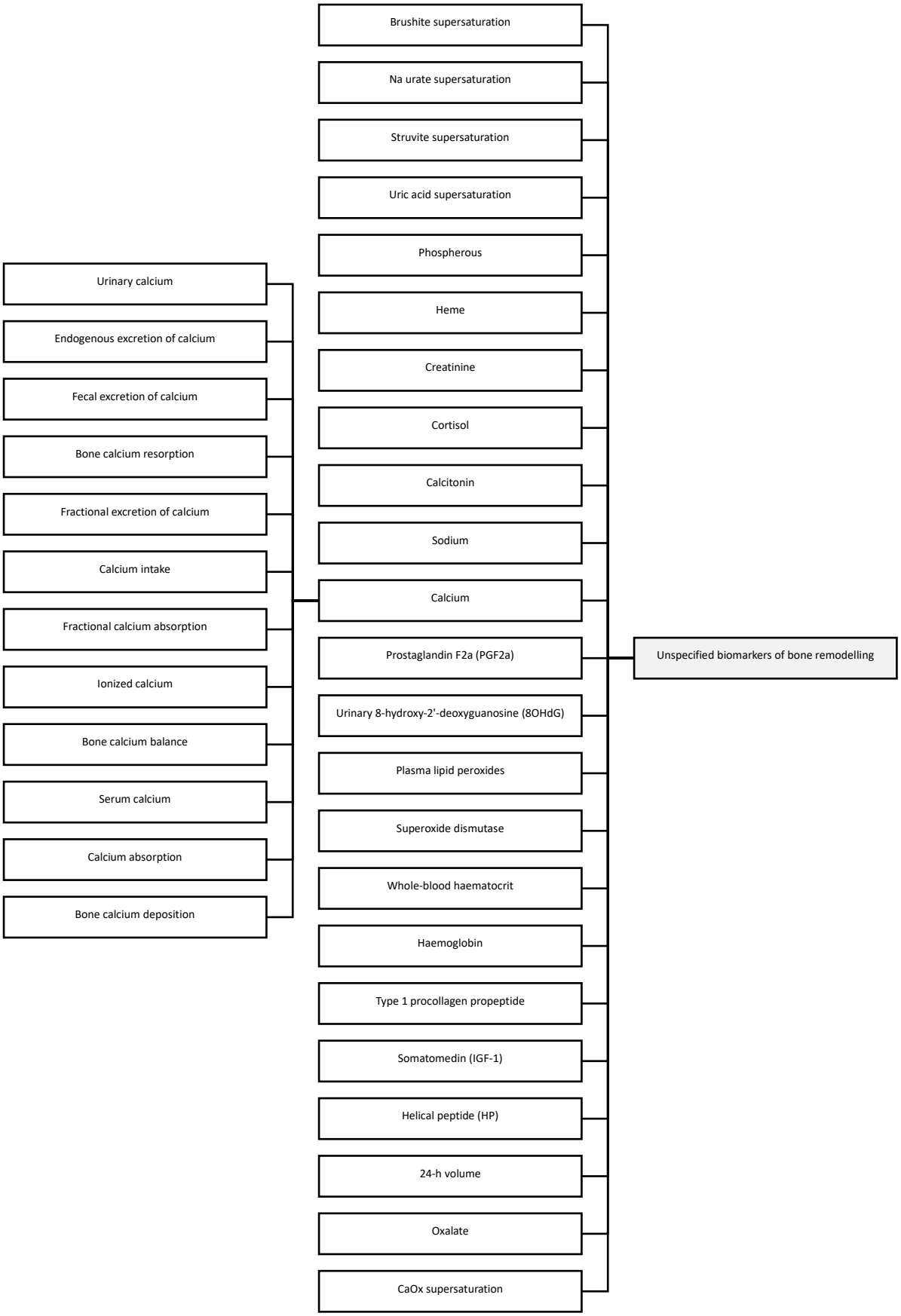

Figure 3.25 Thematic map of the unspecified biomarkers of bone resorption. Higher order themes are shown in light grey and individual outcomes are shown in white.

3.3.3.2.2.3. Biomarkers of Bone Formation

For biomarkers of bone formation, there were medium effect size increases in alkaline phosphatase, bone calcium deposition, and bone alkaline phosphatase between pre- and post-spaceflight. One paper also reported that bone alkaline phosphatase significantly decreased, rather than increased, between pre-and post-spaceflight. There were also small effect size increases in bone specific alkaline phosphatase and parathyroid mid-molecule. There was also an increase in parathyroid intact molecule and 1,25-dihydroxyvitamin D, however these did not reach the threshold for a small effect size increase. In the case of 1,25-dihydroxyvitamin D another study also reported a small effect size decrease. Except for parathyroid hormone and osteocalcin, where there was no statistically significant difference between pre- and post-flight scores and no effect size change, respectively. All the remaining outcomes showed decreases. There was a small decrease in pH and 25-hydroxyvitamin D, although in the case of 25-hydroxyvitamin D another paper also reported a medium effect size decrease. There was a significant decrease in Carboxyl-terminal propeptide of human type 1 procollagen.

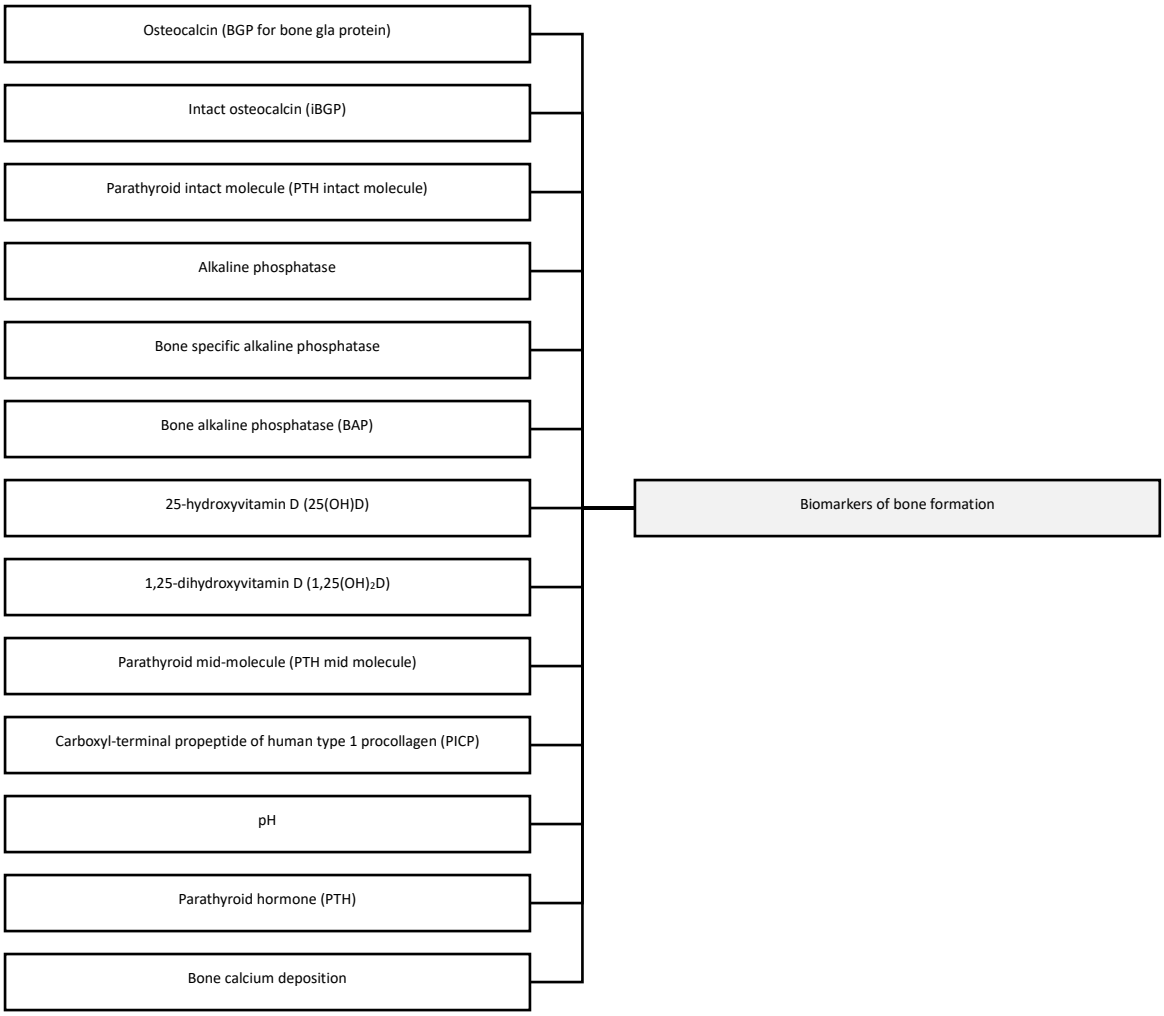

Figure 3.26 Thematic map of the biomarkers of bone formation. Higher order themes are shown in light grey and individual outcomes are shown in white.

3.3.3.2.3. Skeletal Functional and Mechanical Properties

Outcomes related to the functional and mechanical properties of skeletal deconditioning are shown in Figure 3.27. Of the three outcomes related to skeletal functional and mechanical properties, only two reported enough information to calculate effect size changes. There was a medium effect size decrease in the femoral neck compressive strength index and a small effect size decrease in the femoral neck bending/torsional strength index.

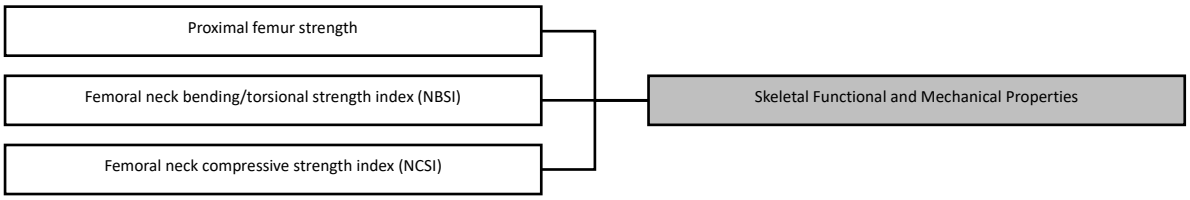

Figure 3.27 Thematic map of skeletal functional and mechanical properties. Major themes are shown in dark grey and individual outcomes are shown in white

3.3.3.2.4. Measures of Volumetric Bone Mineral Density

Outcome groups identified in this review that fall under the measures of volumetric bone mineral density include: volumetric Bone Mineral Density (vBMD) and volumetric Bone Mineral Content (vBMC) (Figure 3.28). All measures of vBMD identified in this review were reported to decrease between pre- and post-spaceflight. There was a large effect size decrease in femoral neck trabecular vBMD, however two studies also reported a medium effect size decrease in this outcome. There were medium effect size decreases in: total hip integral and trabecular vBMD; femur and overall proximal femur trabecular vBMD; overall proximal femur integral vBMD; trochanter integral vBMD; total hip trabecular and integral vBMC; femoral neck cortical and integral vBMC; and trochanter cortical and integral vBMC. There were also medium effect size decreases in femoral neck integral and cortical vBMD and trochanter cortical and trabecular vBMD, however other studies also reported small effect size decreases in these outcomes, with two studies reporting a small effect size decrease for femoral neck cortical vBMD. Small effect size decreases were reported for: overall proximal femur cortical vBMD; femur cortical vBMD; total hip cortical vBMD and vBMC; femoral neck trabecular vBMC; and trochanter trabecular vBMC.

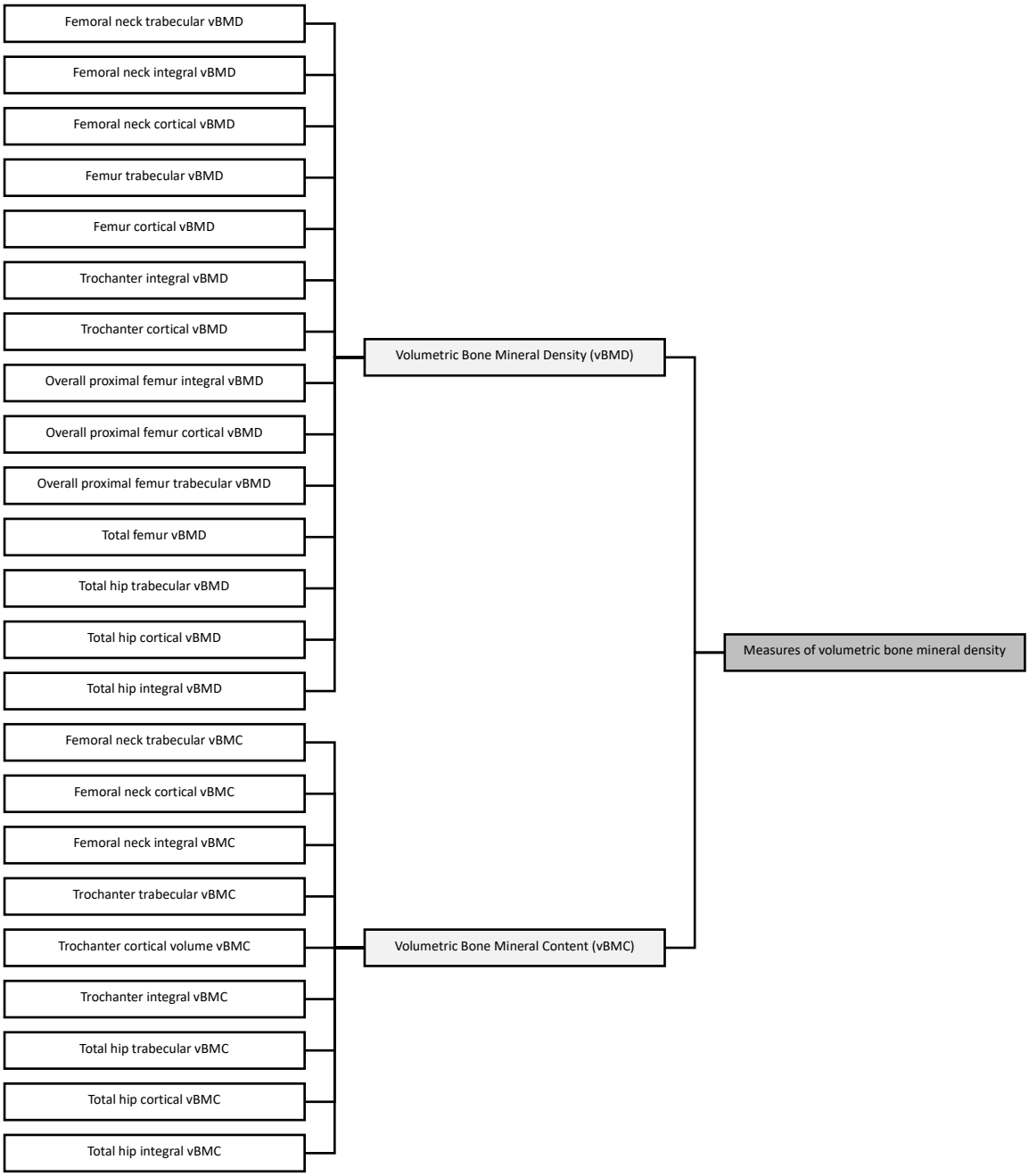

Figure 3.28 Thematic map of the measures of volumetric bone mineral density outcomes. Major themes are shown in dark grey, while higher order themes are shown in light grey and individual outcomes are shown in white.

3.3.3.2.5. Skeletal Architectural and Structural Properties

Outcomes identified in this review that are related to the architectural and structural properties are shown in Figure 3.29. All measures of the architectural and structural properties of skeletal deconditioning identified during this review were reported to decrease between pre-and post - spaceflight, except for five outcomes. There was no statistically significant difference in L3 bone marrow functional cellular fraction and no effect size change in the cross-sectional area of the femoral neck. There was an increase in the femoral neck cross-section of minimal area and cross-sectional area of the mid-trochanter, however neither outcome reached the threshold for a small effect size

change. There was also a statistically significant increase in the transverse relaxation time of L3 bone marrow functional cellular fraction. Of the remaining outcomes, there were medium effect size decreases in: the intervertebral disc height; total femoral neck and cortical neck mass; total femur and total femur cortical mass; femoral neck cortical volume; total femur cortical volume; and overall proximal femur cortical volume. There were also small effect size decreases in femoral neck integral volume and trochanter cortical volume. There were also five outcomes that reported a decrease but did not reach the threshold for a small effect size change. These included: total femoral neck volume; total femur volume; trochanter integral volume; overall proximal femur integral volume; and cross-sectional area of the mid-vertebrae.

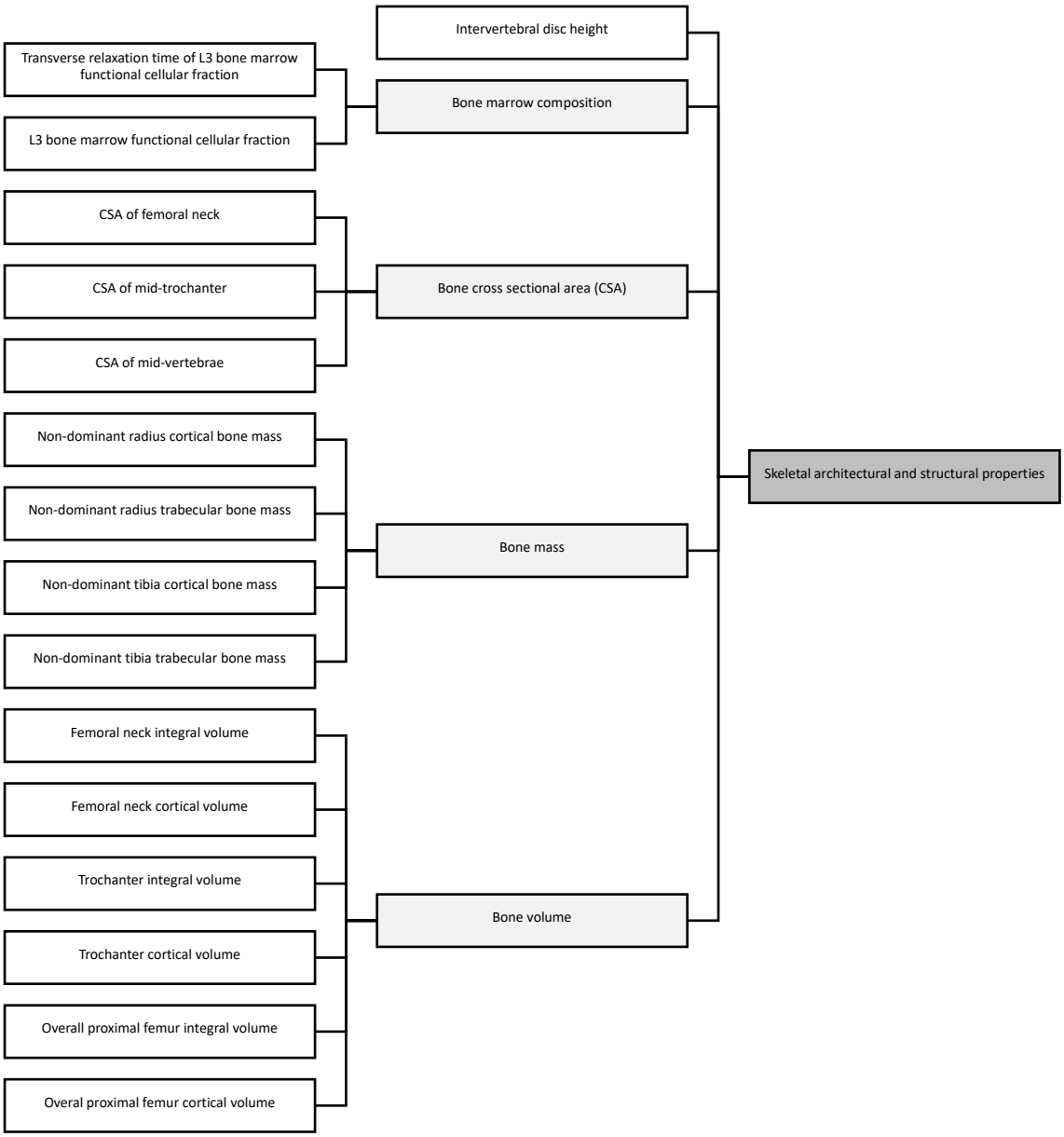

Figure 3.29 Thematic map of skeletal architectural and structural properties outcomes. Major themes are shown in dark grey, while higher order themes are shown in light grey and individual outcomes are shown in white.

3.3.3.3. Cardiovascular deconditioning

Thematic analysis of the included documents indicated that the outcomes can be categorised into four major themes: hemodynamics and vascular function, cardiac muscle deconditioning, biomarkers of cardiovascular deconditioning, and pulmonary ventilation and gas exchange. These major themes are underpinned by 10 higher order themes: cardiac architectural and structural properties; cardiac functional and mechanical properties; pulmonary architectural and structural properties; pulmonary functional and mechanical properties; chest wall mechanics; pulmonary perfusion ratio; spirometry; pulmonary dead space; and pulmonary vital capacity.

Within each of these higher order themes were categorised the individual physiological outcomes related to cardiovascular deconditioning. For example, heart rate would be categorised under the higher order theme cardiac functional and mechanical properties which is itself categorised under the major theme of cardiac deconditioning. The thematic map displaying the relationship between the major and higher order themes can be seen in Figure 3.30.

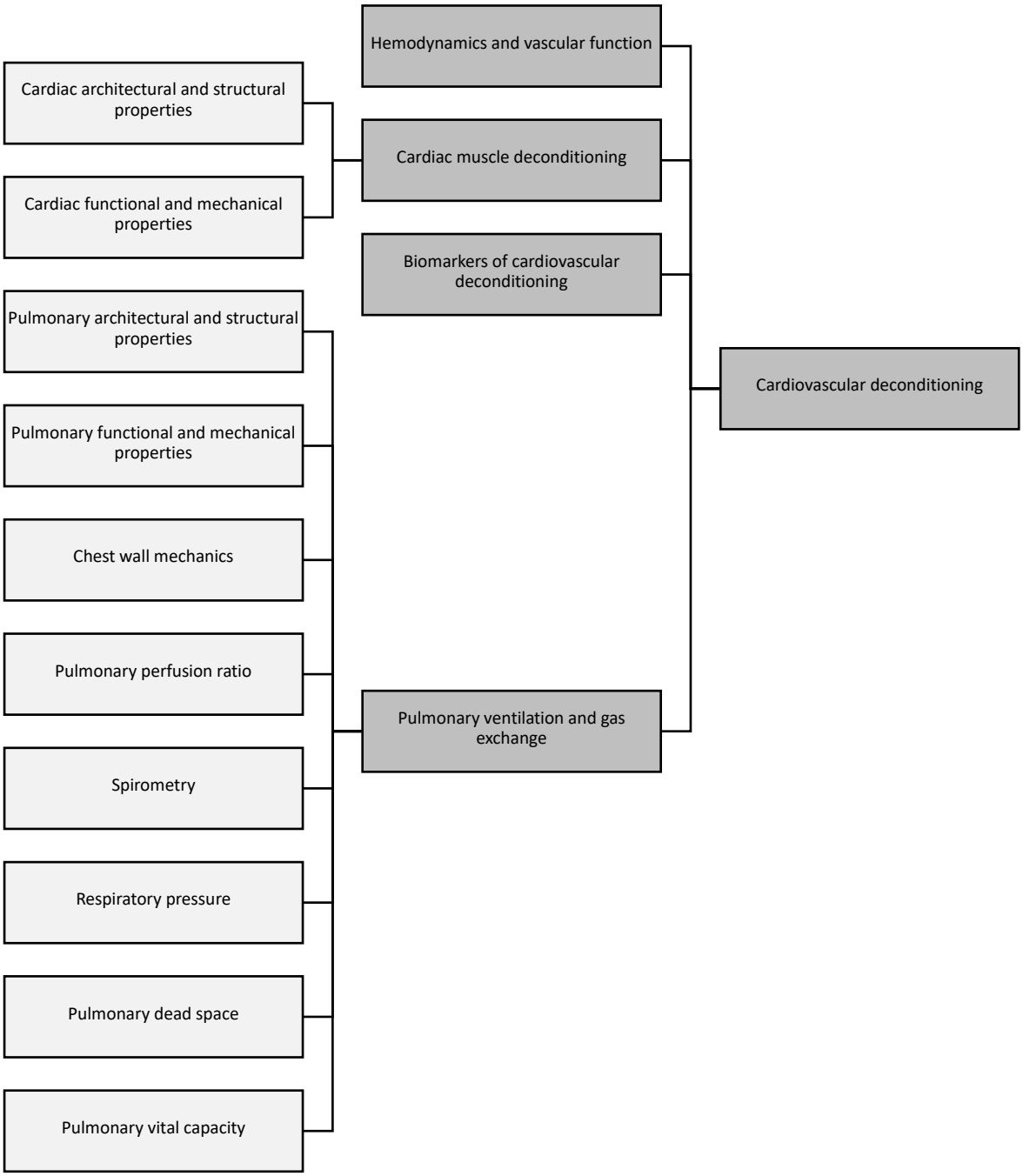

Figure 3.30 Thematic map of the major and higher order themes of cardiovascular deconditioning. Major themes are shown in dark grey while higher order themes are shown in light grey. The thematic maps presented throughout the results branch off from this thematic map, exploring the individual outcomes reported within each of these themes. As such, the thematic maps can be used to trace the relationship of each individual outcome.

The major themes were ranked 1-4 based upon the medical risk each theme presents to astronaut health and mission success (evidence-based justifications for these rankings are provided in Table 3.7). The order of medical ranking in descending importance were outcomes related to: hemodynamics and vascular function; cardiac muscle deconditioning; biomarkers of cardiovascular deconditioning; and pulmonary ventilation and gas exchange. .

Table 3.7 Ranking of major themes, based on impact on mission success and the number of times individual outcomes within each theme were reported

Major theme	Higher order themes	Major theme medical ranking	Number of times outcomes in this major theme were reported (ranking)	Justification for medical ranking
Hemodynamics and vascular function	N/A	1	97 (1)	Microgravity exposure results in a major central fluid shift from the lower limbs towards the head (Buckey Jr et al., 1996; Williams et al., 2009). This leads to the development of orthostatic intolerance which creates difficulties for astronauts to stand up when returning to a gravity-loaded environment and places them at risk of falling (Evans et al., 2018; Kaderka et al., 2010). As hemodynamic fluid shifts are responsible for the cardiovascular changes that lead to orthostatic intolerance, which put astronauts at medical risk (Evans et al., 2018; Kaderka et al., 2010), they are ranked the most medically relevant to astronaut health and operational mission success in this review.
Cardiac muscle deconditioning	Cardiac architectural and structural properties Cardiac functional and mechanical properties	2	81 (2)	Cardiac deconditioning occurs during microgravity exposure because the heart no longer has to work as hard to send blood towards the head against gravity (Tanaka et al., 2017), as fluid shifts towards the head have already occurred during weightlessness (Williams et al., 2009). In combination with decreased plasma volume, atrophy of the heart may be largely responsible for inducing orthostatic intolerance upon return to Earth (Tanaka et al., 2017), which presents a risk to astronauts as they may be unable to stand and be at greater risk of falling (Evans et al., 2018; Kaderka et al., 2010). While cardiac muscle atrophy may be largely responsible for the medical risk to astronauts upon return to Earth, it is ranked lower that hemodynamics as it is the fluid shift during microgravity exposure that results in cardiac muscle atrophy (Tanaka et al., 2017). As the functional risks (e.g. cardiac arrest (Tanaka et al., 2017)) are of greatest concern, priority is given to function over structural properties.

Major theme	Higher order themes	Major theme medical ranking	Number of times outcomes in this major theme were reported (ranking)	Justification for medical ranking
Biomarkers of cardiovascular deconditioning	N/A	3	20 (4)	Chemical biomarkers may be useful as a method to assess the functional state of the cardiovascular system and provide indirect information on the relationship between proteomic data and the physiological effects of spaceflight (Pastushkova et al., 2019). While biomarkers may provide a method by which cardiovascular changes can be more easily assessed (Pastushkova et al., 2019), they are indirect measures which make it difficult to determine exactly what meaningful changes are occurring during spaceflight. As such, they were ranked lower in terms of the medical value to astronaut health and mission success than the more direct outcomes related to hemodynamics and cardiac muscle atrophy.
Pulmonary ventilation and gas exchange	Pulmonary architectural and structural properties Pulmonary functional and mechanical properties Chest wall mechanics Pulmonary perfusion ratio Spirometry Respiratory pressure Pulmonary vital capacity Pulmonary dead space	4	79 (3)	While pulmonary function may in some cases be slightly altered because of microgravity exposure it is not seriously impaired (Hinkelbein, Russomano, Hinkelbein, & Komorowski, 2018; Prisk et al., 2006). So long as normal oxygen levels are maintained during spaceflight there should be no physiologically significant deconditioning of the pulmonary system (Prisk et al., 2006). As such, outcomes related to pulmonary ventilation and gas exchange were ranked the least medically relevant to astronaut health and mission success.

The column “medical ranking” was rank scored from 1-4, with one being most impactful on astronaut health and mission success and three being least impactful, as determined by a medical doctor with a space medicine research background and supported by data extracted during thematic analysis. The column “number of times outcomes in this group were reported” was rank scored from 1-4, with one being most reported and three being least reported during studies included in this systematic review.

Medical rankings were not always directly reflected in the number of times each theme of outcomes were reported. Outcomes related to hemodynamics and vascular function were reported 97 times, those related to cardiac muscle deconditioning were reported 81 times, while those related to biomarkers of cardiovascular deconditioning were reported 20 times, and outcomes related to pulmonary ventilation and gas exchange were reported 79 times.

3.3.3.3.1. Hemodynamics

Outcomes related to hemodynamics and vascular function identified in this review can be seen in Figure 3.31. Summaries of effect size changes are presented below (based upon the information presented in Appendix C) for outcomes which reported enough information to generate effect sizes or reported if changes were statistically significant. All reported results are pre- to post-spaceflight changes. Outcomes related to hemodynamics and vascular function showed little consistency in the effect size changes reported. There were medium effect size increases in total peripheral resistance between pre- and post-spaceflight reported in two studies and another study reported that total peripheral resistance decreased, however this change did not meet the threshold for a small effect size decrease. Except for one study, which reported an increase that did not meet the threshold for a small effect size change, all studies reported stroke volume to decrease between pre- and post-spaceflight. One study reported a small effect size decrease, one reported a large effect size decrease, and two reported a very large effect size decrease. Blood pressure was reported to experience a medium effect size increase in one study, but in two others the increase did not reach the threshold for a small effect size increase. Systolic blood pressure was reported to not change in one study, to experience a small effect size decrease in another, a medium effect size increase in another, and a very large effect size increase in one other study. Three additional studies reported increases (two of the studies) and a decrease (one of the studies), but these did not meet the criteria for a small effect size change. For diastolic blood pressure, one study reported no significant change, while two reported a decrease (although only one of these studies met the criteria for a small effect size decrease). The remaining studies reported increases, with three small effect size increases and one medium effect size increase. There was a small effect size increase in pulse pressure for one study, and a decrease that did not meet the threshold for a small effect size change in another. There was a medium effect size decrease in leg blood volume and a medium effect size increase in baroreflex sensitivity. Two studies reported a small effect size increase in mean arterial pressure. Systolic arterial pressure was reported to experience a small effect size increase. Diastolic arterial pressure increased with a small effect size. Muscle sympathetic nerve activity increased across both studies that reported the outcome, with a small effect size increase in one and a large effect size increase in the other. Maximum rate of change in arterial pressure showed a small effect size increase and systemic vascular resistance experienced a medium effect size decrease. All remaining hemodynamic outcomes were not reported in enough

detail to calculate effect size changes, or to determine if changes reported were statistically significant.

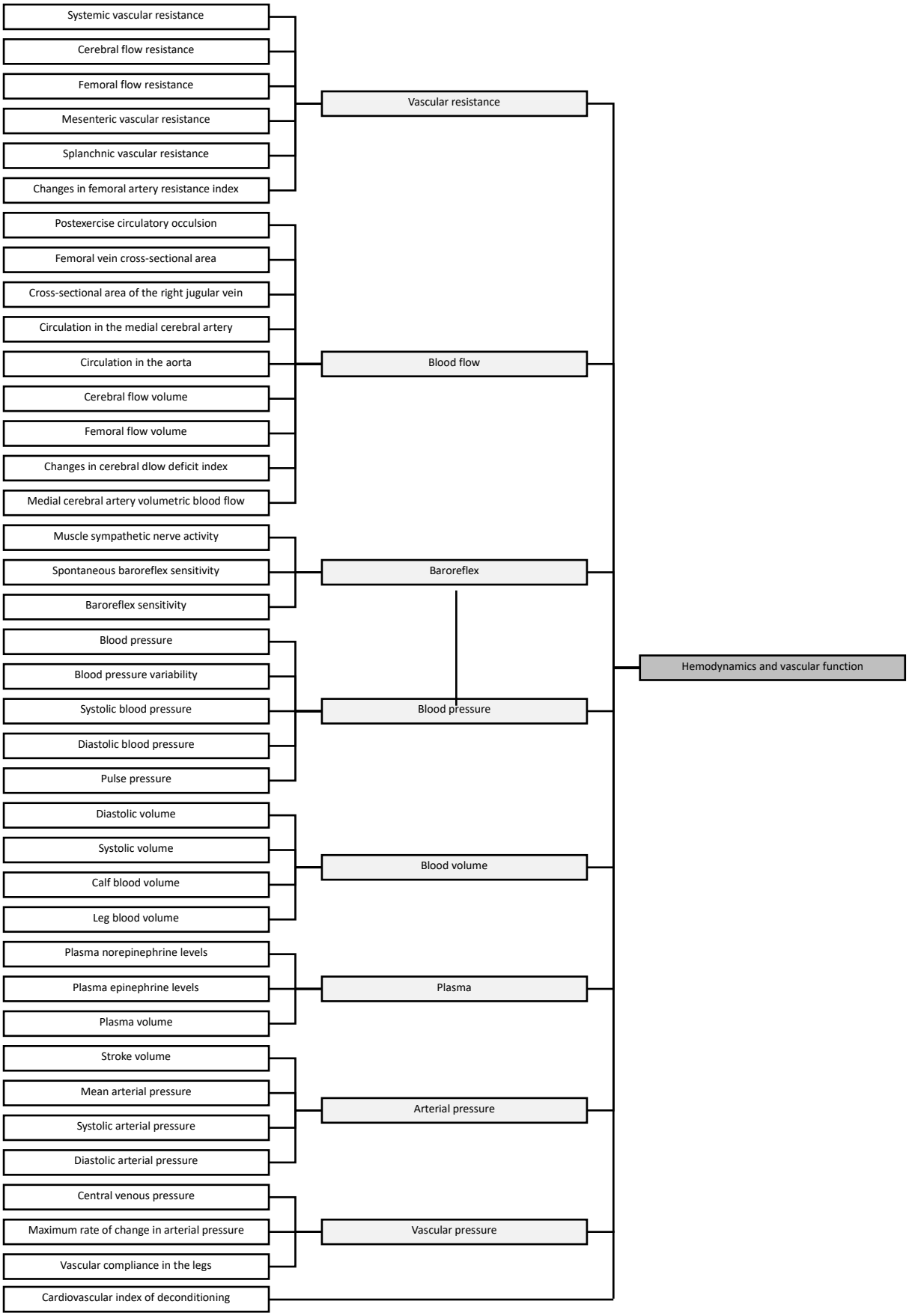

Figure 3.31 Thematic map of hemodynamics and vascular function. Major themes are shown in dark grey, while higher order themes are shown in light grey and individual outcomes are shown in white.

3.3.3.3.2. Cardiac muscle deconditioning

Outcome groups related to cardiac muscle deconditioning identified in this review include cardiac architectural and structural properties (Figure 3.32) and cardiac functional and mechanical properties (Figure 3.33).

3.3.3.3.2.1. Cardiac architectural and structural properties

Of the five outcomes related to cardiac muscle architectural and structural properties, no outcome was reported in enough detail to calculate standardised effect size changes, or to determine if changes reported were statistically significant.

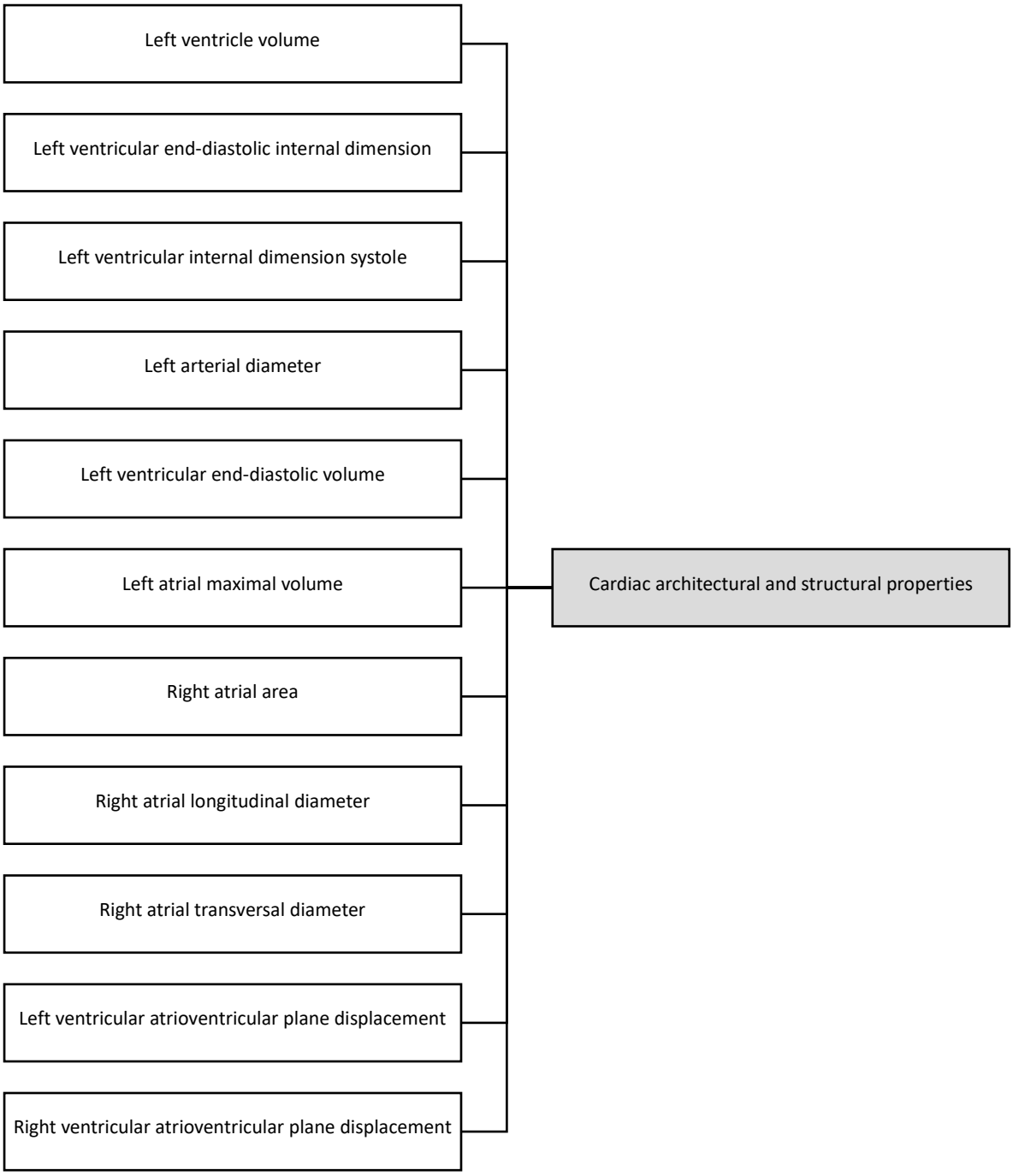

Figure 3.32 Thematic map of cardiac architectural and structural properties. Higher order themes are shown in light grey and individual outcomes are shown in white.

3.3.3.3.2.2. Cardiac functional and mechanical properties

There was a medium effect size decrease in cardiac output reported in one study, a medium effect size increase reported in another, and a decrease that did not meet the threshold for a small effect size change reported in a third study. There was a large difference in the duration of spaceflight between the two studies that reported a medium effect size change (9-14 days for the decrease, 153-180 for the increase) suggesting that cardiac output may decrease initially during spaceflight but then increase as flight duration lengthens. Heart rate increased in all studies which reported suitable data, except for

one which reported a small effect size decrease. Three studies reported very large effect size increases, six studies reported medium effect size increases, one study reported a small effect size increase, one study reported a significant increase and one study reported an increase that did not reach the threshold for a small effect size change. Heart rate variability was reported to not change significantly in one study and to decrease in another, however this decrease did not meet the threshold for a small effect size change. Left-ventricular ejection time index decreased but did not meet the threshold for a small effect size change. Respiratory sinus arrhythmia was reported to experience a medium effect size decrease. For ECG activities, there was a small effect size increase for supraventricular beats, ECG p-wave duration. There were small effect size decreases for ECG p-wave amplitude II, ECG p-wave amplitude III, ECG P-wave amplitude aVr, ECG p-wave amplitude aVF, ECG p-wave amplitude V1, ECG p-wave amplitude V5, and ECG p-wave amplitude V6. There was a medium effect size decrease for ECG p-wave amplitude V3. There was a large effect size decrease for ECG p-wave amplitude V4. There was a very large effect size decrease for ECG p-wave amplitude V2. ECG filtered p-wave duration decreased, but this did not meet the criteria for a small effect size change. ECG RMS20 increased, but this did not meet the criteria for a small effect size change. There was no change in ECG p-wave amplitude I.

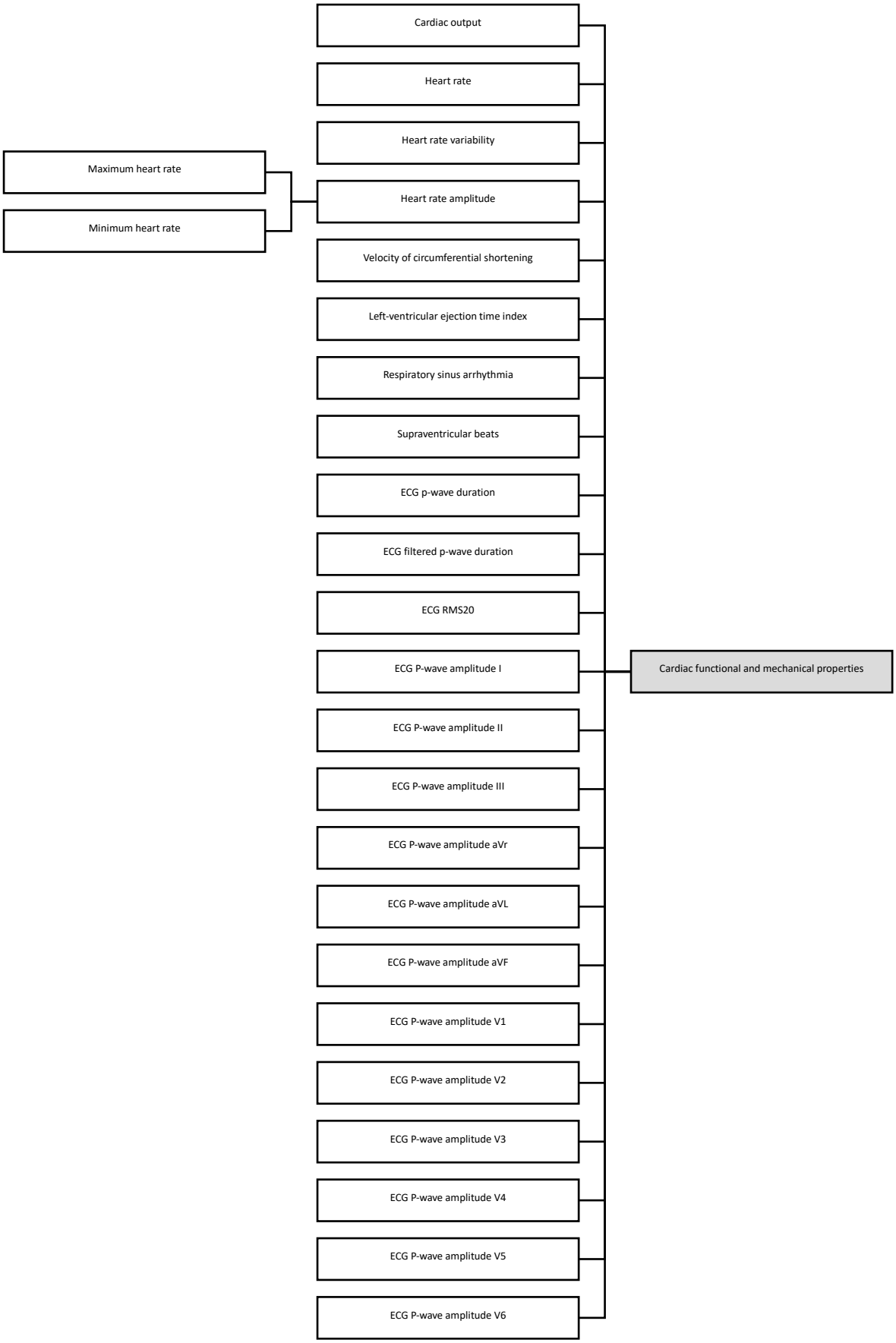

Figure 3.33 Thematic map of cardiac functional and mechanical properties. Major themes are shown in dark grey, while higher order themes are shown in light grey and individual outcomes are shown in white.

3.3.3.3.3. Biomarkers of cardiovascular deconditioning

Outcomes related to biomarkers of cardiovascular deconditioning can be seen in Figure 3.34. Of the 20 outcomes related to biomarkers of cardiovascular deconditioning, no outcome was reported in enough detail to calculate standardised effect size changes, or to determine if changes reported were statistically significant.

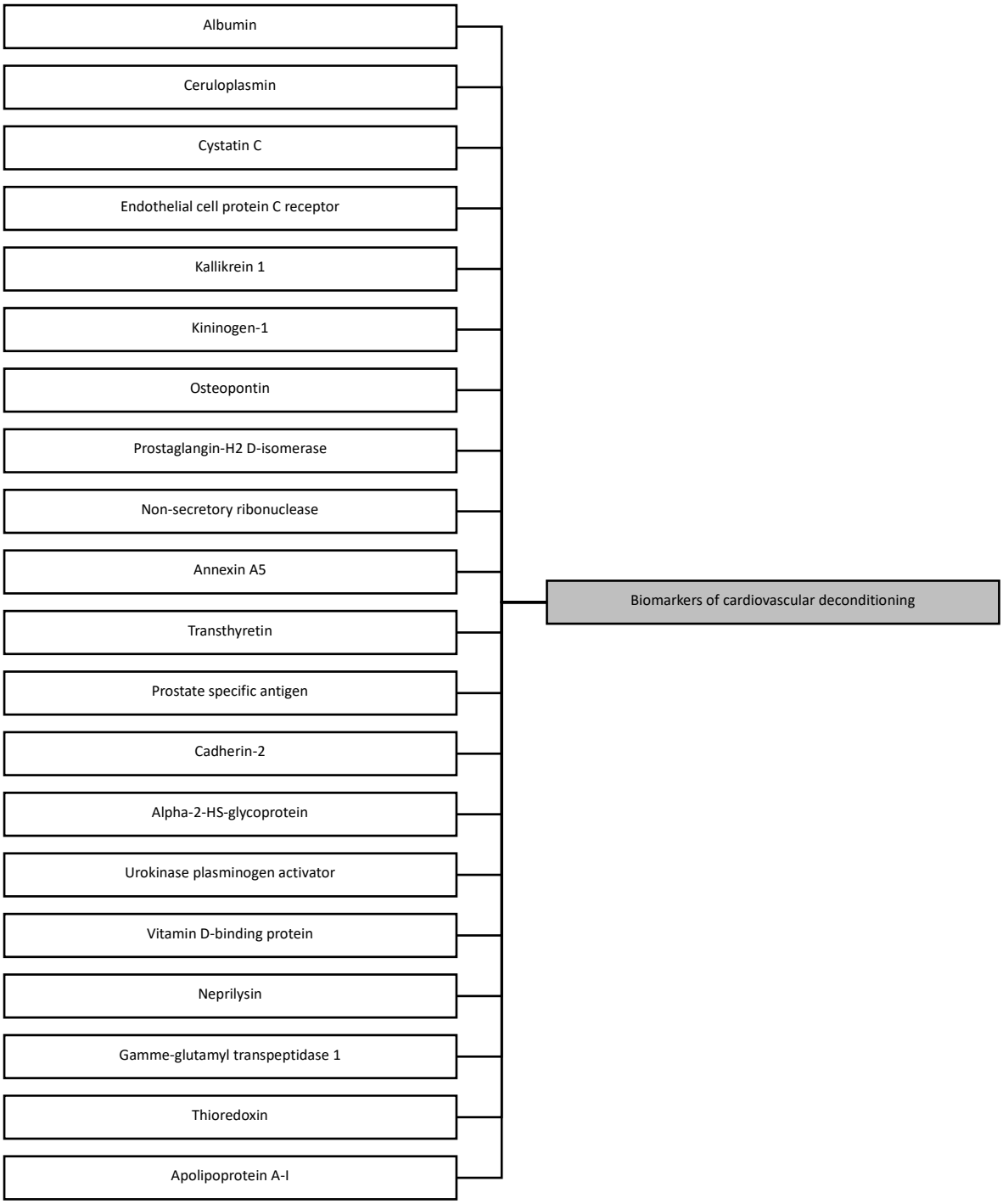

Figure 3.34 Thematic map of the biomarkers of cardiovascular deconditioning. Major themes are shown in dark grey, while individual outcomes are shown in white.

3.3.3.3.4. Pulmonary ventilation and gas exchange

Outcome groups related to pulmonary ventilation and gas exchange include pulmonary architectural and structural properties (Figure 3.35), pulmonary functional and mechanical properties (Figure 3.36), chest wall mechanics (Figure 3.37), pulmonary perfusion ratio (Figure 3.38), spirometry (Figure 3.39), respiratory pressure (Figure 3.40), pulmonary dead space (Figure 3.41), and pulmonary vital capacity (Figure 3.42).

3.3.3.3.4.1. Pulmonary architectural and structural properties

Lung tissue volume was reported to decrease significantly between pre- and post-spaceflight. The remaining two outcomes were not reported in enough detail to calculate standardised effect size changes, or to determine if changes reported were statistically significant.

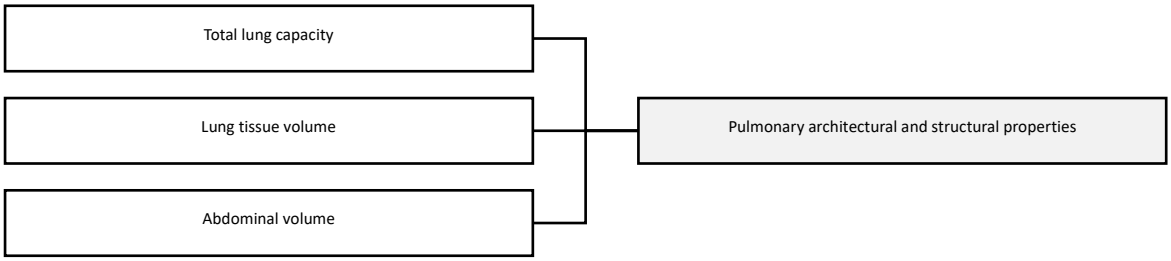

Figure 3.35 Thematic map of pulmonary architectural and structural properties. Higher order themes are shown in light grey and individual outcomes are shown in white.

3.3.3.3.4.2. Pulmonary functional and mechanical properties

There was a small effect size decrease in hyperventilation breath-hold cardiogenic oscillation size and membrane diffusing capacity. There was also a decrease in hyperventilation-breath-hold vertical height of phase IV and slope ratio of mixed-expired washouts, but these did not meet the threshold for a small effect size change. A medium effect size decrease was reported for diffusing capacity for carbon monoxide and alveolar volume. There was also a medium effect size increase in total ventilation reported in one study, while another reported a statistically significant increase. The same results were found for alveolar ventilation. A large effect size decrease was reported for pulmonary capillary blood volume. There was a small effect size increase in sympathovagal balance and carbon dioxide production. There was a medium effect size increase in oxygen consumption, breathing frequency, and respiratory exchange ratio. A very large effect size increase was reported for diffusing capacity per unit alveolar volume. No significant differences between pre- and post-flight scores were reported for inspiratory time as a function of total breath time, inspiratory time as a function of average inspiratory flow rate, end-tidal partial pressure of oxygen in blood, oxygen uptake, respiratory rate, and carbon dioxide output. Some outcomes were reported with conflicting results. A very large effect size decrease was reported for cardiogenic oscillation size in one study, while no statistically significant difference was reported in another, the differences in which do not appear to be accounted for by flight duration. A similar situation was seen for height of phase IV, in which no statistically significant difference was reported in one study but a significant decrease in another, which was also not accounted for by flight duration. For respiratory frequency, one study reported a significant decrease while another reported a large effect size increase. This may be explained by flight duration,

as the decrease was reported over a flight duration of 8 days, while the increase was reported over a flight duration of 52-199 days, suggesting that respiratory frequency may decrease initially during spaceflight but then increase as flight duration continues. In a similar way, there was no statistically significant difference in end-tidal partial pressure of carbon dioxide in one study, while a small effect size decrease was reported in another, but these differences may be accounted for by flight duration (9-14 days in the first study and 130-196 days in the second). The remaining pulmonary functional and mechanical properties outcomes were not reported in enough detail to determine if there was an effect size change or if changes were statistically significant.

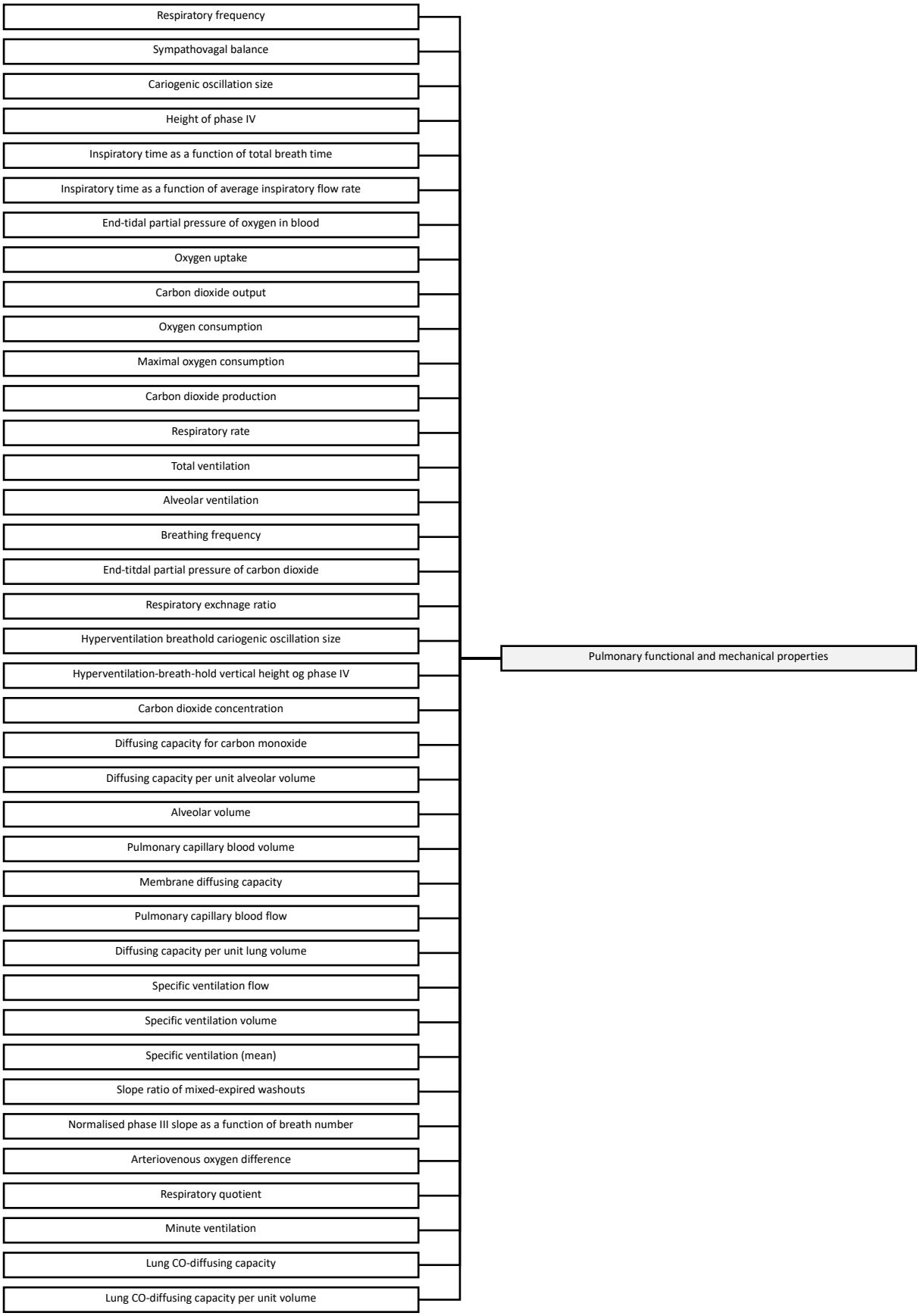

Figure 3.36 Thematic map of pulmonary functional and mechanical properties. Higher order themes are shown in light grey and individual outcomes are shown in white.

3.3.3.3.4.3. Chest wall mechanics

There was no change in tidal volume between pre- and post-spaceflight. The remaining two outcomes related to chest wall mechanics were not reported in enough detail to calculate effect size changes or to determine if changes were statistically significant.

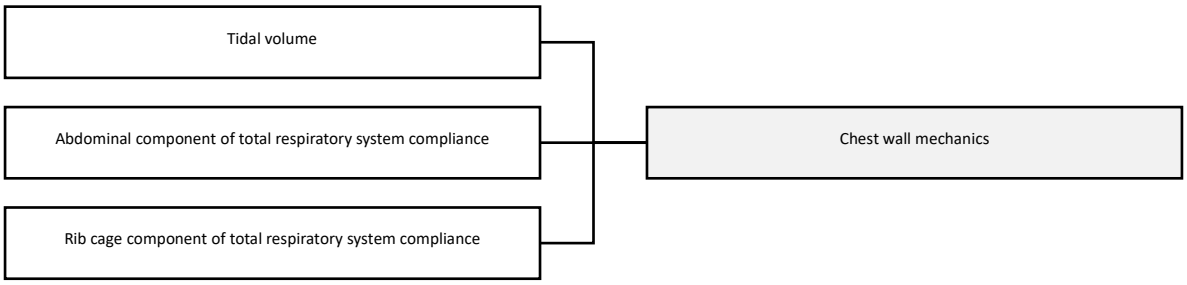

Figure 3.37 Thematic map of chest wall mechanics. Higher order themes are shown in light grey and individual outcomes are shown in white.

3.3.3.3.4.4. Pulmonary perfusion ratio

There was a medium effect size increase in slope of intrabreath ventilation perfusion ratio vs volume over first half of phase III, a very large effect size increase in slope of intrabreath ventilation perfusion ratio range over phase IV, and no statistically significant difference in range of ventilation-perfusion ratio over phase III and range of ventilation-perfusion ratio over phase IV. While there was no statistically significant difference in range of ventilation-perfusion ratio over phase III and range of ventilation-perfusion ratio over phase IV, these occurred over a short flight duration (9-14 days). There was a medium effect size increase in slope of intrabreath ventilation perfusion ratio vs volume over first half of phase III, a very large effect size increase in slope of intrabreath ventilation perfusion ratio range over phase IV, which occurred during flight durations of 130-196 days. This may suggest that pulmonary perfusion ratio is only affected by spaceflight during longer duration spaceflight missions.

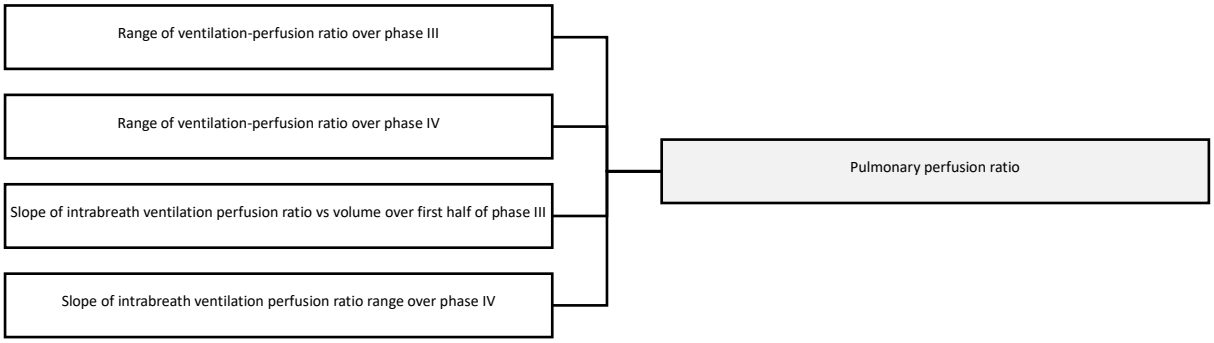

Figure 3.38 Thematic map of pulmonary perfusion ratio. Higher order themes are shown in light grey and individual outcomes are shown in white.

3.3.3.3.4.5. Spirometry

All spirometry measures, other than forced expiratory volume in 1 second, increased between pre- and post-spaceflight. Forced expiratory volume in 1 second was reported to show no statistically significant difference in one study, but a large effect size decrease in another. As the studies took part over different lengths of spaceflight (9-14 days for the first study and 130-196 for the second) it may suggest that forced expiratory volume in 1 second is only affected during longer-duration spaceflight.

Small effect size increases were shown for forced expiratory flow after exhalation of 50% vital capacity, forced expiratory flow at 25-75% vital capacity, forced inspiratory flow at 25-75% of vital capacity, forced expiratory flow rate at 50% of inspired volume, and peak inspiratory flow rate.

A large effect size increase was shown for peak expiratory flow rate.

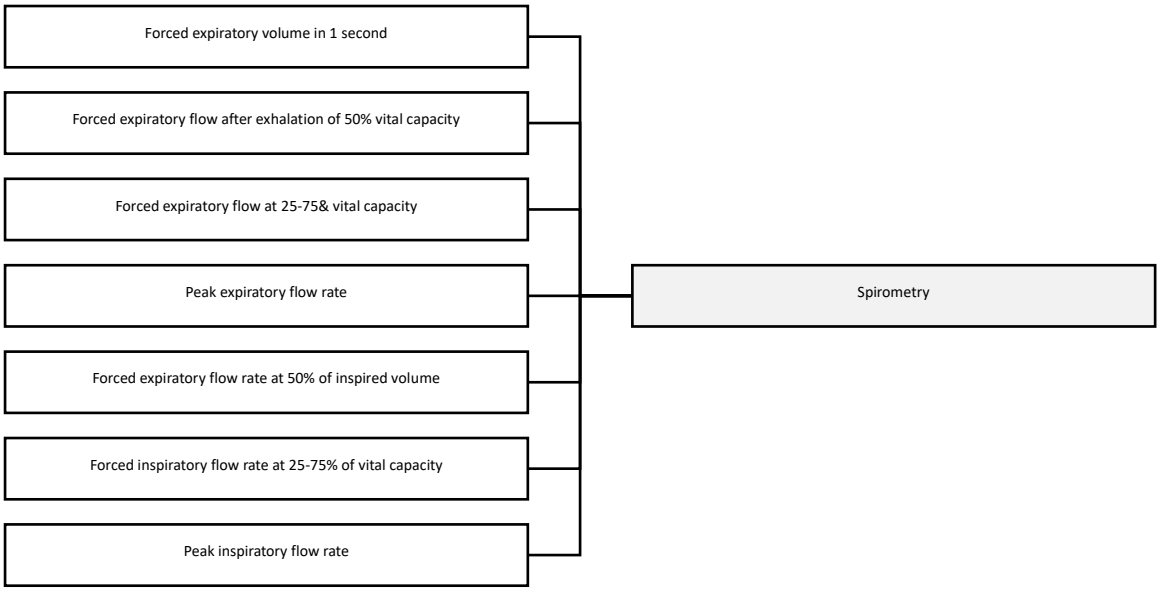

Figure 3.39 Thematic map of spirometry. Higher order themes are shown in light grey and individual outcomes are shown in white.

3.3.3.3.4.6. Respiratory pressure

A small effect size decrease was reported for maximum inspiratory pressure. While maximum expiratory pressure reported a decrease, it did not meet the threshold of a small effect size change. The remaining two outcomes were not reported in enough detail to calculate effect size changes or to determine if changes were statistically significant.

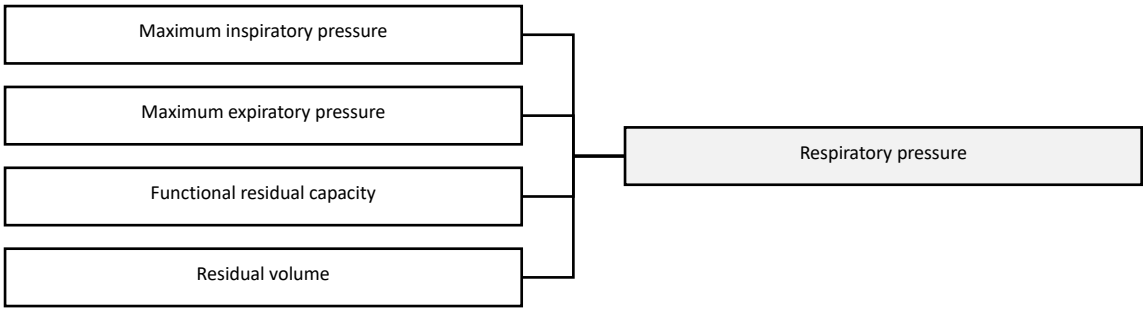

Figure 3.40 Thematic map of respiratory pressure. Higher order themes are shown in light grey and individual outcomes are shown in white.

3.3.3.3.4.7. Pulmonary dead space

There was no statistically significant difference in anatomic dead space and physiologic dead space between pre- and post-spaceflight. The three remaining outcomes were not reported in enough detail to calculate effect size changes or to determine if changes were statistically significant.

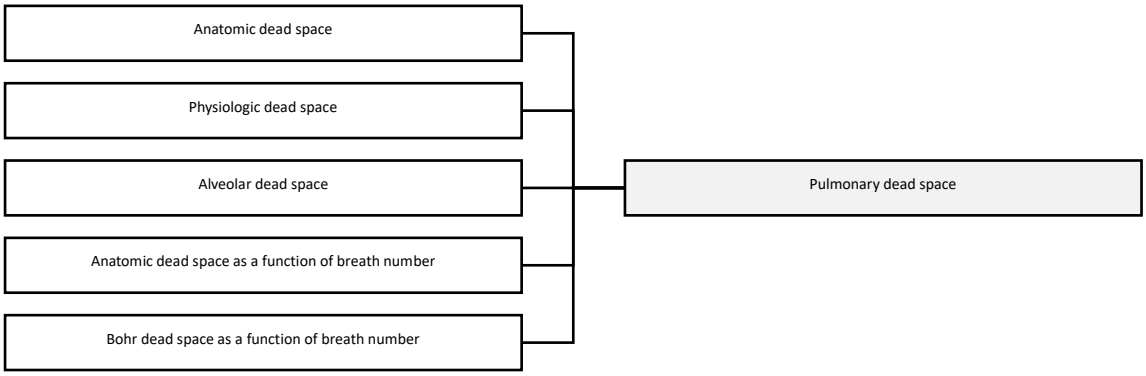

Figure 3.41 Thematic map of pulmonary dead space. Higher order themes are shown in light grey and individual outcomes are shown in white.

3.3.3.3.4.8. Pulmonary vital capacity

Forced vital capacity was reported to experience a small effect size decrease in one study, and there was no statistically significant difference between pre- and post-spaceflight values in another. This may be accounted for by spaceflight duration (130-196 in the first study and 9-14 days in the second), suggesting that a decrease in vital capacity only occurs during longer duration spaceflight. The remaining two outcomes reported no statistically significant difference between pre- and post-spaceflight values. As these two outcomes were only reported over short-duration spaceflight of 9-14

days it is unclear if longer-duration spaceflight may affect them in the same way that forced vital capacity was affected.

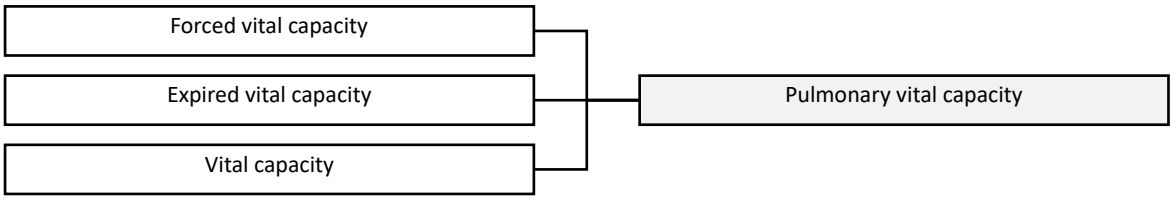

Figure 3.42 Thematic map of pulmonary vital capacity. Higher order themes are shown in light grey and individual outcomes are shown in white.

3.4. Discussion

3.4.1. Summary of Evidence

The main outcomes of this review were the identification of broad major themes of musculoskeletal and cardiovascular outcomes and the medical ranking of these themes according to their impact on astronaut health and operational mission success. For muscle outcomes, in descending order of importance, these were outcomes related to muscle functional and mechanical properties, muscle architectural and structural properties, and then biomarkers of muscular deconditioning. For skeletal outcomes, these were functional and mechanical properties, measures of volumetric bone mineral density, biomarkers of bone remodelling, measures of bone mineral density, and then architectural and structural properties. For cardiovascular outcomes, these were outcomes related to hemodynamics and vascular function, cardiac muscle deconditioning, biomarkers of cardiovascular deconditioning, and then pulmonary ventilation and gas exchange

It was not possible to identify which individual outcomes were of greatest medical relevance due to the small sample sizes of included studies, the use of extremely heterogeneous outcome measures, the pooling of data across multiple spaceflights of different lengths, and widespread inadequate or missing reporting of results data, all of which contributed to preventing meta analysis.

3.4.2. Muscular deconditioning

3.4.2.1. Muscle Functional and Mechanical Properties

Losses to the functional and mechanical properties of muscles, particularly of muscle strength and power during spaceflight presents a medical risk to astronauts and an operational risk to mission success (English et al., 2015). Astronauts must be capable of producing high levels of force to accomplish mission tasks, such as freeing jammed hardware during extravehicular activities (English

et al., 2015) or undertaking a spacewalk to repair a damaged spacecraft (Moore et al., 2010). Optimal strength is also needed on return to the 1G environment of Earth in the case of emergency egress as astronauts may need to open and then remove themselves from a space capsule (English et al., 2015). Muscle functional and mechanical properties also contribute to locomotion and balance, which may become compromised upon return to Earth (English et al., 2015; Holviala et al., 2012).

Of the studies included in this review there was a clear focus upon the antigravity muscles of the back and lower limbs, in particular the triceps surae: the gastrocnemius and soleus muscles. This is unsurprising as the triceps surae is one of the most affected muscle groups when exposed to microgravity (Akima et al., 2002; Alkner et al., 2004). The triceps surae is important for postural control and locomotion (Loram, Maganaris, & Lakie, 2004), and deficits in these muscles may reduce postural balance and increase the risk of falling over (Koryak, 2018). In terms of the medical ranking provided in this review, the soleus' functional and mechanical properties and architectural and structural properties were ranked higher than the gastrocnemius. This is because the soleus is composed of approximately 90% slow red type I (oxidative) muscle fibres, which are heavily altered by microgravity exposure (Widrick et al., 2001). The gastrocnemius in comparison is approximately half slow type I fibres and half fast type II (glycolytic) fibres (Widrick et al., 2001) and as such the soleus is more likely to be heavily altered by microgravity exposure than the gastrocnemius.

Given the importance of the functional and mechanical properties of muscles, particularly muscle strength and power for mission critical tasks during spaceflight, it could be argued that out of the three major themes identified in this review this is the most relevant for astronaut health and mission success during spaceflight. Deficits in the functional and mechanical properties of muscles may be more relevant to the health and safety of astronauts and mission success than deficits to the architectural and structural properties, such as changes in muscle volume. This is because while changes in the muscle architectural and structural properties may suggest functional changes, they are not direct measures of functional change (Koryak, 2018) and reductions in the strength of a muscle may exceed losses in the dimensions of that muscle (Alkner et al., 2004). For example, Di Prampero, Narici, and Tesch (2001) reported that in one astronaut the explosive force of the calf muscles was reduced by 50% after a six-month mission, while the calf muscle volume was only reduced by 20%. This may be because muscle atrophy is not the only factor involved in the weakening of muscles during spaceflight (Koryak, 2018). Williams et al. (2009) suggest that the discrepancy may be a result of alterations to motor unit recruitment, electromechanical efficiency, muscle damage or alterations to contractile apparatus. As a result, changes in the architectural and structural properties of any given muscle may not accurately reflect the deficits to the functional and mechanical changes that have occurred and the risks to astronaut health and mission success associated with those changes.

3.4.2.2. Muscle Architectural and Structural Properties

Exposure to the weightless conditions of microgravity during spaceflight leaves weight-bearing musculature unloaded of the gravitational forces they experience on Earth (Hargens et al., 2013). As a result, the muscles begin to decondition because of spaceflight adaptation (Ploutz-Snyder et al., 2015). These alterations to the architectural and structural properties of muscles during spaceflight have been used to indirectly infer changes about a muscle's functional and mechanical properties (Rittweger et al., 2018; Wilson & Lichtwark, 2011), the deconditioning of which may present medical and operational risks during spaceflight (English et al., 2015). For example, reductions in the muscle volume of the lumbopelvic muscles may lead to increased risk of low back pain and herniated nucleus pulposus in astronauts during spaceflight or on return to Earth (Johnston, Campbell, Scheuring, & Feiveson, 2010; Richter et al., 2017; Wang et al., 2019).

Studies included in this review that focused on architectural and structural changes exclusively examined outcomes related to the back and lower limbs. One reason for this may be that current ISS exercise countermeasures are not completely effective for reducing muscular deconditioning of the lumbopelvic area, lower back and lower limbs (Williams et al., 2009; Winnard et al., 2017) and as such the research focus has been on these areas. As with the functional and mechanical properties theme, there was a large focus on the triceps surae muscles and the architectural and structural properties of their muscle fibres in the included documents.

3.4.2.3. Biomarkers of Muscular Deconditioning

Biomarkers of muscular deconditioning describe alterations in specific proteins, enzymes and blood/plasma metabolomics from which muscle loading history and muscular deconditioning may be inferred (Capri et al., 2019; Rindom & Vissing, 2016; Salanova et al., 2014). The examination of biomarkers instead of the direct examination of the functional and mechanical or the architectural and structural properties of muscles may be advantageous in that they offer an option of monitoring astronaut health more easily than gaining direct contact to the astronaut population, which are often difficult to access for research purposes (Capri et al., 2019). For example, rather than directly measuring muscle mass or volume, which can be costly (Koryak, 2018), changes in c-markers could be measured in blood/plasma samples to infer a loss of muscle mass or volume (Calder et al., 2017; Capri et al., 2019; Franceschi et al., 2007). However, these biomarkers are indicators of stress response (Calder et al., 2017; Capri et al., 2019; Franceschi et al., 2007) and as such it is difficult to distinguish based upon biomarkers alone where or to what extent structural changes are occurring, or if the origins of these adaptations are due to muscular deconditioning or other factors, such as psychological stressors. If biomarkers are used as an indirect assessment of the architectural and structural properties of a muscle (Capri et al., 2019) (which are in themselves indirect measurements

of the functional and mechanical properties of a muscle (Rittweger et al., 2018; Wilson et al., 2011)), then biomarkers are indirect measures of indirect measures, further contributing to the difficulties in establishing what meaningful changes are occurring to astronaut musculature during spaceflight.

3.4.3. Skeletal deconditioning

3.4.3.1. Measures of bone mineral density

Measures of bone mineral density describe the use of Dual Energy X-ray Absorptiometry (DEXA) to study the density and strength of bones in terrestrial populations (McCarthy et al., 2000). The measurement of Bone Mineral Density (BMD) through DEXA is one of the best ways to estimate risk of bone fracture (Syed et al., 2002), which astronauts are susceptible to during extended spaceflight due to the bone loss that occurs in microgravity conditions (Nelson, Lewandowski, Licata, & Myers, 2009). Bone Mineral Content (BMC) outcomes are included under this theme as they are used to calculate BMD by dividing BMC by bone area (Eapen et al., 2008). BMD is a representation of areal density (aBMD) as it measures the bone mineral grams per square centimetre (a 2-D projected area of bone) (Ott, O'Hanlan, Lipkin, & Newell-Morris, 1997; Tatoń, Rokita, Wróbel, & Korkosz, 2013).

In terms of operational and astronaut health risks during microgravity exposure, one of the major research concerns is spaceflight osteoporosis (Cappellesso, Nicole, Guido, & Pizzol, 2015). Osteoporosis is a disorder of the skeletal system in which bone strength is compromised, resulting in an increased risk of bone fracture (Leali et al., 2011). Gravitational loading increases BMD, which is an important factor in overall bone strength (Havill, Mahaney, L Binkley, & L Specker, 2007). 60-70% of bone strength is accounted for by BMD (Rizzoli & Ammannn, 2003) and between 10-44% of fracture occurrences (Stone et al., 2003), depending upon the bone site (Havill et al., 2007).

However, BMD is not the only factor in determining bone strength (and therefore fracture risk), as demonstrated by most fractures in terrestrial settings occurring in those whose aBMD is above the ‘osteoporosis threshold’ (Black et al., 2008). An approach which encompasses multiple methods of determining skeletal fragility, such as also using measures of bone remodelling biomarkers, may be more useful in fully understanding the risk of fracture to astronauts during and after spaceflight than to use measures of BMD alone.

3.4.3.2. Biomarkers of bone remodelling

Bone remodelling is the replacement of damaged bone tissue with healthy intact bone during skeletal homeostasis, distributed according to the loads placed upon the bone (Eapen et al., 2008; Leali et al., 2011). The human skeleton is continuously remodelling itself in order to maintain strength, calcium homeostasis, and repair microfractures (Manolagas & Jilka, 1995). Biomarkers of bone remodelling

reflect formation of bone by osteoblasts and resorption of bone by osteoclasts, which can be assessed for diagnostic, prognostic, and medical management purposes (Eapen et al., 2008). Skeletal biomarkers provide early warning of skeletal adaptation while also serving as an indirect measure of skeletal deconditioning (Eapen et al., 2008).

It has been previously suggested that, during spaceflight, biomarkers that indicate bone formation typically decrease while biomarkers of bone resorption typically increase (Caillot-Augusseau et al., 2000). While this was, for the majority, true of biomarkers of bone resorption, this review did not find clear evidence that biomarkers of bone formation typically decreasing during spaceflight. Instead, it appeared that over half of the bone formation biomarkers increased between pre- and post-spaceflight. Bone formation in excess of what is required to replace damaged bone tissue weakens the skeleton (Leali et al., 2011). As a result, excess bone formation during spaceflight can present a danger to astronauts' health. Pharmacological interventions, such as antiresorptive or estrogen-like drugs, may provide an effective agent to reduce excessive remodelling to optimal levels (Leali et al., 2011).

Findings have been inconsistent on whether biomarker alterations alone indicate risk of fracture (Dai et al., 2016). There also remains some debate over the usefulness of biomarkers in a clinical setting due to individual variability in the biomarkers (Gertz et al., 1994) and lack of adequate standardisation of the assay testing procedures (Syed et al., 2002). However, biomarkers are useful as an independent risk factor of bone fracture (Garnero, 2008; Garnero et al., 1996), and biomarkers are very sensitive to early detection of skeletal adaptations during microgravity exposure, which is not achievable using DEXA (Eapen et al., 2008). Biomarkers are also inexpensive and non-invasive measures of studying bone remodelling (Eastell & Hannon, 2008), which may account partly for why they are the most widely reported outcome measures found in this review.

3.4.3.3. Skeletal functional and mechanical properties

Skeletal functional and mechanical properties describe the operations and actions of the skeletal system in withstanding stressors and strains placed upon it, such as imposed loads via gravitational loading and adapting to specific mechanical responses (Burr, 1980). It is crucial to maintain the function of the skeletal system, such as bone strength, to reduce the risk of bone fracture during and after spaceflight (Keyak et al., 2009).

Bone fractures occur when the force applied to a bone exceeds the strength (fracture load) of that bone (Keyak et al., 2009). Astronauts may be at an increased risk of fracture as the weakening of the bone during microgravity exposure may reduce the bone strength of the astronaut below that of the forces applied to it during operational tasks (Keyak et al., 2009). This is particularly problematic upon return to a gravity-loaded environment where walking, running, or falling could result in bone fracture (Keyak et al., 2009). While DEXA measurements of BMD may be used as an imperfect surrogate for

assessing functional properties, it is ultimately changes in the functional and mechanical properties, such as bone strength, that present an operational and health risk to astronauts (Keyak et al., 2009) and as such this theme was ranked the most medically relevant to astronaut health and operational mission success.

While information on bone function can be useful, they are not widely reported across the included literature when compared to DEXA and QCT measurements of BMD, biomarkers of bone remodelling, or skeletal architectural and structural properties. As the functional and mechanical responses of the skeletal system can be inferred from the bone's mineral content and density with little difficulty (Burr, 1980), it may explain why few studies that directly examine the skeleton's functional properties during spaceflight exist. However, changes in the functional properties do not necessarily translate directly into losses in BMD. For example, a decrease in proximal femoral strength can be greater than losses to total femur BMD (Keyak et al., 2009). Loss of bone density can provide only an imperfect surrogate for structural integrity that does not directly translate to functional outcomes (Keyak et al., 2009). The risk of using indirect structural data to assess functional changes was also recognised by NASA's Research and Clinical Advisory Panel, who recommended collecting more functional information on skeletal deconditioning, rather than relying upon inferring such information from structural outcomes (Sibonga, 2019).

3.4.3.4. Measures of volumetric bone mineral density

Measures of volumetric bone mineral density describe the use of Quantitative Computed Tomography (QCT) to evaluate the volumetric density, content, and strength of bones (Eapen et al., 2008). QCT is a three-dimensional measure that can be used to estimate risk of bone fracture (Syed et al., 2002), which astronauts are susceptible to during extended spaceflight due to the bone loss that occurs in microgravity conditions (Nelson et al., 2009). Volumetric Bone Mineral Content (vBMC) outcomes are also included under this theme as they are used to calculate vBMD by dividing vBMC by bone area (Eapen et al., 2008). QCT can be utilized for measuring vBMD in grams per centimetre cubed (producing a 3D image, as opposed to DEXA's grams per square centimetre 2D image) (Dall'Ara, Pahr, Varga, Kainberger, & Zysset, 2012). As a result, QCT measures of vBMD are more accurate for some anatomical regions, such as the lumbar spine, than DEXA BMD measures (Bauer et al., 2007).

While measures of vBMD present an advantage in terms of precision and accuracy over BMD measurements (Bauer et al., 2007), it also leads to greater exposure of x-ray radiation than DEXA measurements (Bauer, Virmani, & Mueller, 2010). Radiation exposure increases susceptibility to cancer and degenerative diseases (Durante & Manti, 2008) and astronauts are already exposed to high levels of cosmic radiation during spaceflight (Durante et al., 2008). Specifically, astronauts are exposed to between 73 mSv/year and 912.5 mSv/year on the International Space Station (320

mSv/year by NASA estimates) (Durante et al., 2008; NASA, 2006). DEXA exposes astronauts to further effective dose of 0.001-0.006 mSv (equivalent to 3 hours of background terrestrial radiation), whereas QCT exposes astronauts to between 0.09 and 1 mSv (equivalent to one-third of the annual effective dose of background radiation exposure on Earth) (Bauer et al., 2010; Durante et al., 2008). The benefits of additional precision from measuring vBMD must be considered against the additional radiation astronauts would be exposed to.

3.4.3.5. Skeletal architectural and structural properties

Architectural and structural properties describe changes in the size, shape, and dimensions of the skeletal system: it is their properties, quality, and physical arrangement (Beck et al., 2001; Leali et al., 2011; Ruff & Runestad, 1992). Changes in the architectural and structural properties of the skeletal system because of spaceflight deconditioning are linked to and can be used to infer functional and mechanical changes (Burr, 1980; Havill et al., 2007). In doing so, architectural and structural changes may be useful in determining risk of fracture (Havill et al., 2007).

The capability of a bone to resist fracture is dependent upon the amount of bone, the bone's mass, the spatial distribution of that bone, and the intrinsic properties of the materials that form that bone (Leali et al., 2011). The architecture of the bone, for example, as measured by cross-sectional area, contributes significantly to bone strength and is a factor in the risk of fracture (Havill et al., 2007). Changes in the architectural and structural properties of the skeletal system may also increase fracture risk at later stages in life, such as during age-related osteoporosis (Keyak et al., 2009). However, alterations may not correspond directly to changes in bone strength (and therefore risk of fracture) (Keyak et al., 2009). For example, the recovery of bone mass after returning from long-duration microgravity exposure may not translate directly into the recovery of bone strength (Burr, 1980). An attention to the wider number of factors, including the functional and architectural components of the skeletal system, may be more useful for assessing fracture risk and managing therapeutic response (Leali et al., 2011).

Changes in bone structure have not been well explored, as indicated by this theme being the 4th least reported set of outcomes out of the five themes explored in this review. Collet et al. (1997) had previously remarked that little research had been conducted on bone structure, despite its potential to indicate bone fragility using ultrasound. This may be because architectural changes are a consequence of other, more well-researched factors such as bone remodelling and BMD alterations (Negredo et al., 2012). For example, reductions in BMD lead to deteriorations of the bone architecture, as determined by the intensity of bone remodelling (Negredo et al., 2012). As a result, the architectural and structural properties were considered the least relevant medically to astronaut health as they are a consequence, not a cause of, BMD deteriorations.

3.4.4. Cardiovascular deconditioning

3.4.4.1. Hemodynamics

Hemodynamics and vascular function describes the flow of fluids, specifically blood flow, within the circulatory system (Tortora & Derrickson, 2018). Microgravity exposure results in a major central fluid shift, likely from the lower limbs towards the head, resulting in a unique puffy appearance in the face and decreased fluid volume in the lower limbs (Buckey, Gaffney, et al., 1996; Williams et al., 2009). This fluid shift results in alterations to central venous pressure, sensitivity of the vagal baroreflex, plasma volume, blood pressure, cardiac output, and heart rate (Arbeille et al., 1995; Evans et al., 2018).

The redistribution of fluids upon return to Earth leads to a pooling of blood volume into the lower body and a decrease in intravascular blood volume, contributing to orthostatic stress upon landing (Williams et al., 2009). These effects place astronauts' health at risk, as they become light-headed, experience heart palpitations and syncope, and one in every four are unable to stand quietly for more than 10 minutes (Williams et al., 2009). Countermeasures during spaceflight to reduce this orthostatic intolerance are not completely effective (Williams et al., 2009). Other major cardiovascular conditions that may impact astronauts upon return from spaceflight include decreased plasma volume, hematocrit, decreased aerobic activity, and decreased vascular responsiveness when standing (Evans et al., 2018). As hemodynamic fluid shifts are responsible for the cardiovascular changes that lead to orthostatic intolerance, which put astronauts at medical risk (Evans et al., 2018; Kaderka et al., 2010), they are ranked the most medically relevant to astronaut health and operational mission success in this review.

The reported changes to hemodynamic outcomes varied greatly across the included studies, with many providing contradictory effect size changes that did not appear to be accounted for by the flight duration, leaving it unclear as to why there appears to be such great variability in hemodynamic outcomes. Meta-analysis could not be conducted to determine in what direction, if any, pooled effects occurred due to the study designs used. Even if meta-analysis was a possibility, many of the remaining hemodynamic outcomes were not reported in enough detail to calculate effect size changes or to determine if changes were statistically significant. It would be beneficial for the space medicine sector to address these issues by setting minimum reporting standards so that these problems are not repeated in future research and so that meta-analysis in enabled in space medicine research.

3.4.4.2. Cardiac muscle deconditioning

Cardiac muscle deconditioning occurs during microgravity exposure because the heart no longer has to work as hard to send blood towards the head against gravity (Tanaka et al., 2017), as fluid shifts

towards the head have already occurred during weightlessness (Williams et al., 2009). This leads to reduced load on the heart, which no longer requires large contractility, resulting in cardiac muscle atrophy (Tanaka et al., 2017). While the risk of cardiac arrest is a concern during spaceflight, the risk amongst the astronaut population is low due to selection and medical screening procedures (Hinkelbein et al., 2018). Upon return to Earth, however, cardiac muscle atrophy becomes a greater concern (Evans et al., 2018).

Upon return to a gravity loaded environment, astronauts need the full functionality of the heart to maintain hemodynamics, but due to cardiac muscle atrophy during spaceflight the heart may be deconditioned to a point that there is risk of syncope (Tanaka et al., 2017). In combination with decreased plasma volume, atrophy of the heart may be partially responsible for inducing orthostatic intolerance upon return to Earth (Tanaka et al., 2017), which presents a risk to astronauts as they may be unable to stand and be at greater risk of falling (Evans et al., 2018; Kaderka et al., 2010). While cardiac muscle atrophy may be partially responsible for the medical risk to astronauts upon return to Earth, it is ranked lower that hemodynamics and vascular function as it is the fluid shift during microgravity exposure that results in cardiac muscle atrophy (Tanaka et al., 2017; Williams et al., 2009).

3.4.4.3. Biomarkers of cardiovascular deconditioning

Biomarkers of cardiovascular deconditioning describes the use of chemical biomarkers to assess the functional state of the cardiovascular system and provide indirect information on the relationship between proteomic data and the physiological effects of spaceflight (Pastushkova et al., 2019). Using biomarkers can provide some technical advantages over direct measures of cardiovascular function, such as greater availability, stability (Pastushkova et al., 2019), and easier access to astronauts who are a difficult to access study population (Capri et al., 2019). However, biomarkers are indirect measures which make it difficult to determine, based on these outcomes alone, what meaningful changes are occurring during spaceflight. As such, they were ranked lower in terms of the medical value to astronaut health and mission success than the more direct outcomes related to hemodynamics and vascular function, and cardiac muscle atrophy.

3.4.4.4. Pulmonary ventilation and gas exchange

Pulmonary ventilation and gas exchange describe outcomes involved in the exchange of gas between air and blood, which is the primary function of the respiratory system (Rudolf, 1983). Pulmonary ventilation and gas exchange are imperative for maintaining consciousness (Larson, Drew, Folkow, Milton, & Park, 2014). The interruption of oxygen supply to the brain for only a few minutes can lead

to irreversible damage to the brain (Larson et al., 2014). As such, it is important to ensure pulmonary and gas exchange alterations during microgravity do not present a danger to astronauts.

While bed-rest studies have suggested that pulmonary ventilation and gas exchange, such as respiratory muscle strength and pulmonary ventilation, may be compromised during spaceflight (Montmerle, Spaak, & Linnarsson, 2002; Prisk et al., 2006), operational spaceflight studies have indicated that exposure to microgravity leaves the pulmonary system largely unaltered (Hinkelbein et al., 2018; Prisk et al., 2006). Most outcomes that reported a change between pre- and post-flight values did so only during spaceflight of over 100 days. No change was often reported for shorter-duration spaceflight, particularly between 9 and 14 days. This may indicate that microgravity related adaptations of the pulmonary system primarily occur during longer-duration spaceflights and as such may only be medically relevant during extended stays in outer-space or during future missions to other planets. However, so long as normal oxygen levels are maintained during spaceflight there should be not be clinically significant deconditioning of the pulmonary system (Prisk et al., 2006). As such, outcomes related to pulmonary ventilation and gas exchange were ranked the least medically relevant to astronaut health and mission success.

3.4.5. Research Gaps and Limitations

The conclusions of this review are limited by a common failure of studies across the evidence base to report key outcome data, and the use of pooled measurements across spaceflights of different lengths. Specifically, this review identified: a lack of study replication and standardisation, evidenced by the extreme heterogeneity in the use of outcome measures; a failure to report pre-flight mean and standard deviation scores necessary for calculating standardised effect size scores; and the reporting of pooled data if spaceflight took place over multiple flights, which created difficulty in establishing additional sources of heterogeneity such as the exercise countermeasures used or the days of spaceflight the study took place over for individual astronauts. These limitations have made it both difficult to compare results using standardised effect sizes and have made gold-standard meta-analysis impossible to achieve as the evidence-base is too heterogeneous or would break statistical assumptions of the meta-analysis conducted (Peters et al., 2008).

Of the 616 outcomes unique outcomes identified in this review, only 63 had been reported in more than a single study, highlighting the extremely high level of heterogeneity in the use of outcome measures. This finding demonstrates the difficulty in comparing interventions across the evidence base when studies are not employing standardized outcome measures, which may undermine evidence-based medical practice. It is rare that a single study can provide enough evidence to address any given research question, and study replication is the preferred approach for addressing this issue (Cheung, 2019). Given that many of the results reported in this review are supported by only a single

study, it suggests that medical guidance may be based upon information where no attempt at replication has been made. This is further exacerbated by astronaut samples often being low in number (Winnard, Bruce-Martin, et al., 2020) which may lead to a failure to detect an important effect or not provide enough statistical power to the study for it to be of use in evidence-based medicine (Hickey, Grant, Dunning, & Siepe, 2018). These problems may have occurred because space agencies can reject research proposals that are not original. Funders may need to acknowledge the value of standardized outcome measures to enable researchers to produce a consistent evidence base that can be pooled with systematic review methods, including meta-analysis. It may be useful to consider an oversight group with representation from medical operations, researchers, and systematic review methods experts to enable a careful balance between standardized outcomes and improving measures over time. This may help to ensure that methods are useful to end users, logistically workable, valid, and reliable for researchers, and that the results are able to feed into high quality systematic review synthesis for reviewers. In doing so, high quality and auditable synthesis for evidence-based practice can be supported and enabled. It is recommended that space agencies consider accepting studies that involve replication and that researchers push to use homogenous outcome measures of relevance that have been identified in this review. For example, there are several methods of measuring muscle fibre types, and over the past decade the case has been made that myosin heavy chain isoform identification has become the preferred method of fibre typing in the skeletal muscle literature (Pandorf et al., 2010). It would be beneficial for space agencies and researchers to discuss and reach consensus upon standardized measurements and outcome measures, such as the use of myosin heavy chain isoform identification, in order to produce more homogenous research.

Most of the studies identified in this review failed to report the necessary information to calculate effect sizes. Studies that fail to provide the necessary information to calculate effect size changes or include statistics which are not suitable for use in meta-analysis (e.g. statistical significance) are common challenges encountered when conducting a meta-analysis and not unique to the space medicine field (Morris & DeShon, 2002). However, this limitation also makes it difficult to compare the impact of spaceflight between individual outcomes using standardized effect sizes as they could not be reported for every outcome. While this review has reported if an outcome changed significantly between pre and post flight scores when effect sizes scores could not be calculated, some studies have also not reported if changes observed were statistically significant. It is strongly recommended that future spaceflight studies report both the pre- and post-flight mean (and standard deviation) scores and the number of participants in both, within the manuscript or include a supplementary materials addition to their manuscript in which these scores are provided so that standardized effect sizes can be calculated and compared. Doing so will reduce the heterogeneity of measures and bring the field closer to enabling meta-analysis.

Many studies included pooled data from multiple spaceflights (which may have used different exercise countermeasures) or multiple astronauts who took part in differing lengths of spaceflights, obscuring which countermeasures were used during that study or how long individual astronauts were exposed to microgravity conditions, making it difficult to draw conclusions on the effects of microgravity exposure on individual outcomes. Several studies did not report the number of days of spaceflight, or did not report them individually for each astronaut and instead reported only the minimum and maximum days of spaceflight across all participants, further exacerbating the difficulty in determining how long individual astronauts were exposed to microgravity conditions and what impact this had on outcomes. Where it would not break anonymity, it is recommended that future spaceflight studies include the exercise countermeasures used during that spaceflight for each astronaut, the specific number of days during which individual astronauts were involved in spaceflight, and that results are presented individually if there are inconsistencies in the number of days of spaceflight or spaceflight missions the astronauts took part in.

Where a large pool of empirical studies is available which examine the same outcome, meta-analysis is appropriate for the pooling of this data (Cheung, 2019). However, traditional meta-analysis assumes independence of observations (Cheung, 2019; Peters et al., 2008) which is not ethically possible during spaceflight as it would involve placing a no-countermeasure control group in outer-space. While some suggestions have been made for implementing meta-analysis within repeated measure studies (Cheung, 2019; Peters et al., 2008), these methods can often violate statistical assumptions or may not be applicable due to methodological issues within the included studies (Peters et al., 2008). This is particularly true of human spaceflight research which is subject to a number of methodological issues, such as a difficulty obtaining pre- and post-flight data at the same time across multiple studies, which may introduce bias or eliminate some methods of a repeated measures meta-analysis (Peters et al., 2008). This presents a serious challenge for spaceflight research as the lack of controlled trials prevents the sector as a whole from implementing meta-analysis, which is considered the gold standard and highest level of evidence possible within medicine-based research (Sutton et al., 2007). By implementing the recommendations made in this review to reduce the heterogeneity of outcomes and encourage standardized reporting, many of the challenges preventing repeated-measure meta-analysis in space medicine studies will be addressed.

It is possible that data or additional evidence exists within internal or classified space agency documents that are not yet publicly available, published for researchers, or peer-reviewed, which are used in decision making. While this data cannot be accessed, this review provides the most comprehensive identification and synthesises of the publicly available data and barriers to existing and future research goals. However, evidence-based practice requires full synthesis of all available data so that it can be independently audited, subject to scrutiny, and scored for quality (Gopalakrishnan & Ganeshkumar, 2013; Liberati et al., 2009; Stevens, 2001). The AMSRG advocates

an evidence-based medicine approach to space medical operations, as described by Cochrane, to integrate clinical expertise with the best available external clinical evidence from systematic reviews (Tanjong-Ghogomu, Tugwell, & Welch, 2009). In this context evidence based-medicine is defined as a process to strengthen the scientific foundation of medicine and reduce uncertainties in operational decision making. Within this, clinical experience and clinical evidence differ, and evidence-based medicine is not meant to diminish operational experience but add to it by presenting the best quality synthesis of all currently available external research. The best synthesis is achieved when trial data and sources of grey and unpublished data are able to be combined to represent the true complete evidence base (Shah & Chung, 2009). There is evidence that unpublished data are occasionally misleading and may not include sufficient methods details to assess quality or bias that risks them being unreliable (Ziai, Zhang, Chan, & Persaud, 2017). For this reason, it is recommended that agencies move towards publishing data used in medical decision making so it can be included in independent, high quality synthesis as part of a fully evidence based practice approach to the sector, conforming to Cochrane and PRISMA standards as the globally recognised leaders of evidence based medicine approaches (Liberati et al., 2009; Moher et al., 2015; Shah et al., 2009). In doing so, complete data synthesis and review can be undertaken and so that the research community can provide more thoroughly informed recommendations and conclusions regarding skeletal deconditioning during spaceflight. This recommendation follows previous calls from Chapter 2 for data to be made public in an officially published document, preferably through the peer-reviewed process, rather than through disparate gray literature. The detailed methodological information provided in this review provides a means to update this review when currently unpublished space agency data is released to the public. To continue failing to develop the space medicine field in the ways these reviews recommend places future space medicine professionals in a difficult position of trying to make sense of an ever growing, disparate and highly complex evidence base that will remain impossible to synthesise using the gold standard, globally accepted methods that have already been used in terrestrial medicine for many years (Sutton et al., 2007). This is particularly important for space medicine, as astronaut studies often use low sample studies (Winnard, Bruce-Martin, et al., 2020), the results of which must be cumulated through meta-analysis to provide an indication of both if the results are consistent and if so what the magnitude of those findings are estimated to be (Levine, Asada, & Carpenter, 2009).

That these issues were commonly identified across the muscle, skeletal and cardiovascular evidence base (accounting for the majority of physiological spaceflight related outcomes) is evidence of an extreme, sector wide problem that may need to be addressed at a sector level. Of greatest concern is the extreme level of heterogeneity in the use of outcome measures and the severe lack of study replication that prevents the implementation of gold-standard meta-analysis techniques (Sutton et al., 2007). For clarity, across the entire musculoskeletal and cardiovascular fields of space medicine,

where a total of 616 outcomes have been reported across 84 published studies concerning spaceflight deconditioning, only 63 of the 616 outcomes have been reported in more than a single study. That the same limitation was identified across all three evidence-bases suggest that as a whole the current space medical guidance for the prevention of musculoskeletal and cardiovascular deconditioning is not based upon the highest possible level of the evidence hierarchy (meta-analysis) (Sutton et al., 2007) and is instead based upon low-sample data that in most cases has not been replicated.

That the same limitations exist in three of the most prominent sectors of the space medicine evidence base adds further weight to the need to review and take action to improve standards across the musculoskeletal and cardiovascular fields. If space medicine guidance is to be based upon reliable information then it is imperative that researchers aim to improve the standardisation of outcome measures and implement minimal reporting standards to bring space medicine in line with terrestrial medicine fields, such as through the use of meta-analysis. Without the capability to implement meta-analysis, space medicine is prevented from implementing the highest level of the evidence hierarchy (Sutton et al., 2007), which undermines the capability of space medicine decision making and operational guidelines to be truly evidence based in a transparent and auditable way. The continued and extremely heterogeneous use of outcome measures identified in this review demonstrates the difficulties that future space medicine professionals will be placed in when trying to make sense of an ever-growing, disparate and highly complex evidence base. If the recommended actions called for in both this review and the previous two reviews are not enacted, then it will remain impossible to synthesise these outcomes using the gold standard, globally accepted methods that have already been used in terrestrial medicine for many years (Sutton et al., 2007). The inherent limitations of spaceflight research that result in low-sample size study populations, such as the time and financial cost of training astronauts (Winnard, Bruce-Martin, et al., 2020), increase the need to reduce the heterogeneity of study outcomes and increase study replication of the most medically and operationally relevant physiological outcomes. This is because the results of space medicine studies can then be cumulated through meta-analysis to provide an indication of both if the results are consistent and if so what the magnitude of those findings are estimated to be (Levine et al., 2009).

Methodological limitations of the review should also be considered. The Cochrane handbook recognises that it is possible studies may be missing from a review, which can occur because the data were never published, were published in obscure places, were inappropriately indexed in databases, or were rarely cited (Higgins et al., 2020). While every step, following both Cochrane and AMSRG guidelines has been taken to reduce the risk of missing data, it should be acknowledged that the possibility of missing data exists.

To address the limitations identified across the space medicine evidence base, it is strongly recommended that space agencies encourage the replication of existing studies to help increase

statistical power, and that they prioritise the use of relevant pre-existing outcomes, as identified in these reviews, to standardise the evidence base. Future researchers are also recommended to report both pre- and post-spaceflight data, specifically the mean, standard deviation and number of participants, so that standardised effect size scores can be calculated. Where possible, and where it would not break the anonymity of participants, researchers should report the exercise countermeasures used during spaceflight for each astronaut; and the report the number of days of spaceflight (for each mission, if multiple spaceflights are reported for a single astronaut) that each astronaut took part in. Implementing these recommendations will help to increase the statistical power of samples heterogeneous enough to be pooled from the evidence base, and allow for comparisons between outcomes using standardised effect size measures. It would be beneficial for researchers to discuss and agree upon standardised measurements, common outcome measures, and study protocols that can lead to more homogeneous outcome reporting (Winnard et al., 2021). The medical and operational rankings listed within this review could also form a basis for discussion and reaching consensus upon which outcomes are most relevant to undergo study replication, given the inherent time and financial costs of spaceflight research.

3.4.6. Conclusions

This review identified 616 individual physiological outcome measures related to musculoskeletal and cardiovascular health, placing them into broad themes and ranking their relevance to astronaut health and operational success using thematic analysis. For muscle outcomes, functional and mechanical properties were of greatest relevance, followed by architectural and structural properties and then biomarkers of muscular deconditioning. For skeletal outcomes, skeletal functional and mechanical properties were the most relevant, followed by measures of volumetric bone mineral density; then biomarkers of bone remodelling; followed by measures of bone mineral density, and then skeletal architectural and structural properties. For cardiovascular outcomes, hemodynamics and vascular function were of greatest relevance, followed by cardiac muscle deconditioning, biomarkers of cardiovascular deconditioning, and then pulmonary ventilation and gas exchange. Common limitations were identified that are shared by the entire musculoskeletal and cardiovascular evidence-base, placing a serious limitation on the current use of space medicine guidance which appears to be based upon mostly un-replicated research that does not implement the highest possible level of the evidence hierarchy, meta-analysis. These limitations included the extremely heterogeneous use of outcome measures, the small sample sizes of studies included, the inability to perform meta-analysis, a lack of reported data, and the pooling of data across multiple spaceflight of different lengths. Space agencies are recommended to prioritise the replication of studies that use relevant, pre-existing outcomes as identified in this review. Future researchers are recommended to report the pre- and post-flight data necessary to calculate standardised effect sizes and, where possible, to report the exercise

countermeasures used and to not pool data across spaceflights of different lengths. By implementing the recommendations made in this review, medical guidance can be based upon replicated evidence that can undergo gold-standard meta-analysis and the information can be used to improve astronaut safety guidelines, and aid the development of countermeasure design for future Lunar and Mars exploration missions. Doing so will enable truly evidence based guidelines based on transparent and auditable data, which is a necessary measure for the sector to be able to claim it engages in high-standard evidence based medicine.

4. Chapter Four: Identifying the most effective exercise countermeasures for musculoskeletal and cardiovascular deconditioning

4.1. Introduction

To enable recommendations of relevant exercise countermeasures for use on-board the MPCV, it was first necessary to identify the technical constraints of the MPCV that would limit or prevent current ISS countermeasures and to identify the musculoskeletal and cardiovascular outcomes of relevance to astronaut health and operational mission success. Chapter 2 identified the technical constraints of the Orion MPCV, which included low volume of exercise space, low upload mass for exercise equipment, low/no power supply, noise limits, maximum duration of exercise to comply with environmental system filters, and data transmission restrictions. Chapter 3 then identified the most relevant musculoskeletal and cardiovascular outcomes during microgravity exposure. For muscle outcomes, in descending order of importance, these were functional and mechanical properties, architectural and structural properties, and biomarkers of muscular deconditioning. For skeletal outcomes, these were skeletal functional and mechanical properties, measures of volumetric bone mineral density, biomarkers of bone remodelling, measures of bone mineral density, and skeletal architectural and structural properties. For cardiovascular outcomes, these were hemodynamics and vascular function, cardiac muscle deconditioning, biomarkers of cardiovascular deconditioning, and then pulmonary ventilation and gas exchange.

To overcome the technical constraints of the MPCV, NASA has opted to implement a flywheel-based exercise device for use on Orion missions of up to 30 days in space (M. Downs, personal communication, October 1, 2020). The flywheel (Figure 4.1) is a gravity-independent exercise countermeasure which generates resistance during the eccentric phase of movement from energy applied to the device during the concentric phase of movement (Belavý, Ohshima, Rittweger, & Felsenberg, 2017).

Figure 4.1 A commercial flywheel device with harness attachment (Simplifaster, 2017)

While a flywheel-based device has been selected for use on-board Orion, there is no publicly available synthesis of the available literature to evidence if a flywheel exercise device is the most suitable exercise countermeasure available. A range of other exercise devices and prescriptions exist which may also meet (or may potentially be modified to meet) the technical constraints of Orion, including the gravity independent inertial ergometer (Trappe, Burd, Louis, Lee, & Trappe, 2007), cycle ergometer (Shibata, Perhonen, & Levine, 2010), treadmill (Schneider et al., 2016), resistive exercise (Trappe et al., 2008), resistive vibration exercise (Salanova et al., 2014), rowing ergometer (Krainski et al., 2014), horizontal leg press (Akima et al., 2003), horizontal sledge jump system (Koschate, Thieschäfer, Drescher, & Hoffmann, 2018), or a combination of these exercise devices. The synthesis of countermeasure trials from both spaceflight and terrestrial microgravity simulations could help to inform stakeholders which exercise device is the most appropriate exercise countermeasure for use on-board Orion and whether any priority musculoskeletal or cardiovascular outcomes, as identified in Chapter 3, are found to be unaccounted for by these exercise prescriptions. The results of this synthesis can then be used to help inform countermeasure device design and implementation by recommending exercise interventions based upon the publicly available data.

The aim of this systematic review was to identify and synthesise evidence from actual or simulated microgravity exercise countermeasure trials to determine the most effective intervention for reducing musculoskeletal and cardiovascular deconditioning during spaceflight.

4.2. Methods and Materials

4.2.1. Pre-scoping

A pre-scoping search of the literature was carried out using Cochrane Library Central Database, which also integrates records from MEDLINE/PubMed, CINAHL, ClinicalTrials.gov, and WHO's ICTRP RCTs and CTs, Embase RCTs, and KoreaMed RTs (Cochrane, 2020), to determine the participants/population, interest/intervention, context/control and type of studies (PICOS (Higgins et al., 2011)) to be included in this review (Appendix C). Pre-scoping was also used to identify relevant MeSH terms for use during the systematic search.

The search strategy for the databases was informed by pre-scoping in order to ensure each search would capture the most relevant results possible. The final search terms were decided based upon pre-scoping and then confirmed through a review of academic colleagues within the AMSRG (JL and AW).

4.2.2. Search Strategy

The search strategy implemented a range of terms (Table 4.1) that were used in combinations to search the Cochrane Library Central Database in October 2020.

Table 4.1 Systematic Review Search Strategy

Search number	Term	Key words in Boolean search format	Reason	Search mask
1	Microgravity and simulations	(spaceflight OR “space flight” OR space-flight OR astronaut* OR cosmonaut* OR taikonaut* OR microgravity OR “micro gravity” OR weightless* OR “space simulation” OR “spaceflight simulation” OR “space-flight simulation” OR “microgravity simulation” OR “bed rest” OR bedrest OR bed-rest OR “dry immersion” OR dry-immersion OR unloading OR unloaded OR “parabolic flight”)	Limiting studies to microgravity or simulations	Title, Abstract, Keyword
2	[MeSH] Microgravity and simulations	Weightlessness Simulation OR Weightlessness OR Space Flight	MeSH terms for Microgravity and simulations	Single MeSH term, unexploded
3	Exercise interventions/countermeasures/Rehabilitation	(Exercis* OR train* OR program* OR countermeasure* OR counter* OR protect* OR “physical activity” OR sport OR rehabilitate OR rehabilitation OR recover* OR maintain OR prevent* OR treat*)	Locate studies which consider exercise countermeasures	Title, Abstract, Keyword
4	[MeSH] Exercise interventions/countermeasures/Rehabilitation	Weightlessness Countermeasures	MeSH terms for exercise interventions/countermeasures/rehabilitation	Single MeSH term, unexploded
5	Musculoskeletal and Cardiovascular outcomes	(“Muscle strength” OR “muscular strength” OR “muscle function” OR “muscular function” OR “muscle power” OR “muscular power” OR “muscle force” OR “muscular force” OR musc* OR Skeletal OR skeleton OR bone OR Cardiovascular OR vascular OR heart* OR cardiopulmonary OR pulmonary)	Locate studies which consider musculoskeletal or cardiovascular outcomes	Title, Abstract, Keyword
6	[MeSH] Musculoskeletal and Cardiovascular outcomes	Musculoskeletal System OR Cardiovascular Deconditioning	MeSH terms for musculoskeletal and cardiovascular outcomes	Single MeSH term, unexploded
7	Microgravity and simulations + MeSH	(#1 OR #2)	Combine results for microgravity and simulations and their MeSH terms.	Title, Abstract, Keyword / Single MeSH term, unexploded
8	Exercise countermeasures + MeSH	(#3 OR #4)	Combine results for exercise countermeasures and their MeSH terms	Title, Abstract, Keyword/Single MeSH term, unexploded

Search number	Term	Key words in Boolean search format	Reason	Search mask
9	Musculoskeletal and cardiovascular outcomes + MeSH	(#5 OR #6)	Combine results for musculoskeletal and cardiovascular outcomes and their MeSH terms	Title, Abstract, Keyword/ Single MeSH term, unexploded
10	Combined Search	#7 #8 #9	Search for trials (RCTs and CTs) that include actual or simulated microgravity exposure, exercise countermeasures, and musculoskeletal or cardiovascular outcomes	Title, Abstract, Keyword/ Single MeSH term, unexploded

4.2.3. Inclusion Criteria

Studies that did not meet the PICOS inclusion criteria were excluded. No restrictions on publication date or status were applied. Only documents in English were included. The full inclusion criteria are presented in Table 4.2.

Table 4.2 PICOS Eligibility criteria

Participants/**P**opulations	**I**nterventions/**I**nterest	**C**ontrols/**C**omparisons	**O**utcome Measures	**S**tudies
Healthy human participants with no comorbidities that could impact exercise capabilities or muscle outcomes.	Exercise intervention/ countermeasure only and not in combination with pharmacological treatments. Exercise intervention/countermeasure must be used during/as a countermeasure to microgravity/microgravity simulation. Microgravity simulations must be capable of producing fluid shift in order to examine cardiovascular effects.	Non-exercise control group, treated equally to intervention group in all other aspects of the trial (prevention of performance bias).	Any musculoskeletal or cardiovascular outcomes, e.g. as identified in Chapter 3.	Peer-reviewed independent groups Randomised Controlled Trials (RCT) and peer-reviewed independent groups Controlled Trials (CT), English language only.

4.2.4. Study Selection and Data Extraction

The initial screening of documents, using abstracts and titles, was carried out by the lead author (JL) and an academic colleague (PS) using the Rayyan systematic review web app software (Ouzzani et al., 2016). Each colleague was blinded to the inclusion or exclusion of documents by the other. If it was unclear from the initial screening whether a study met the inclusion criteria, the full text of the document was obtained. Any conflict or uncertainty in study inclusion was discussed once blinded screening had been completed to come to a decision and decided upon by a third co-author (JD) if consensus could not be reached. Data were extracted using the AMSRG study information and data extraction spreadsheet (Winnard et al., 2018) by the lead author (JL) and two academic colleagues (AL and KL), and disagreements were discussed to reach consensus.

4.2.5. Quality Assessment

The quality of included studies was assessed using the Physiotherapy Evidence Database Scale (PEDro) risk of bias assessment tool (Maher, Sherrington, Herbert, Moseley, & Elkins, 2003) by the lead author (JL) and an academic colleague (JD), and disagreements were discussed to reach consensus. PEDro is one of the most used methodological tools for scoring methodological quality in physiotherapy and exercise trials (Yamato, Maher, Koes, & Moseley, 2017) and has been externally evaluated for use as a suitable tool in the evaluation of methodological quality (Moseley et al., 2015) and quantifying risk of bias (Moseley et al., 2019). While Cochrane have developed a risk of bias tool, the Cochrane Risk of Bias Tool 2 (Sterne et al., 2019), it has been shown to have low interrater reliability and challenges in its implementation even for raters with substantial systematic reviewing experience (Minozzi, Cinquini, Gianola, Gonzalez-Lorenzo, & Banzi, 2020).

PEDro assesses quality of randomised and quasi-randomised controlled physiotherapy trials across 11 items: inclusion criteria and source; random allocation; allocation concealment; baseline comparability; blinding of subjects; blinding of therapists; blinding of assessors; over 85% follow-up; intention-to-treat analysis; between-group comparison; and point estimates and variability (Yamato et al., 2017). The number of "yes" responses across items 2-11 are totalled for an overall score which ranges from 0-10, with item 1 not being used in the calculation as it is a measure of external validity (Yamato et al., 2017). A higher score indicated a lower risk of bias.

4.2.6. Data Analysis

Data analysis followed the procedures outlined and recommended by the AMSRG (Winnard et al., 2021). Quantitative data (mean, standard deviation and number of participants) for the intervention and control groups were extracted using the AMSRG data extraction spreadsheet (Winnard et al., 2018), and from these data Hedge's *g* effect size scores were calculated. The calculated effect sizes

were bias corrected using the Hedge's *g* method to account for sample size by using weighted pooled standard deviations (Ellis, 2010). Hedge's *g* effect sizes are more suitable to space medicine reviews than traditional Cohen's *d* effect sizes as astronaut and bedrest study sample sizes are often small in comparison to traditional medicine reviews (Stokes et al., 2016). To interpret the magnitude of effect sizes, thresholds reported by Rosenthal (1996) were used, as recommended by the AMSRG quantitative systematic review guide (Winnard, Bruce-Martin, et al., 2020). These thresholds were defined as small (0.2), medium (0.5), large (0.8), and very large (1.3) between pre and post spaceflight scores. Confidence interval level for effect size comparison was set at 95%. It should be noted that Rosenthal (1996) emphasised that these effect size cut offs are generic and not specific to any one review area. Where a study reported results from multiple time points, the data immediately prior (for baseline scores) and following (for post-experimental scores) actual or simulated microgravity were used to ensure the greatest consistency across all studies.

Where sufficient data existed, outcomes were arranged into groups based upon the outcome groups developed in Chapter 3 (e.g. all muscle volume outcomes were grouped together) to undergo meta-analysis, following a χ^2 (with I_2) test which assessed homogeneity of the included studies. I_2 can be used as a measure of the impact of heterogeneity, representing the proportion in total variability that can be attributed to heterogeneity rather than random chance (Purgato & Adams, 2012). Following thresholds from the Cochrane systematic review handbook (Higgins et al., 2020), studies which were both above a P value of 0.10 in the χ^2 test and scored less than or equal to 40% for heterogeneity on the I_2 test were included for meta-analysis. It should be noted that the handbook also discusses that care must be taken with the interpretation of the χ^2 test, as it has low power in meta-analysis when sample sizes are small, and debate exists over if heterogeneity is inevitable in meta-analysis due to clinical and methodological diversity (Higgins et al., 2020). Groupings that were too heterogenous to undergo meta-analysis were not included in the ranking system. Where sufficient data were not available for meta-analysis, un-pooled Hedge's *g* effect sizes were reported instead.

To determine which exercise interventions were the most effective, a multi-factor ranking system was developed. All data for use within the ranking system used absolute values. Initial points were given based on beneficial effect size: one for small, two for medium, three for large, and four for very large. Additional points were awarded for the outcomes previously deemed most relevant to astronaut health and space medicine operations in Chapter 3: zero points for outcomes of the lowest rank, one point for the next highest rank, two points for the next highest rank, and so on (for example, muscle outcomes relating to architectural and structural properties would receive no additional points, while outcomes related to functional and mechanical properties would receive one additional point). Negative points were given following the same scale for both the initial and health rankings where outcomes showed harmful effects. This system allowed conclusions to be made regarding the most effective and

medically relevant interventions to utilise in the Orion MPCV. The ranking system was formulated between the lead author (JL) and an academic colleague (AW) and this chapter provides the first trial of this ranking system.

4.3. Results

1139 studies were identified, including 12 studies following the screening of reference lists, which were reduced to 1086 after duplicates were removed. 954 studies were excluded following title and abstract screening. Full text screening of the remaining 132 studies led to 66 additional exclusions. The final number of studies included in the review were 66 (Figure 7.1).

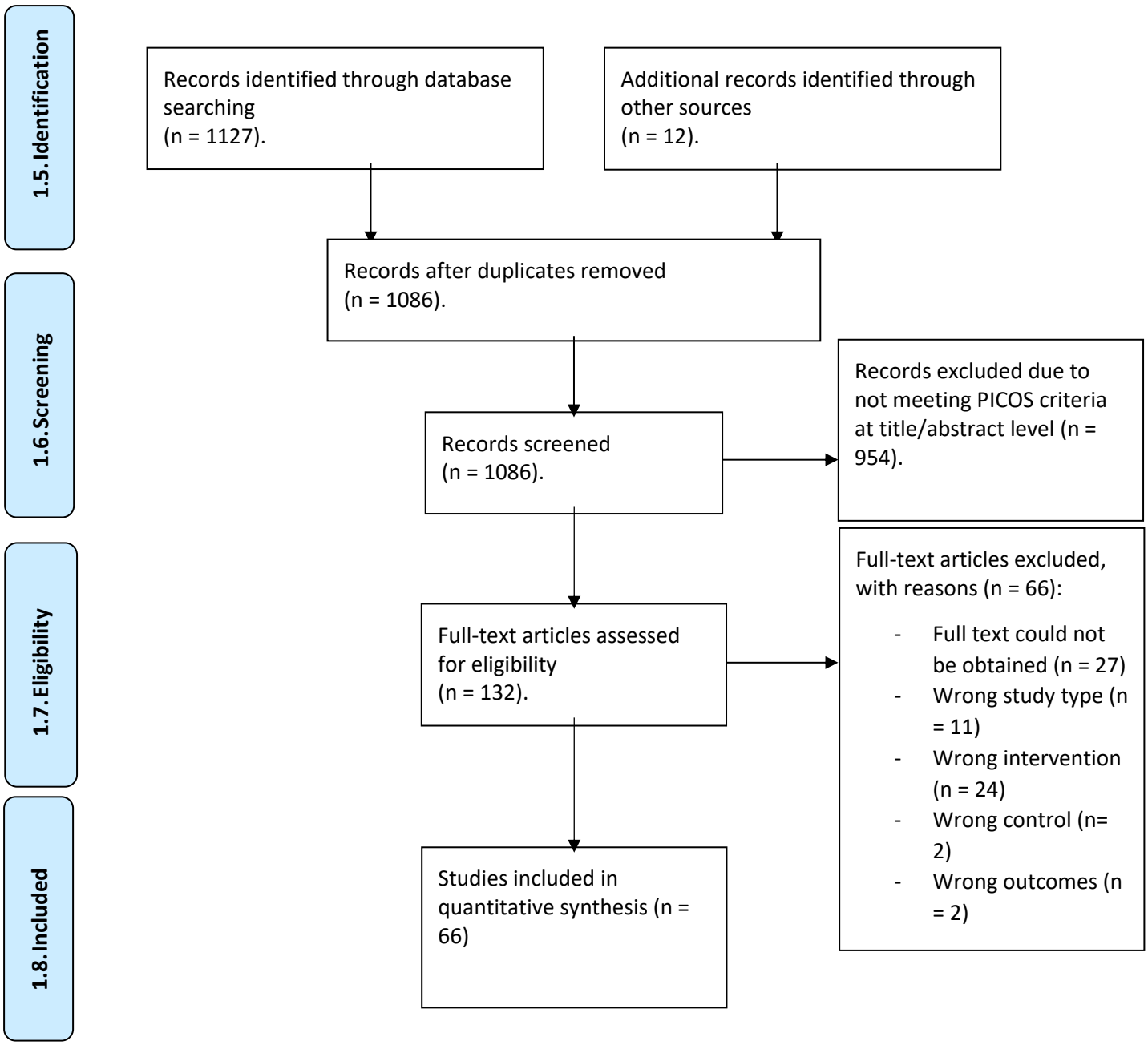

Figure 4.2 PRISMA flow diagram

4.3.1. Characteristics of Included Studies

There were 51 RCTs and 15 CTs. All studies simulated microgravity exposure using the head-down tilt bed rest method, which is a common model to assess the effects of spaceflight upon the human body in a terrestrial setting (Belavý, Ohshima, et al., 2017). No RCTs or CTs from actual spaceflight were identified. Exercise countermeasures used included (alone or in combination): flywheel; treadmill (sometimes with lower body negative pressure); cycle ergometer; rowing ergometer; horizontal leg press; resistive exercise; resistive vibration exercise; horizontal sledge jump system; and the gravity independent inertial ergometer. The characteristics of the included studies are summarised in Table 4.3.

Table 4.3 Characteristics of the Included Studies

Author(s)	Study type	Intervention	N (intervention)	N (control)	Length of simulation (days)	Outcome measure(s)
Akima, Kubo, et al. (2000)	RCT	HLP	5	4	20, HDT	Muscle
Akima et al. (2003)	CT	HLP	6	6	20, HDT	Muscle
Alkner et al. (2004)	CT	FW	8	9	90, HDT	Muscle
Arbeille, Kerbeci, Mattar, Shoemaker, and Hughson (2008)	RCT	FW + Treadmill LBNP	8	8	60, HDT	Cardiovascular
Arinell, Christensen, Blanc, Larsson, and Fröbert (2011)	RCT	FW + Treadmill	8	8	60, HDT	Cardiovascular
Armbrecht et al. (2011)	RCT	FW + Treadmill LBNP	8	8	60, HDT	Skeletal
Bamman, Hunter, Stevens, Guilliams, and Greenisen (1997)	RCT	HLP	8	8	14, HDT	Muscle
Bamman et al. (1998)	RCT	HLP	8	8	14, HDT	Muscle
Belavý et al. (2010)	RCT	RE or RVE	7 (RVE), 8 RE	9	60, HDT	Muscle & Skeletal
Belavy, Beller, Ritter, and Felsenberg (2011)	RCT	RE or RVE	7 (RVE), 8 RE	9	60, HDT	Skeletal
Belavý et al. (2016)	RCT	RE or RVE	7 (RVE), 8 RE	9	60, HDT	Skeletal
Belavý, Gast, and Felsenberg (2017)	RCT	RE or RVE	7 (RVE), 8 RE	9	60, HDT	Muscle & Skeletal
Cao et al. (2005)	RCT	Treadmill LBNP	12	12	28, HDT	Skeletal
Cavanagh et al. (2016)	RCT	Zero-gravity treadmill	5	6	84, HDT	Muscle & Skeletal
Belin de Chantemèle et al. (2004)	RCT	FW	9	9	90, HDT	Cardiovascular
Chopard, Arrighi, Carnino, and Marini (2005)	RCT	FW	8	9	90, HDT	Muscle
Coupé et al. (2011)	RCT	RVE	7	7	60, HDT	Cardiovascular
Crandall, Shibasaki, Wilson, Cui, and Levine (2003)	RCT	Cycle ergometer	12	8	14, HDT	Cardiovascular
Demiot et al. (2007)	RCT	Treadmill LBNP	8	8	60, HDT	Cardiovascular
Dorfman et al. (2007)	RCT	Treadmill LBNP	8	8	60, HDT	Cardiovascular

Author(s)	Study type	Intervention	N (intervention)	N (control)	Length of simulation (days)	Outcome measure(s)
Ferrando, Tipton, Bamman, and Wolfe (1997)	CT	HLP	5	6	14, HDT	Muscle
Germain, Güell, and Marini (1995)	CT	Cycle ergometer + Rowing ergometer	6	6	28, HDT	Muscle
Guinet et al. (2009)	CT	Treadmill LBNP	8	8	60, HDT	Cardiovascular
Hastings et al. (2012)	RCT	Rowing ergometer + RE	18	9	28, HDT	Cardiovascular
Holt et al. (2016)	RCT	FW + Treadmill LBNP	8	8	60 HDT	Muscle
Hughson, Yamamoto, et al. (1994)	CT	RE + LBNP	6	6	28, HDT	Cardiovascular
Hughson, Maillet, et al. (1994)	CT	RE + LBNP	6	6	28, HDT	Cardiovascular
Kawakami et al. (2001)	CT	RE	5	4	20, HDT	Muscle
Koppelmans et al. (2018)	RCT	FW or Cycle ergometer + Treadmill	8 (FW), 5	5	70, HDT	Muscle
Koschate et al. (2018)	RCT	Horizontal sledge jump system	11	11	60, HDT	Cardiovascular
Kouzaki et al. (2007)	RCT	HLP	6	6	20, HDT	Muscle
Krainski et al. (2014)	RCT	Rowing ergometer + RE	18	9	28, HDT	Muscle
Kramer, Gollhofer, Armbrecht, Felsenberg, and Gruber (2017)	RCT	Horizontal sledge jump system	12	11	60, HDT	Muscle & Skeletal & Cardiovascular
Kramer, Kuemmel, et al. (2017)	RCT	Horizontal sledge jump system	12	11	60, HDT	Cardiovascular
Lee et al. (2014)	CT	FW + Treadmill LBNP	8	8	60, HDT	Muscle
Macias, Cao, Watenpaugh, and Hargens (2007)	RCT	Treadmill LBNP	15	15	28, HDT	Skeletal
Maggioni et al. (2018)	RCT	Horizontal sledge jump system	12	11	60, HDT	Cardiovascular
(Miokovic, Armbrecht, Felsenberg, & Belavý, 2011)	RCT	RE or RVE	7 (RVE), 8 (RE)	9	60, HDT	Muscle
Miokovic et al. (2014)	RCT	RE or RVE	7 (RVE), 8 (RE)	9	60, HDT	Muscle
Mulder et al. (2009)	RCT	RE or RVE	7 (RVE), 8 (RE)	9	60, HDT	Muscle

Author(s)	Study type	Intervention	N (intervention)	N (control)	Length of simulation (days)	Outcome measure(s)
Ploutz-Snyder et al. (2018)	RCT	Zero-gravity Treadmill + Cycle ergometer or FW	9 (Treadmill + cycle ergometer), 8 (FW)	9	70, HDT	Muscle & Skeletal & Cardiovascular
Reeves, Maganaris, Ferretti, and Narici (2005)	CT	FW	9	9	90, HDT	Muscle
Rittweger et al. (2005)	RCT	FW	9	9	90, HDT	Muscle & Skeletal
Rittweger, Felsenberg, Maganaris, and Ferretti (2007)	CT	FW	9	9	90, HDT	Muscle
Rittweger and Felsenberg (2009)	RCT	FW	9	9	90, HDT	Muscle & Skeletal
Rittweger, Moller, Bareille, Felsenberg, and Zange (2013)	RCT	FW	9	9	90, HDT	Muscle
Rudnick et al. (2004)	CT	FW	9	9	90, HDT	Muscle
Salanova, Schiffl, Püttmann, Schoser, and Blottner (2008)	RCT	FW	8	8	60, HDT	Muscle
Salanova et al. (2013)	RCT	RE or RVE	8 (RE), 7 (RVE)	9	60, HDT	Muscle
Salanova et al. (2014)	RCT	RVE	8 (RE), 7 (RVE)	9	60, HDT	Muscle
Schneider et al. (2016)	RCT	Treadmill LBNP	15	15	30, HDT	Muscle & Cardiovascular
Scott et al. (2018)	RCT	Zero-gravity Treadmill + Cycle ergometer	9	9	70, HDT	Cardiovascular
Shibata et al. (2010)	CT	Cycle ergometer	14	7	18, HDT	Cardiovascular
Shinohara, Yoshitake, Kouzaki, Fukuoka, and Fukunaga (2003)	RCT	HLP	6	6	20, HDT	Muscle
Smith et al. (2003)	RCT	Treadmill LBNP	8	8	30, HDT	Skeletal
Smith et al. (2008)	RCT	FW + Treadmill LBNP	8	8	60, HDT	Skeletal
Trappe et al. (2007)	CT	Gravity-independent inertial ergometer	8	8	60, HDT	Muscle
Trappe et al. (2008)	CT	RE	8	8	60, HDT	Muscle
van Duijnhoven, Green, et al. (2010)	RCT	RE or RVE	8 (RE), 7 (RVE)	9	60, HDT	Cardiovascular

Author(s)	Study type	Intervention	N (intervention)	N (control)	Length of simulation (days)	Outcome measure(s)
van Duijnhoven, Thijssen, et al. (2010)	RCT	RE or RVE	8 (RE), 7 (RVE)	9	60, HDT	Cardiovascular
Wang et al. (2012)	RCT	RVE	7	7	60, HDT	Skeletal
Watanabe et al. (2004)	RCT	FW	9	9	90, HDT	Skeletal
Watenpaugh et al. (2007)	RCT	Treadmill LBNP	15	15	30, HDT	Cardiovascular
Yang et al. (2014)	RCT	RVE	7	7	60, HDT	Skeletal
Zuj et al. (2012)	RCT	Treadmill LBNP	8	8	60, HDT	Cardiovascular
Zwart et al. (2007)	RCT	Treadmill LBNP	7	7	28, HDT	Skeletal

RCT randomised control trial; *CT* control trials; *RE* resistive exercise; *RVE* resistive vibration exercise; *FW* Flywheel*; LBNP* lower body negative pressure; *HLP* Horizontal Leg-Press; *N* number of participants in each condition; *HDT* Head-down Tilt (Bed Rest).

4.3.2. Quality Scoring

Studies that met the PEDro criteria are considered low RoB for that criteria. A high RoB score does not necessarily indicate that an element (e.g. blinding of outcome assessors) was not used in the study, but rather that it was not reported or unclear. In many cases, a high RoB score was due to a failure to report information accurately, or the needed information was reported elsewhere (e.g. in another study from the same project).

The highest total score was 6, while the lowest was 0. Thirteen studies reported the eligibility criteria (PEDro 1). Thirty-seven studies reported (true) random allocation (quasi-randomisation is not considered randomisation for the PEDro scale) (PEDro 2). Two studies reported the use of concealed allocation (PEDro 3). Twenty-four studies reported groups to be similar at baseline (PEDro 4). No study reported blinding of all subjects (PEDro 5). One study reported blinding of all researchers who administered the intervention (PEDro 6). Eleven studies reported blinding of assessors who measured at least one key outcome (PEDro 7). Thirty-seven studies obtained measures of at least one key outcome for more than 86% of participants initially allocated to groups (PEDro 8). Fourteen studies reported that all subjects for whom outcome measures were available received the treatment or control as allocated, or, where this was not the case, data for at least one key outcome were analysed by "intention to treat" (PEDro 9). Forty-five studies reported the data necessary for between-group statistical comparisons for at least one key outcome (PEDro 10). Two studies provided both point measures and measured of variability for at least one key outcome (PEDro 11). Full reporting of PEDro risk of bias scores for each of the included studies can be seen in Table 4.4.

Table 4.4 PEDro Risk of Bias Scores

Author(s)	PEDro 1	PEDro 2	PEDro 3	PEDro 4	PEDro 5	PEDro 6	PEDro 7	PEDro 8	PEDro 9	PEDro 10	PEDro 11	Total score /10
Akima, Kubo, et al. (2000)	✗	✓	✗	✓	✗	✗	✗	✓	✗	✓	✗	**4**
Akima et al. (2003)	✗	✗	✗	✓	✗	✗	✗	✓	✗	✓	✗	**3**
Alkner et al. (2004)	✗	✗	✗	✓	✗	✗	✗	✓	✗	✓	✗	**3**
Arbeille et al. (2008)	✗	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗	**2**
Arinell et al. (2011)	✓	✓	✗	✓	✗	✗	✗	✗	✗	✗	✗	**2**
Armbrecht et al. (2011)	✓	✓	✗	✓	✗	✗	✗	✓	✗	✓	✗	**4**
Bamman et al. (1997)	✓	✓	✗	✓	✗	✗	✗	✓	✗	✓	✗	**4**
Bamman et al. (1998)	✓	✓	✗	✗	✗	✗	✗	✓	✗	✓	✗	**3**
Belavý et al. (2010)	✗	✓	✗	✓	✗	✗	✓	✓	✗	✓	✗	**5**
Belavy et al. (2011)	✗	✓	✗	✓	✗	✗	✗	✗	✗	✓	✗	**3**
Belavý et al. (2016)	✗	✓	✗	✓	✗	✗	✗	✓	✗	✓	✗	**4**
Belavý, Gast, et al. (2017)	✓	✓	✗	✓	✗	✗	✓	✓	✓	✓	✗	**6**
Cao et al. (2005)	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	**0**
Cavanagh et al. (2016)	✓	✗	✗	✗	✗	✗	✗	✓	✗	✗	✗	**1**
Belin de Chantemèle et al. (2004)	✗	✓	✗	✓	✗	✗	✗	✓	✗	✓	✗	**3**
Chopard et al. (2005)	✗	✓	✗	✗	✗	✗	✗	✗	✗	✓	✗	**2**
Coupé et al. (2011)	✗	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗	**1**
Crandall et al. (2003)	✗	✓	✗	✗	✗	✗	✗	✓	✓	✓	✗	**4**
Demiot et al. (2007)	✗	✓	✗	✗	✗	✗	✓	✓	✓	✓	✗	**5**
Dorfman et al. (2007)	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	**0**
Ferrando et al. (1997)	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	**0**
Germain et al. (1995)	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	**0**
Guinet et al. (2009)	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	**0**
Hastings et al. (2012)	✗	✗	✗	✓	✗	✗	✗	✓	✓	✓	✗	**4**
Holt et al. (2016)	✗	✗	✗	✓	✗	✗	✓	✗	✗	✗	✗	**2**
Hughson, Yamamoto, et al. (1994)	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	**0**
Hughson, Maillet, et al. (1994)	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	**0**

Author(s)	PEDro 1	PEDro 2	PEDro 3	PEDro 4	PEDro 5	PEDro 6	PEDro 7	PEDro 8	PEDro 9	PEDro 10	PEDro 11	Total score /10
Kawakami et al. (2001)	✗	✗	✗	✗	✗	✗	✗	✓	✓	✓	✗	**3**
Koppelmans et al. (2018)	✓	✓	✗	✓	✗	✗	✗	✓	✗	✓	✓	**5**
Koschate et al. (2018)	✗	✓	✗	✗	✗	✗	✗	✗	✗	✓	✗	**2**
Kouzaki et al. (2007)	✗	✓	✗	✗	✗	✗	✗	✗	✗	✓	✗	**2**
Krainski et al. (2014)	✗	✗	✗	✓	✗	✗	✓	✓	✗	✓	✗	**4**
Kramer, Gollhofer, et al. (2017)	✓	✓	✓	✓	✗	✗	✗	✗	✗	✓	✓	**5**
Kramer, Kuemmel, et al. (2017)	✓	✓	✓	✗	✗	✗	✗	✓	✗	✓	✗	**4**
Lee et al. (2014)	✗	✗	✗	✗	✗	✗	✗	✓	✗	✗	✗	**1**
Macias et al. (2007)	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	**0**
Maggioni et al. (2018)	✗	✗	✗	✗	✗	✗	✗	✓	✗	✗	✗	**1**
Miokovic et al. (2011)	✗	✓	✗	✓	✗	✗	✓	✓	✗	✓	✗	**5**
Miokovic et al. (2014)	✗	✓	✗	✗	✗	✗	✓	✓	✗	✓	✗	**4**
Mulder et al. (2009)	✗	✓	✗	✗	✗	✗	✓	✓	✗	✓	✗	**4**
Ploutz-Snyder et al. (2018)	✗	✓	✗	✗	✗	✗	✗	✓	✓	✓	✗	**4**
Reeves et al. (2005)	✗	✗	✗	✓	✗	✗	✗	✗	✗	✗	✗	**1**
Rittweger et al. (2005)	✗	✓	✗	✗	✗	✗	✗	✓	✓	✓	✗	**4**
Rittweger et al. (2007)	✗	✗	✗	✓	✗	✗	✗	✓	✗	✓	✗	**3**
Rittweger et al. (2009)	✗	✓	✗	✓	✗	✗	✗	✓	✓	✓	✗	**4**
Rittweger et al. (2013)	✓	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗	**1**
Rudnick et al. (2004)	✗	✗	✗	✗	✗	✗	✗	✗	✗	✓	✗	**1**
Salanova et al. (2008)	✗	✗	✗	✓	✗	✗	✗	✗	✗	✓	✗	**2**
Salanova et al. (2013)	✗	✓	✗	✗	✗	✗	✓	✗	✗	✗	✗	**2**
Salanova et al. (2014)	✗	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗	**1**
Schneider et al. (2016)	✗	✗	✗	✗	✗	✓	✗	✗	✗	✓	✗	**2**
Scott et al. (2018)	✗	✗	✗	✓	✗	✗	✓	✓	✗	✓	✗	**4**
Shibata et al. (2010)	✗	✗	✗	✗	✗	✗	✗	✗	✗	✓	✗	**1**
Shinohara et al. (2003)	✗	✓	✗	✗	✗	✗	✗	✓	✓	✓	✗	**4**
Smith et al. (2003)	✗	✗	✗	✗	✗	✗	✗	✓	✗	✓	✗	**2**

Author(s)	PEDro 1	PEDro 2	PEDro 3	PEDro 4	PEDro 5	PEDro 6	PEDro 7	PEDro 8	PEDro 9	PEDro 10	PEDro 11	Total score /10
Smith et al. (2008)	✓	✓	✗	✗	✗	✗	✗	✓	✓	✓	✗	**4**
Trappe et al. (2007)	✗	✗	✗	✗	✗	✗	✗	✗	✗	✓	✗	**1**
Trappe et al. (2008)	✗	✗	✗	✗	✗	✗	✗	✓	✗	✓	✗	**2**
van Duijnhoven, Green, et al. (2010)	✗	✓	✗	✗	✗	✗	✓	✗	✗	✓	✗	**3**
van Duijnhoven, Thijssen, et al. (2010)	✗	✓	✗	✗	✗	✗	✗	✓	✓	✓	✗	**4**
Wang et al. (2012)	✗	✓	✗	✓	✗	✗	✗	✓	✓	✓	✗	**5**
Watanabe et al. (2004)	✗	✓	✗	✓	✗	✗	✗	✓	✓	✓	✗	**5**
Watenpaugh et al. (2007)	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	**0**
Yang et al. (2014)	✓	✓	✗	✗	✗	✗	✗	✓	✓	✓	✗	**4**
Zuj et al. (2012)	✗	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗	**1**
Zwart et al. (2007)	✗	✗	✗	✗	✗	✗	✗	✓	✗	✓	✗	**2**

✓ = Low risk of bias/PEDro criteria was met; ✗ = High risk of bias/PEDro criteria was not met; PEDro 1 = eligibility criteria were specified; PEDro 2 = subjects were randomly allocated to groups; PEDro 3 = allocation was concealed; PEDro 4 = The groups were similar at baseline regarding the most important prognostic indicators; PEDro 5 = There was blinding of all subjects; PEDro 6 = There was blinding of all therapists who administered therapy; PEDro 7 = There was blinding of all assessors who measured at least one key outcome; PEDro 8 = Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups; PEDro 9 = All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat"; PEDro 10 = The results of between-group statistical comparisons are reported for at least one key outcome; PEDro 11 = The study provides both point measures and measured of variability for at least one key outcome. Higher total scores indicate lower overall risk of bias.

4.3.3. Outcomes Assessed

4.3.3.1. Effect of exercise countermeasures on muscle outcomes

The effect size changes and pooled effect size changes between the exercise and control groups for individual muscle-related outcome groups can be found in Appendix E.

4.3.3.1.1. EMG activity

For EMG activity, there was a very large effect size difference in favour of the exercise condition for the resistive exercise intervention (g = 1.50) (Appendix E, Figure 9.1). A large effect size difference in favour of the exercise group was also observed for the flywheel intervention (g = 0.97) (Appendix E, Figure 9.2) and a medium difference in favour of the exercise condition was displayed for the resistive vibration exercise intervention (g = 0.73) (Appendix E, Figure 9.3). There was a trivial effect size difference in favour of the control group for horizontal leg press (g = 0.07) (Appendix E, Figure 9.4), which did not meet the threshold for a small effect size difference.

4.3.3.1.2. Muscle biomarkers

Muscle biomarker remained unpooled due to the large heterogeneity in the direction of effect for individual biomarkers. This is likely because biomarkers are often indirect measures of a range of other functional, mechanical, structural or architectural outcomes (Capri et al., 2019) and so should be considered individually rather than as a grouped set. For the rowing ergometer + resistive exercise intervention, effect size differences ranged from large (g = 1.14) to very large (g = 1.54) in favour of the exercise condition (Appendix E, Figure 9.5). For the flywheel intervention, effect size differences ranged from medium (g = 0.69) to very large (g = 1.63) in favour of the exercise condition (Appendix E, Figure 9.6).

4.3.3.1.3. Fibre diameter

For fibre diameter, there was a trivial effect size difference in favour of the control condition for the rowing ergometer + resistive exercise intervention (g = 0.08) (Appendix E, Figure 9.7). Data from the resistive vibration exercise intervention were too heterogeneous (P = 0.15, I_2 = 44%) to pool results, which ranged from a small effect size to a very large effect size difference in favour of the exercise condition (g = 0.47 to 2.67) (Appendix E, Figure 9.8).

4.3.3.1.4. Fibre force

For fibre force, the resistive vibration exercise intervention data were too heterogenous to pool results (P = 0.10, I_2 = 41%), however the range of effect size differences spanned from medium (g = 0.58) to very large (g = 3.02) in favour of the exercise condition (Appendix E, Figure 9.9).

4.3.3.1.5. Fibre power

For fibre power, data for the resistive vibration exercise intervention were too heterogeneous (P = 0.006, I_2 = 65%) to pool results, but effect size differences spanned from trivial (g = 0.01) to very large (g = 3.73) in favour of the exercise condition (Appendix E, Figure 9.10).

4.3.3.1.6. Fibre shortening velocity

For fibre shortening velocity, data for the resistive vibration exercise intervention were too heterogeneous to pool results (P = 0.11, I_2 = 50%), but effect size differences ranged from trivial in favour of the control condition (g = 0.01) to very large in favour of the exercise condition (g = 1.69) (Appendix E, Figure 9.11).

4.3.3.1.7. Jump height and power

For jump height and power, the zero-gravity treadmill + cycle ergometer intervention displayed a very large effect size difference in favour of the exercise condition (g = 1.41) (Appendix E, Figure 9.12). Data from the flywheel intervention were too heterogeneous (P = 0.02, I_2 = 58%) to pool results, which ranged from a trivial difference in favour of the control group (g = 0.07) to a very large effect size difference in favour of the exercise condition (g = 2.25) (Appendix E, Figure 9.13).

4.3.3.1.8. Muscle mass

For muscle mass, the treadmill LBNP intervention displayed a trivial difference in favour of the control condition that did not meet the threshold for a small effect size change (g = 0.05) (Appendix E, Figure 9.14). For flywheel + treadmill LBNP, there was a very large effect size difference in leg lean tissue mass in favour of the exercise condition (g = 3.01) (Appendix E, Figure 9.15).

4.3.3.1.9. Muscle strength

For muscle strength, the flywheel + treadmill LBNP intervention studied only leg press load lifted which showed a large effect size difference in favour of the exercise condition (g = 0.89) (Appendix

E, Figure 9.16). For the horizontal sledge jump system intervention, handgrip strength displayed a trivial effect size difference in favour of the exercise condition (g = 0.16) (Appendix E, Figure 9.17). Horizontal leg press data were too heterogeneous to pool results (P = 0.13, I_2 = 57%), but displayed a trivial effect size difference in favour of the exercise condition for one-repetition maximum leg press (g = 0.04) and a large effect size difference in favour of the exercise condition for one-repetition maximum heel raise (g = 1.20) (Appendix E, Figure 9.18).

4.3.3.1.10. T2 relaxation

For T2 relaxation, the horizontal leg press intervention displayed a trivial effect size difference in favour of the exercise intervention (g = 0.13) (Appendix E, Figure 9.19).

4.3.3.1.11. Muscle power

For muscle power, there were very large effect size differences in favour of the exercise group for both the gravity-independent inertial ergometer (g = 2.14) (Appendix E, Figure 9.20) and the flywheel (g = 1.64) (Appendix E, Figure 9.21) interventions. The zero-gravity treadmill + cycle ergometer intervention studied only a single outcome, leg press max power, which indicated a medium effect size difference in favour of the exercise group (g = 0.77) (Appendix E, Figure 9.22).

4.3.3.1.12. Maximal voluntary contraction/muscle force

For maximal voluntary contraction/muscle force, there was a large effect size difference in favour of the exercise group for the flywheel intervention (g = 1.14) (Appendix E, Figure 9.23) and a medium effect size difference in favour of the exercise group for the resistive exercise intervention (g = 0.79) (Appendix E, Figure 9.24). For the zero-gravity treadmill + cycle ergometer intervention only one outcome was studied, leg press isometric force, which displayed a small effect size difference in favour of the exercise group (g = 0.46) (Appendix E, Figure 9.25). Results were too heterogeneous to pool data from the horizontal leg press intervention (P = 0.13, I_2 = 47%), which displayed effect sizes ranging from a small effect size difference in favour of the control group (g = 0.39) to a very large effect size difference in favour of the exercise group (g = 1.42) (Appendix E, Figure 9.26). The resistive vibration exercise intervention was also too heterogeneous to pool data (P = 0.18, I_2 = 45.3%), but showed a small effect size difference in favour of the exercise group for plantar flexion, maximal voluntary contraction (g = 0.43) and a very large effect size difference in favour of the exercise group for knee extension, maximal voluntary contraction (g = 1.50) (Appendix E, Figure 9.27).

4.3.3.1.13. Muscle velocity

For muscle velocity, there was a large effect size difference in favour of the exercise group for the flywheel intervention (g = 0.92) (Appendix E, Figure 9.28).

4.3.3.1.14. Muscle work

For muscle work, a very large effect size difference in favour of the exercise group were observed for both the gravity-independent inertial ergometer (g = 1.63) (Appendix E, Figure 9.29) and flywheel (g = 1.40) (Appendix E, Figure 9.30) interventions. A large effect size difference in favour of the exercise group was displayed for the horizontal leg press intervention (g = 1.19) (Appendix E, Figure 9.31). There was a medium effect size difference in favour of the exercise group for the zero-gravity treadmill + cycle ergometer intervention (g = 0.71) (Appendix E, Figure 9.32). A trivial effect size difference in favour of the exercise group was shown for the treadmill LBNP intervention (g = 0.06) (Appendix E, Figure 9.33). Data were too heterogeneous to pool for the flywheel + treadmill LBNP intervention (P = 0.03, I_2 = 80%), but results showed a very large effect size difference in favour of the exercise group for total work, knee extension (g = 1.85), and a trivial effect size difference in favour of the exercise group for total work, knee flexion (g = 0.08) (Appendix E, Figure 9.34).

4.3.3.1.15. Muscle CSA

For muscle CSA, there was a large effect size difference in favour of the exercise condition for the resistive exercise intervention (g = 0.89) (Appendix E, Figure 9.35). There were medium effect size differences in favour of the exercise condition for the horizontal leg press (g = 0.54) (Appendix E, Figure 9.36), flywheel + treadmill LBNP (g = 0.61) (Appendix E, Figure 9.37), zero-gravity treadmill + cycle ergometer (g = 0.73) (Appendix E, Figure 9.38), and resistive vibration exercise (g = 0.79) (Appendix E, Figure 9.39) interventions. Data were too heterogeneous to pool for the flywheel intervention (P = 0.01, I_2 = 65%), but effect sizes ranged from trivial in favour of the control condition (g = 0.10) to very large in favour of the exercise condition (g = 1.88) (Appendix E, Figure 9.40).

4.3.3.1.16. Fibre CSA

For fibre CSA, there was a large effect size difference in favour of the exercise group for the flywheel intervention (g = 1.04) (Appendix E, Figure 9.41) and a medium effect size difference in favour of the exercise group for the horizontal leg press intervention (g = 0.62) (Appendix E, Figure 9.42). Data were too heterogeneous to pool for the resistive vibration exercise intervention (P < 0.01, I_2 = 97%), but there was a very large effect size difference in favour of the control group for the soleus type I myofibre cross-sectional area (g = -2.18), and a very large effect size difference in favour of the

exercise group for the vastus lateralis type II myofibre cross-sectional area (g = 6.58) (Appendix E, Figure 9.43).

4.3.3.1.17. Fibre composition

For fibre composition, there was a small effect size difference in favour of the exercise condition for the flywheel intervention (g = 0.20) (Appendix E, Figure 9.44), and trivial differences in favour of the control group for the horizontal leg press (g = 0.08) (Appendix E, Figure 9.45) and resistive vibration exercise (g = 0.08) (Appendix E, Figure 9.46) interventions. There was no effect size change for the rowing ergometer + resistive exercise intervention (g = 0.00) (Appendix E, Figure 9.47).

4.3.3.1.18. Muscle thickness

For muscle thickness, there was a small effect size difference in favour of the exercise group for the resistive exercise intervention (g = 0.23) (Appendix E, Figure 9.48) and a trivial effect size difference in favour of the exercise group for the resistive vibration exercise intervention (g = 0.14) (Appendix E, Figure 9.49).

4.3.3.1.19. Muscle volume

For muscle volume, there was a large effect size difference in favour of the exercise group for the gravity-independent inertial ergometer intervention (g = 0.84) (Appendix E, Figure 9.50). There were medium effect size changes in favour of the exercise group for the resistive exercise (g = 0.62) (Appendix E, Figure 9.51) and resistive vibration exercise (g = 0.52) (Appendix E, Figure 9.52) interventions. There was a small effect size change in favour of the exercise condition for the horizontal leg press intervention (g = 0.36) (Appendix E, Figure 9.53).

4.3.3.1.20. Muscle torque

For muscle torque, there were large effect size differences in favour of the exercise conditions for the horizontal leg press (g = 0.84) (Appendix E, Figure 9.54), zero-gravity treadmill + cyce egometer (g = 0.84) (Appendix E, Figure 9.55), and flywheel (g = 0.81) (Appendix E, Figure 9.56) interventions. There was a medium effect size difference in favour of the exercise condition for the resistive vibration exercise intervention (g = 0.53) (Appendix E, Figure 9.57). There were small effect size differences in favour of the exercise conditions for the resistive exercise (g = 0.25) (Appendix E, Figure 9.58), zero-gravity treadmill (g = 0.35) (Appendix E, Figure 9.59), and rowing ergometer + resistive exercise (g = 0.32) (Appendix E, Figure 9.60) interventions. There was a trivial effect size

difference in favour of the exercise condition for the treadmill LBNP intervention (g = 0.08) (Appendix E, Figure 9.61). Data were too heterogeneous to pool for the flywheel + treadmill LBNP intervention (P = 0.05, I_2 = 63%), but effect sizes ranged from trivial (g = 0.11) to very large (g = 2.07) in favour of the exercise condition (Appendix E, Figure 9.62). Data were too heterogeneous to pool for the horizontal sledge jump system (P < 0.01, I_2 = 75%), but effect sizes ranged from trivial (g = 0.13) to very large (g = 2.36) in favour of the exercise condition (Appendix E, Figure 9.63).

4.3.3.2. Effect of exercise countermeasures on skeletal outcomes

4.3.3.2.1. Skeletal biomarkers

Similar to muscle biomarkers, skeletal biomarkers remained unpooled due to the large heterogeneity in the direction of effect for individual biomarkers. There was a small effect size difference in favour of the exercise condition for the flywheel + treadmill LBNP intervention (g = 0.36) (Appendix E, Figure 9.64), while for the treadmill LBNP intervention alone there was a trivial effect size difference in favour of the control condition (g = 0.11) (Appendix E, Figure 9.65). For the flywheel intervention, effect sizes ranged from a large effect size difference in favour of the control condition (g = 1.05) to a very large effect size difference in favour of the exercise condition (g = 1.39) (Appendix E, Figure 9.66). For the zero-gravity treadmill + cycle ergometer intervention, effect sizes ranged from very large in favour of the control condition (g = 1.33) to large in favour of the exercise condition (g = 0.85) (Appendix E, Figure 9.67). For the resistive vibration exercise intervention, effect sizes ranged from large in favour of the control group (g = 1.28) to very large in favour of the exercise group (g = 1.93) (Appendix E, Figure 9.68).

4.3.3.2.2. Bone loss recovery

Flywheel was the only intervention that examined bone loss recovery and showed a large effect size difference in favour of the exercise condition (g = 0.93) (Appendix E, Figure 9.69).

4.3.3.2.3. Bone strength

Bone strength was only examined during the treadmill LBNP intervention. There was a small effect size difference in favour of the exercise condition for lumbar strength (g = 0.43) (Appendix E, Figure 9.70).

4.3.3.2.4. Bone volume

For bone volume, the flywheel + treadmill LBNP intervention displayed a small effect size difference in favour of the exercise condition (g = 0.29) (Appendix E, Figure 9.71). Resistive exercise and resistive vibration exercise interventions only examined a single outcome each, disc volume. Intervertebral disc (IVD) volume displayed a trivial effect size difference in favour of the exercise group for the resistive exercise intervention (g = 0.06) (Appendix E, Figure 9.72) and a small effect size difference in favour of the control condition for the resistive vibration exercise intervention (g = 0.36) (Appendix E, Figure 9.73).

4.3.3.2.5. Skeletal CSA

For skeletal CSA there were trivial effect size differences in favour of the control condition for the resistive exercise (g = 0.04) (Appendix E, Figure 9.74) and resistive vibration exercise (g = 0.02) (Appendix E, Figure 9.75) interventions.

4.3.3.2.6. IVD Height

For IVD height there was a trivial effect size difference in favour of the exercise group for the resistive vibration exercise intervention (g = 0.15) (Appendix E, Figure 9.76). There was a trivial effect size difference in favour of the control group for the resistive exercise intervention (g = 0.13) (Appendix E, Figure 9.77).

4.3.3.2.7. Lumbar lordosis

For lumbar lordosis, the resistive exercise intervention displayed a trivial difference in favour of the exercise condition for L1-S1 lordosis that did not meet the threshold for a small effect size change (g = 0.11) (Appendix E, Figure 9.78). There was a trivial difference in favour of the control group for the resistive vibration exercise intervention for L1-S1 lordosis (g = 0.13) (Appendix E, Figure 9.79). Change in lumbar lordosis with 50% body weight axial load showed a trivial effect size difference in favour of the control condition for the treadmill LBNP intervention (g = 0.18) (Appendix E, Figure 9.80).

4.3.3.2.8. Lumbar compressibility

Lumbar compressibility with 50% body weight axial load showed a medium effect size difference in favour of the exercise condition for the treadmill LBNP intervention (g = 0.77) (Appendix E, Figure 9.81).

4.3.3.2.9. Spinal length

For spinal length, L1-S1 length displayed a medium effect size difference for the resistive exercise intervention in favour of the control group (g = 0.60) (Appendix E, Figure 9.82) and a small effect size difference in favour of the control group for the resistive vibration exercise intervention (g = 0.26) (Appendix E, Figure 9.83).

4.3.3.2.10. Periosteal perimeter

For periosteal perimeter, there was a trivial effect size difference in favour of the control group for the resistive exercise intervention (g = 0.05) (Appendix E, Figure 9.84) and a medium effect size difference in favour of the control group for the resistive vibration exercise intervention (g = 0.65) (Appendix E, Figure 9.85).

4.3.3.2.11. Trabecular network inhomogeneity

Interventions for trabecular network inhomogeneity would be considered beneficial if effect size differences favoured the control condition (indicating the intervention led to lower trabecular network inhomogeneity than no intervention). There was a trivial effect size difference in favour of the exercise group for the resistive vibration exercise intervention (g =0.03) (Appendix E, Figure 9.86) and a small effect size difference in favour of the control group for the resistive exercise intervention (g = 0.31) (Appendix E, Figure 9.87).

4.3.3.2.12. Trabecular number

For trabecular number, there was a small effect size difference in favour of the exercise group for both the resistive exercise intervention (g = 0.39) (Appendix E, Figure 9.88) and the flywheel + treadmill LBNP intervention (g = 0.22) (Appendix E, Figure 9.89). There was a trivial difference in favour of the control group for the resistive vibration exercise intervention (g = 0.03) (Appendix E, Figure 9.90).

4.3.3.2.13. Trabecular separation

Interventions for trabecular separation would be considered beneficial if effect size differences favoured the control condition (indicating the intervention led to lower trabecular separation than no intervention). There was a trivial effect size difference in favour of the control group for both the flywheel + treadmill LBNP (g = 0.12) (Appendix E, Figure 9.91) and the resistive vibration exercise

(g = 0.12) (Appendix E, Figure 9.92) interventions. There was a small effect size difference in favour of the control group for the resistive exercise intervention (g = 0.46) (Appendix E, Figure 9.93).

4.3.3.2.14. Volumetric bone mineral density

For volumetric bone mineral density, there was a medium effect size difference in favour of the exercise group (g = 0.62) for the zero-gravity treadmill intervention (Appendix E, Figure 9.94).

4.3.3.2.15. Bone mineral content

For bone mineral content, there was a medium effect size difference in favour of the exercise condition for the resistive exercise intervention (g = 0.56) (Appendix E, Figure 9.95). There was a trivial effect size difference in favour of the exercise condition for the flywheel intervention (g = 0.15) (Appendix E, Figure 9.96) and there was also a trivial effect size difference in favour of the control condition for the horizontal sledge jump system intervention (g = 0.11) (Appendix E, Figure 9.97). Data were too heterogeneous to pool for the resistive vibration exercise intervention (P = 0.08, I_2 = 44%), but effect size differences ranged from a medium effect size difference in favour of the control group (g = -0.79) to a very large effect size difference in favour of the exercise condition (g = 1.40) (Appendix E, Figure 9.98).

4.3.3.2.16. Bone mineral density

For bone mineral density, there was a small effect size difference in favour of the exercise condition for the flywheel + treadmill LBNP intervention (g = 0.46) (Appendix E, Figure 9.99). There were trivial effect size differences in favour of the exercise condition for the resistive vibration exercise (g = 0.09) (Appendix E, Figure 9.100) and horizontal sledge jump system (g = 0.10) (Appendix E, Figure 9.101) interventions. There was a trivial effect size difference in favour of the control condition for the resistive exercise intervention (g = 0.02) (Appendix E, Figure 9.102).

4.3.3.2.17. Bone thickness

For bone thickness, there were trivial effect size differences in favour of the exercise group for the flywheel + treadmill LBNP (g = 0.18) (Appendix E, Figure 9.103) and resistive vibration exercise (g = 0.04) (Appendix E, Figure 9.104) interventions. A trivial effect size difference in favour of the control group was observed for the resistive exercise intervention (g = 0.11) (Appendix E, Figure 9.105).

4.3.3.3. Effect of exercise countermeasures on cardiovascular outcomes

4.3.3.3.1. Arterial/blood pressure

Interventions for arterial/blood pressure would be considered beneficial if effect size differences favoured the control condition (indicating the intervention led to lower blood pressure than the control condition). For systolic blood pressure only, there was a medium effect size difference in favour of the exercise group for the resistive exercise + LBNP intervention (g = 0.57) (Appendix E, Figure 9.106). There were small effect size increases in favour of the exercise condition for the rowing ergometer + resistive exercise (g = 0.37) (Appendix E, Figure 9.107), cycle ergometer (g = 0.34) (Appendix E, Figure 9.108), and flywheel + treadmill LBNP (g = 0.31) (Appendix E, Figure 9.109) interventions. There was a trivial effect size difference in favour of the exercise condition for the resistive vibration exercise intervention (g = 0.08) (Appendix E, Figure 9.110). There was a small effect size difference in favour of the control group for the resistive exercise intervention (g = 0.25) (Appendix E, Figure 9.111). Data from the horizontal sledge jump system intervention were too heterogeneous to be pooled (P = 0.02, I_2 = 52%), but effect size changes ranged from a medium effect size difference in favour of the control condition (g = 0.76) to a very large effect size difference in favour of the exercise condition (g = 1.31) (Appendix E, Figure 9.112).

4.3.3.3.2. Artery diameter

For the artery diameter outcomes, there was a trivial effect size difference in favour of the exercise group for the resistive vibration exercise intervention (g = 0.15) (Appendix E, Figure 9.113). For carotid artery diameter, there was no difference between the exercise and control conditions for the resistive exercise intervention (g = 0.00) (Appendix E, Figure 9.114).

4.3.3.3.3. Artery thickness

Interventions for artery thickness would be considered beneficial if effect size differences favoured the control condition (indicating the intervention led to lower artery thickness than no intervention). There was a large effect size difference in favour of the control group for the resistive vibration exercise intervention (g = 0.91) (Appendix E, Figure 9.115).

4.3.3.3.4. Baroreflex

Resistive exercise + LBNP was the only intervention that studied baroreflex, but it was too heterogeneous (P = 0.14, I_2 = 55%) to be pooled for meta-analysis. For this intervention, baroreflex slope displayed a medium effect size difference in favour of the exercise condition (g = 0.65) and the

number of baroreflex slopes showed a medium effect size difference in favour of the control group (g = 0.61) (Appendix E, Figure 9.116).

4.3.3.3.5. Cardiovascular biomarkers

Similar to both muscle and skeletal biomarker, cardiovascular biomarker remained unpooled due to the large heterogeneity in the direction of effect for individual biomarkers.

There were effect size changes ranging from no change (g = 0.00) to trivial in favour of the exercise group (g = 0.28) for the horizontal sledge jump system intervention (Appendix E, Figure 9.117). There were effect size differences ranging from large (g = 0.98) in favour of the control group to medium in favour of the exercise condition for the zero-gravity treadmill + cycle ergometer intervention (g = 0.73) (Appendix E, Figure 9.118).

4.3.3.3.6. Blood flow

For blood flow, the zero-gravity treadmill + cycle ergometer intervention only had one outcome, mitral deceleration, which showed a large effect size difference in favour of the exercise condition (g = 1.23) (Appendix E, Figure 9.119). There was a small effect size difference in favour of the exercise condition for the cycle ergometer intervention (g = 0.46) (Appendix E, Figure 9.120). There was a trivial effect size difference in favour of the exercise condition for the rowing ergometer + resistive exercise intervention (g = 0.03) (Appendix E, Figure 9.121). Resistive vibration exercise had two outcomes, carotid and superficial femoral resting blood flow, but the data were too heterogeneous to be pooled (P = 0.34, I_2 = 65%). Carotid artery resting blood flow showed a trivial effect size difference in favour of the exercise condition (g = 0.01), and superficial femoral artery resting blood flow displayed a large effect size difference in favour of the exercise condition (g = 1.52) (Appendix E, Figure 9.122).

4.3.3.3.7. Cardiac output

Interventions for cardiac output would be considered beneficial if effect size differences favoured the control condition (indicating the intervention led to lower cardiac output than no intervention). The rowing ergometer + resistive exercise intervention showed a small effect size difference in favour of the exercise condition (g = 0.46) (Appendix E, Figure 9.123). Cycle ergometer displayed a trivial effect size difference in favour of the exercise condition (g = 0.17) (Appendix E, Figure 9.124). Horizontal sledge jump displayed a small effect size difference in favour of the control condition (g = 0.49) (Appendix E, Figure 9.125).

4.3.3.3.8. Cardiac structural properties

For cardiac structural properties, the treadmill LBNP intervention which examined only right ventricular mass showed a very large effect size difference in favour of the exercise group (g = 1.49) (Appendix E, Figure 9.126). For the zero-gravity treadmill + cycle ergometer intervention, transmitral lateral wall early diastolic peak tissue velocity displayed a very large effect size increase in favour of the exercise condition (g = 1.45) (Appendix E, Figure 9.127).

4.3.3.3.9. Electrocardiogram

For ECG, the resistive exercise + LBNP intervention displayed a medium effect size difference for R-R interval in favour of the exercise condition (g = 0.67) (Appendix E, Figure 9.128). ECG displayed a trivial effect size difference in favour of the control group for the horizontal sledge jump system intervention (g = 0.02) (Appendix E, Figure 9.129).

4.3.3.3.10. Heart rate

Interventions for heart rate would be considered beneficial if effect size differences favoured the control condition (indicating the intervention led to lower heart rate than no intervention). All effect size differences for heart rate favoured the control condition. Treadmill LBNP (g = 2.09) (Appendix E, Figure 9.130) and resistive vibration exercise (g = 2.08) (Appendix E, Figure 9.131) interventions showed a very large effect size difference. Rowing ergometer + resistive exercise (g = 0.39) (Appendix E, Figure 9.132) and horizontal sledge jump system (g = 0.24) (Appendix E, Figure 9.133) showed a small effect size difference. The flywheel and resistive exercise interventions studied only one outcome, peak heart rate at peak cycle, which displayed a small effect size difference for the flywheel intervention (g = 0.21) and a very large effect size difference for resistive exercise (g = 1.14) (Appendix E, Figure 9.134).

4.3.3.3.11. Hematocrit

For hematocrit, the zero-gravity treadmill + cycle ergometer displayed a medium effect size difference in favour of the exercise condition (g = 0.53) (Appendix E, Figure 9.135), and for the horizontal sledge jump system intervention there was a small effect size change in favour of the exercise condition (g = 0.29) (Appendix E, Figure 9.136).

4.3.3.3.12. Left ventricular architectural properties

For left ventricular architectural properties, the treadmill LBNP intervention examined only left ventricular mass which showed a large effect size difference in favour of the exercise condition (g = 0.95) (Appendix E, Figure 9.137). For rowing ergometer + resistive exercise, there was a medium effect size difference in favour of the exercise intervention (g = 0.66) (Appendix E, Figure 9.138). Cycle ergometer showed a trivial difference (g = 0.04) in favour of the control condition (Appendix E, Figure 9.139). The zero-gravity treadmill + cycle ergometer intervention data were too heterogeneous to pool the results (P < 0.01, I_2 = 75%), which ranged from a very large difference in favour of the control condition (g = 2.55), to a very large difference in favour of the exercise condition (g = 1.58) (Appendix E, Figure 9.140).

4.3.3.3.13. Left ventricular functional properties

For left ventricular functional properties, the zero-gravity treadmill + cycle ergometer displayed a small effect size difference in favour of the exercise condition for left ventricular stroke volume (g = 0.48) (Appendix E, Figure 9.141).

4.3.3.3.14. Pulmonary functional and mechanical properties

For pulmonary functional properties, there were very large effect size differences in favour of the exercise condition for both the zero-gravity treadmill + cycle ergometer (g = 1.61) (Appendix E, Figure 9.142) and flywheel (g = 1.54) (Appendix E, Figure 9.143) interventions. For the cycle ergometer intervention there was a large effect size difference in favour of the exercise intervention for pulmonary capillary wedge pressure (g = 0.93) (Appendix E, Figure 9.144). The horizontal sledge jump system displayed a trivial difference in favour of the exercise condition (g = 0.16) (Appendix E, Figure 9.145). Rowing ergometer + resistive exercise data were too heterogeneous to be pooled (P = 0.17, I_2 = 47%), but maximal oxygen uptake showed a large effect size difference in favour of the exercise condition (g = 1.15), and pulmonary capillary wedge pressure showed a small effect size difference in favour of the exercise condition (g = 0.32) (Appendix E, Figure 9.146).

4.3.3.3.15. Plethysmograph activity

Plethysmograph activity was studied only for the flywheel intervention, which displayed a small (g = 0.48) effect size difference in favour of the exercise group (Appendix E, Figure 9.147).

4.3.3.3.16. Plasma volume

For plasma volume, there were small effect size differences, favouring the exercise condition, for both the rowing ergometer + resistive exercise (g = 0.32) (Appendix E, Figure 9.148) and the cycle ergometer (g = 0.21) (Appendix E, Figure 9.149) interventions. There was a small effect size difference favouring the control group for the horizontal sledge jump system intervention (g = 0.45) (Appendix E, Figure 9.150).

4.3.3.3.17. Peripheral resistance

Interventions for peripheral resistance would be considered beneficial if effect size differences favoured the control condition (indicating the intervention led to lower peripheral resistance than no intervention). There was a large effect size difference in favour of the exercise group for the horizontal sledge jump system intervention (g = 0.82) (Appendix E, Figure 9.151). Trivial effect size differences were displayed in favour of the control group for both rowing ergometer + resistive exercise (g = 0.03) (Appendix E, Figure 9.152) and cycle ergometer (g = 0.01) (Appendix E, Figure 9.153) interventions which each studied only the single outcome, total peripheral resistance.

4.3.3.3.18. Vein CSA

For vein CSA, there was a trivial effect size difference in favour of the control group for the flywheel intervention (g = 0.15) (Appendix E, Figure 9.154).

4.3.3.4. Results ranked by effectiveness of intervention

For muscle related outcomes, the flywheel intervention was the most effective exercise countermeasure (Table 4.5). For the skeletal related outcomes, the treadmill LBNP was the most effective intervention (Table 4.6) and for the cardiovascular and pulmonary outcomes the zero-gravity treadmill + cycle ergometer was the most effective intervention (Table 4.7). When the sum of all scores was taken to create an overall score for each exercise intervention across all musculoskeletal and cardiovascular health, the flywheel intervention was the most effective exercise (Table 4.8). To consider the effectiveness of interventions in the context of outcomes most relevant to astronaut health and operational success, outcomes were split into groups based upon the medical rankings in Chapter 3. Muscle outcome groups were split into functional and mechanical properties (EMG activity; fibre force; fibre power; fibre shortening velocity; jump height and power; muscle strength; T2 relaxation; muscle power; maximal voluntary contraction/muscle force; muscle velocity; muscle work; muscle torque) or architectural and structural properties (fibre diameter; muscle mass; muscle

CSA; fibre CSA; fibre composition; muscle thickness; muscle volume). Skeletal outcome groups were split into functional and mechanical properties (bone strength; lumbar compressibility), measures of volumetric bone mineral density (vBMD), and architectural and structural properties (bone loss recovery; bone volume; skeletal CSA; IVD height; lumbar lordosis; spinal length; periosteal perimeter; trabecular network inhomogeneity; trabecular number; trabecular separation; bone thickness). Cardiovascular outcome groups were split into hemodynamics and vascular function (arterial/blood pressure; baroreflex; blood flow; hematocrit; plethysmograph activity; plasma volume; peripheral resistance), cardiac muscle deconditioning (artery diameter; artery thickness; cardiac output; cardiac structural properties; ECG activity; heart rate; left-ventricular architectural properties; left-ventricular functional properties; vein CSA) and pulmonary ventilation and gas exchange (pulmonary functional properties). While the addition of health impact scores changed some of the lower rankings across all domains, the additional of health impact scores did not change the highest ranked intervention overall or for musculoskeletal or cardiovascular health individually.

Table 4.5 Effectiveness of exercise interventions for muscle-related outcomes

Intervention	Rank (rank before health impact score is considered)	Intervention effectiveness score	Health impact score	Total score
Flywheel	1 (1)	26	6	32
Zero-gravity treadmill + cycle ergometer	2 (2)	14	5	19
Resistive exercise	3 (3)	13	3	16
Horizontal leg press	4 (4)	12	2	14
Gravity-independent inertial ergometer	5 (5)	11	2	13
Resistive vibration exercise	6 (6)	8	2	10
Flywheel + treadmill LBNP	7 (7)	6	1	7
Zero-gravity treadmill	8 (8)	2	1	3
Rowing ergometer + resistive exercise	9 (9)	1	1	2
Treadmill LBNP	N/A	N/A	N/A	N/A
Cycle ergometer	N/A	N/A	N/A	N/A
Resistive exercise + LBNP	N/A	N/A	N/A	N/A
Horizontal sledge jump system	N/A	N/A	N/A	N/A

N/A is used where all data from an intervention was not examined, or was too heterogeneous to be pooled, and as such could not be included in the ranking system. Total score is determined by adding together the intervention effectiveness score and health impact score. The final rank is determined by the total score, where 1 is the highest rank.

Table 4.6 Effectiveness of exercise interventions for skeletal-related outcomes

Intervention	Rank (rank before health impact score is considered)	Intervention effectiveness score	Health impact score	Total score
Treadmill LBNP	1 (1)	3	2	5
Flywheel + treadmill LBNP	2 (1)	3	1	4
Flywheel	3 (1)	3	0	3
Zero-gravity treadmill	3 (2)	2	1	3
Resistive exercise	4 (1)	3	-1	2
Resistive vibration exercise	5 (3)	-4	0	-4
Zero-gravity treadmill + cycle ergometer	N/A	N/A	N/A	N/A
Gravity-independent inertial ergometer	N/A	N/A	N/A	N/A
Horizontal leg press	N/A	N/A	N/A	N/A
Cycle ergometer	N/A	N/A	N/A	N/A
Rowing ergometer + resistive exercise	N/A	N/A	N/A	N/A
Resistive exercise + LBNP	N/A	N/A	N/A	N/A
Horizontal sledge jump system	N/A	N/A	N/A	N/A

N/A is used where all data from an intervention was not examined, or was too heterogeneous to be pooled, and as such could not be included in the ranking system. Total score is determined by adding together the intervention effectiveness score and health impact score. The final rank is determined by the total score, where 1 is the highest rank.

Table 4.7 Effectiveness of exercise interventions for cardiovascular and pulmonary related outcomes

Intervention	Rank (rank before health impact score is considered)	Intervention effectiveness score	Health impact score	Total score
Zero-gravity treadmill + cycle ergometer	1 (1)	14	6	20
Treadmill LBNP	2 (2)	12	3	15
Resistive vibration exercise	3 (3)	7	2	9
Flywheel	3 (4)	6	3	9
Resistive exercise	4 (5)	5	3	8
Cycle ergometer	5 (6)	4	2	6
Rowing ergometer + resistive exercise	6 (7)	2	1	3
Resistive exercise + LBNP	7 (8)	0	-1	-1
Horizontal sledge jump system	8 (9)	-1	0	-1
Flywheel + treadmill LBNP	9 (9)	-1	-2	-3
Gravity-independent inertial ergometer	N/A	N/A	N/A	N/A
Horizontal leg press	N/A	N/A	N/A	N/A
Zero-gravity treadmill	N/A	N/A	N/A	N/A

N/A is used where all data from an intervention was not examined, or was too heterogeneous to be pooled, and as such could not be included in the ranking system. Total score is determined by adding together the intervention effectiveness score and health impact score. The final rank is determined by the total score, where 1 is the highest rank.

Table 4.8 Overall effectiveness of exercise interventions for musculoskeletal and cardiovascular health

Intervention	Rank (rank before health impact score is considered)	Intervention effectiveness score	Health impact score	Total score
Flywheel	1 (1)	35	9	44
Zero-gravity treadmill + cycle ergometer	2 (2)	28	11	39
Resistive exercise	3 (3)	21	7	28
Treadmill LBNP	4 (4)	15	5	20
Resistive vibration exercise	5 (6)	11	4	15
Horizontal leg press	6 (5)	12	2	14
Gravity-independent inertial ergometer	7 (6)	11	2	13
Flywheel + treadmill LBNP	8 (7)	8	0	8
Rowing ergometer + resistive exercise	9 (9)	3	4	7
Zero-gravity treadmill	10 (8)	4	2	6
Cycle ergometer	10 (8)	4	2	6
Resistive exercise + LBNP	11 (10)	0	-1	-1
Horizontal sledge jump system	11 (11)	-1	0	-1

N/A is used where all data from an intervention was not examined, or was too heterogeneous to be pooled, and as such could not be included in the ranking system. Total score is determined by adding together the intervention effectiveness score and health impact score. The final rank is determined by the total score, where 1 is the highest rank.

4.4. Discussion

4.4.1. Summary of evidence

The main finding of this chapter was that flywheel was the most effective intervention overall against musculoskeletal and cardiovascular deconditioning during simulated microgravity exposure. When considering the domains of musculoskeletal and cardiovascular health individually, treadmill LBNP was the most effective for skeletal health and the zero-gravity treadmill + cycle ergometer was the most effective for cardiovascular health, with flywheel remaining the most effective for muscular health.

4.4.2. Exercise interventions for muscular deconditioning

Of the nine exercise devices tested, flywheel was the most effective countermeasure for muscle-related outcomes. Flywheel was the most effective countermeasure for maximal voluntary contraction, muscle velocity, fibre CSA, and fibre composition. However, while flywheel was the most effective countermeasure overall it was not the most effective countermeasure for each individual outcome studied. Resistive exercise led to higher EMG activity than flywheel, and the gravity independent inertial ergometer showed greater muscle work than flywheel, although in both cases flywheel was the second most effective countermeasure. For the muscle torque outcome, both horizontal leg press and zero-gravity treadmill + cycle ergometer scored higher than flywheel, but all were still within the same effect size band (large). For jump height and power, the zero-gravity treadmill + cycle ergometer was the most effective intervention, but while flywheel was studied for this outcome the data were too heterogeneous to include in the meta-analysis. Despite not being the most effective countermeasure for all outcomes, flywheel demonstrated very large and large effect sizes across all outcomes studied, with the exception of fibre composition which showed a small effect size difference (although this was still the highest effect size for this outcome).

Chapter 3 identified the outcomes and outcome groups most relevant to astronaut health and operational success. For muscular deconditioning, the most relevant group were outcomes related to the functional and mechanical properties of the muscles as deficits to these outcomes presents both an operational and medical risk to crew (English et al., 2015), for example preventing emergency egress (Moore et al., 2010; Wang et al., 2019). Flywheel was found to be effective for these functional and mechanical related outcomes, specifically: muscle power; maximal voluntary contraction/muscle force; muscle work; EMG activity; muscle velocity; and muscle torque. That flywheel scored highly across these outcomes demonstrates its potential effectiveness as an intervention for muscular deconditioning during spaceflight.

There were also some instances where flywheel was not studied alone, but rather in combination with treadmill LBNP, which included: muscle mass and muscle strength outcomes. While flywheel was not

studied alone for muscle mass, treadmill LBNP had been, and so some conclusions can be drawn regarding the potential effectiveness of flywheel. Treadmill LBNP alone showed only a trivial effect size, where as combined with flywheel it showed a very large effect size. While this could highlight that flywheel may be more effective than the treadmill LBNP as a countermeasure, data from flywheel alone would be needed to determine if it would be as or more effective when not paired with treadmill LBNP. For muscle strength, flywheel + treadmill LBNP was the most effective intervention, but without data from treadmill LBNP and flywheel individually it is not possible to determine if this was due to the effects of flywheel, treadmill LBNP, or the combination of the two.

There were several outcomes for which the flywheel intervention had not been studied at all, including fibre diameter; fibre force; fibre power; fibre shortening velocity; T2 relaxation; muscle thickness; and muscle volume. While most of these are architectural and structural outcomes and were ranked of lesser importance than functional and mechanical outcomes during Chapter 3, more research would be needed to determine the effectiveness of flywheel intervention upon these outcomes. However, architectural and structural properties indicate structural changes and are used as an indirect measure of functional alterations (Koryak, 2018). As such, it may not be as necessary to demonstrate the effectiveness of flywheel for these outcomes as it has already been shown as advantageous for the functional and mechanical properties. When considering the outcomes for which flywheel was not assessed, the rowing ergometer + resistive exercise was the most effective for fibre diameter, resistive exercise was the most effective for muscle CSA and muscle thickness, while the gravity independent inertial ergometer was the most effective for muscle volume. The remaining architectural and structural outcomes included data from interventions that either had a trivial effect or were too heterogeneous to include in the analysis.

High heterogeneity preventing the use of pooled data and missing intervention data for certain outcomes were common amongst the muscle-related data. For example, flywheel scored highest for muscle velocity but it was the only exercise intervention to be tested for this outcome, preventing any comparisons to determine if another intervention would have been more effective. Twelve of the 19 outcome groups included data that were too heterogeneous to be pooled and as such could not be included within the ranking system. In terms of missing intervention data, the cycle ergometer and the horizontal sledge jump system had not been assessed for any muscle outcomes. The ranking system enables an overview of which countermeasure performed best overall, but without data from the missing interventions, or data of greater homogeneity to allow for meta analysis, it is difficult to draw definitive conclusions. Any operational decision making taking into account the effectiveness of these exercise devices should ensure they examine the effectiveness of interventions for individual outcomes and not rely solely upon the ranking system when determining which interventions to implement.

4.4.3. Exercise interventions for skeletal deconditioning

While flywheel was ranked as the most effective exercise intervention overall, the treadmill LBNP was found to be more effective for skeletal health when it was considered individually. One reason flywheel may have scored so low for its effectiveness on skeletal outcomes could be because it was only examined for two outcomes: bone loss recovery and BMC outcomes. As such, flywheel has not been trialed for its effectiveness on bone strength or other functional and mechanical properties of the skeletal system. This is important when determining an effective intervention for skeletal deconditioning as Chapter 3 identified outcomes related to functional and mechanical properties to be the most relevant to astronaut health and operational success. This is because it is ultimately changes to the functional and mechanical properties of the skeleton, such as bone strength, that present an operational and medical risk to astronauts (Keyak et al., 2009). The lack of flywheel data for all remaining skeletal outcomes makes it difficult to determine the effectiveness of the intervention, or to justify its position as the most effective overall exercise countermeasure. That many of these missing outcomes are related to spinal health and postural stability (e.g. IVD height, lumbar lordosis, spinal length) may also indicate a lack of confidence by researchers that flywheel would be effective at reducing these outcomes. As deconditioning of spinal health can have a negative impact upon the health of astronauts, including low back pain, intervertebral disc herniation, and bone fracture (Lazzari, Aria, & Menger, 2021), it would be beneficial for any exercise countermeasure for a future Moon or Mars mission to be capable of protecting spinal health. This also reflects previous evidence from non-trial spaceflight and unloading model data that flywheel-based hardware has generally not been successful in addressing all concerns related to skeletal-deconditioning (Parmar et al., 2016). Parmar et al. (2016) suggested that this may be due to the slow rate of repetitions during flywheel exercise that may impede the rate of strain upon bone segments that are engaged in that exercise. If flywheel hardware could be adapted to impart greater strain rates then this may enable a stronger approach to attenuating skeletal deconditioning (Parmar et al., 2016). However, as flywheel has not been trialled for many outcomes related to skeletal deconditioning, more research would be needed to determine if it would be effective with these changes.

However, it should be noted that the high heterogeneity in the testing of exercise countermeasures for relevant outcomes were not limited to just flywheel. Most of the skeletal outcomes identified were examined by only one or two exercise interventions, making it difficult to provide clear guidance on how effective each countermeasure is for skeletal deconditioning. Furthermore, the available data suggests a primarily ineffective countermeasure suite overall for skeletal deconditioning. RVE and RE showed trivial effects for the majority of outcomes and RVE was shown to be detrimental to IVD volume, spinal length, and periosteal perimeter, while RE was also detrimental to spinal length. Treadmill LBNP, the highest ranked countermeasure for skeletal health, was examined for only three

outcomes: bone strength; lumbar lordosis; and lumbar compressibility, in which it was found be ineffective for lumbar lordosis. Given that flywheel and treadmill LBNP were not examined on any of the same outcomes it makes it difficult to compare and discuss the potential effectiveness of each countermeasure. Even where flywheel and treadmill LBNP were studied as a combined intervention, the outcomes studied were different from both those studied by flywheel and treadmill LBNP individually, preventing cross-comparisons. More research is needed to clearly establish the effectiveness of flywheel, treadmill, and the remaining exercise countermeasures on the skeletal system.

4.4.4. Exercise interventions for cardiovascular deconditioning

The zero-gravity treadmill + cycle ergometer was the most effective countermeasure for cardiovascular deconditioning, despite flywheel being the most effective intervention for musculoskeletal and cardiovascular health overall. Flywheel had been examined only for four outcomes: pulmonary and functional properties; heart rate; plethysmograph activity; and vein CSA. With the exception of pulmonary functional and mechanical properties, for which flywheel demonstrated a very large effect, it displayed only small or trivial effects for the remaining outcomes. As with skeletal deconditioning, the low number of outcomes for which flywheel was studied makes it difficult to determine if this is because flywheel is simply not effective for cardiovascular deconditioning, or if there is not enough data to clearly judge the effectiveness of the intervention. This is particularly important given that flywheel has not been examined for many of the most relevant outcomes identified in Chapter 3, specifically: arterial/blood pressure; baroreflex; blood flow; hematocrit; plasma volume; and peripheral resistance. Chapter 3 identified that these outcomes, related to haemodynamic and vascular function, were the most relevant to astronaut health and mission success, as the central fluid shift from the lower limbs towards the head (Buckey Jr et al., 1996; "The negative effect of unloading exceeds the bone-sparing effect of alkaline supplementation: a bed rest study," 2018; Williams et al., 2009) can lead to the development of orthostatic intolerance and other cardiovascular problems which place astronauts at medical risk (Evans et al., 2018; Kaderka et al., 2010). While flywheel had been examined for one of these outcomes, plethysmograph activity, it was the only intervention assessed for this preventing direct comparisons to the zero-gravity treadmill + cycle ergometer or other interventions. More research is needed to determine the effectiveness of flywheel in relation to cardiovascular outcomes.

In comparison, the zero-gravity treadmill + cycle ergometer intervention had been tested for two haemodynamic and vascular function outcomes, blood flow and hematocrit, and was the most effective countermeasure in both cases. While the zero-gravity treadmill + cycle ergometer intervention was also effective for cardiac structural properties, treadmill LBNP was a more effective

countermeasure. For the left-ventricular functional properties, the zero-gravity treadmill + cycle ergometer was effective, but the effect size was small and no other interventions had been examined. For architectural and structural properties, data for the zero-gravity treadmill + cycle ergometer were too heterogeneous to pool, but results ranged from being effective to having a negative impact. While zero-gravity treadmill + cycle ergometer was effective for pulmonary functional and mechanical properties, flywheel also displayed a very large effect size.

Interventions for cardiovascular deconditioning displayed the largest number of harmful effects of all three physiological domains examined in this review. Resistive exercise + LBNP; flywheel + treadmill LBNP; cycle ergometer; and rowing ergometer + resistive exercise showed harmful effects for systolic blood pressure. Rowing ergometer + resistive exercise also demonstrated harmful effects for cardiac output, while the horizontal sledge jump system displayed harmful effects for plasma volume and peripheral resistance. As the zero-gravity treadmill + cycle ergometer was only studied for 6 of the 18 possible outcome groups, its position in the ranking system does not necessarily represent a widely effective countermeasure, but rather one that was not harmful across many outcomes.

As with both the muscle and skeletal outcomes, the high level of heterogeneity in the testing of interventions for key outcomes has limited the capability to effectively compare and assess the effectiveness of countermeasures. Some interventions, including the gravity-independent inertial ergometer, horizontal leg press, and zero-gravity treadmill were not assessed at all for their effect on cardiovascular deconditioning. Given that flywheel was found to be the most effective countermeasure overall, but was only studied for two cardiovascular outcomes, while the zero-gravity treadmill + cycle ergometer was studied for six, more research is needed to firmly establish which countermeasure is most effective for cardiovascular deconditioning.

4.4.5. Findings within the context of the Orion MPCV and future exploration spacecraft

A key challenge in assessing whether each individual countermeasure would fit within the constraints of Orion identified in Chapter 2 is the lack of publicly available data for each countermeasure pertaining to its size, mass, noise production level, maximum loading, and other relevant variables. Due to this lack of publicly available technical data for each countermeasure, a full analysis in relation to the technical constraints presented in Chapter 2 was not possible, so the following discussion should be interpreted cautiously within this context.

The flywheel exercise device was found to be the most effective intervention overall against musculoskeletal and cardiovascular deconditioning during simulated microgravity exposure. While the treadmill LBNP and the zero-gravity treadmill + cycle ergometer were found to be the most effective interventions for skeletal and cardiovascular health when these domains were considered

individually, their large volume and mass mean it is unlikely they will be able to be implemented within the constraints of the Orion spacecraft identified in Chapter 2 (Owerkowicz et al., 2016; Petersen et al., 2016). In the case of the zero-gravity treadmill + cycle ergometer, the cycle ergometer itself may be small enough to fit within Orion's constraints but a treadmill would not. Chapter 2 identified that the constraints of Orion will likely only leave room for a single exercise device, suggesting that a single flywheel intervention may be the most optimal solution to musculoskeletal and cardiovascular deconditioning, even if the treadmill LBNP and zero-gravity treadmill + cycle ergometer (or cycle ergometer without the treadmill) could be developed into smaller, more compact devices to fit within Orion's constraints alongside the flywheel exercise device. As such, these findings provide some support, and are supported by, the NASA decision to implement a flywheel exercise device on-board Orion for future missions of up to 30 days (M. Downs, personal communication, October 1, 2020).

However, it is not yet clear if the flywheel could be meet the mass and volume requirements necessary to be implemented within the constraints of the Orion MPCV or transferable capsular spacecraft identified in Chapter 2. There is no publicly available information on the dimensions of the flywheel device NASA intend to implement for future Orion missions, which makes it difficult to objectively determine if a flywheel exercise device would be suitable. The ESA have previously implemented a supplementary flywheel-based exercise device on-board the ISS, the Flywheel Exercise Device (FWED), as supplementary equipment to the ISS countermeasure suite (ESA, 2020; ESA, n.d.). The seated design of the device makes it too large and heavy (195 cm length x 57 cm width x 70 cm height, 55 kg) (ESA, n.d.) to fit within the maximum volume and mass constraints of Orion (19.05 cm depth, 53.34 cm width x 34.29 cm height, 10.6 kg) (Sheehan et al., 2016). Estimates made using commercial flywheel devices suggest that the flywheel component itself may be fairly small (1 x 18 x 18 cm, 1.2 kg to 1 x 36 x 36 cm, 4.6 kg) (Exxentric, 2021). However, some of the smallest commercially available flywheel platforms (68 x 43 x 21 cm, 10 kg) are still over the maximum volume limits for Orion (Perform Better, 2021). Implementation of a flywheel-based exercise device for use on-board Orion would need to be designed to meet the maximum volume and mass requirements.

For longer duration mission involving the Orion MPCV, such as to Mars, it may be that additional space will be provided via a deep space habitat (Curley et al., 2012). In such an event, it may be that more exercise countermeasures than just the flywheel could be implemented. However, caution should be taken if using multiple exercise devices. The data assessed in this review indicate that flywheel + treadmill LBNP is less effective than flywheel alone, with the combined interventions ranking 8th place out of 13 in the scoring system, suggesting that combining these exercises devices may not be the most effective strategy as a countermeasure to microgravity deconditioning. While it is possible that this could be due to the prevalence of testing some interventions more than others, more

research would be needed on the combined effects of these countermeasures. There are not yet RCTs or CTs that combine flywheel with the cycle ergometer and so it is difficult to determine if these exercises combined would be more useful than implementing the flywheel alone.

NASA have previously designed other exercise equipment specifically for Orion, such as the Resistive Overload Combined with Kinetic Yo-yo (ROCKY) (Williams, 2016), for which no trial data are available. There is little pubulicly available information available about the design of ROCKY, beyond suggestions that it may be, or function in a similar fashion to, a rowing intervention (Williams, 2016). While this review assessed trials from a rowing ergometer + resistive exercise, which consistently ranked low across all physiological domains, it is unclear to what extent these results would be transferable to ROCKY. Another exercise device, the Advanced Twin Lifting and Aerobic System (ATLAS) built upon the features of ROCKY to provide two t-bar handle cable outputs (where as ROCKY only features one) and a squat bar similar to ARED but on a scale suitable for use within Orion (Funk et al., n.d). As ATLAS provides both rowing capacity and a resistive exercise mode similar to ARED, there may be a greater degree of transferability from the results of the rowing ergometer + resistive exercise intervention studied within this review. However, as no trial data exist for ATLAS more research is needed to determine if it would be a suitable option for an Orion exercise device.

4.4.6. State of the current evidence base

Quality scoring highlighted that of the 66 studies included in the review, 10 studies did not include the necessary raw data to undergo any meta-analysis or report effect size changes between intervention and control group. Nineteen studies, including the previous 10, did not report for a single major outcome the pre-flight scores for the control or intervention groups. These issues were further exacerbated by a failure in 46 of the studies to report if groups were similar at baseline, and a failure in 29 studies to report measures of at least one key outcome for more than 86% of subjects. These findings indicate a serious failure across a large number of studies to accurately report the full data required to enable the highest level of the evidence hierarchy, meta-analysis, and adds to the previous calls from chapters two and three, for a minimum set of reporting standards to be enacted within the space medicine field. There were 35 cases in which only a single outcome had been tested for one intervention, in comparison to multiple outcomes for another intervention, which risks skewing the results of the ranking system used in this review in favour of the single outcome-reported intervention if it is a large effect size. While this is a relatively small number of cases in comparison to the overall number of outcomes examined in this review, it brings to attention a wider issue identified in Chapter 3, within the field of space medicine in which replication of studies has not been prioritised, potentially as a result of the cost of both spaceflight and its simulations. To address the limitations

presented here, future research should endeavour to fully report the mean scores, standard deviations, and number of participants for both the control and intervention groups. Space agencies and funders should further consider accepting research proposals that aim to replicate study findings to reduce heterogeneity of outcomes and reduce the risk of data synthesis becoming skewed using single-outcome intervention reporting. These recommendations to the space medicine field have been promoted previously by the AMSRG in an attempt to develop a set of basic reporting standards for the research base (Winnard et al., 2021).

4.4.7. Limitations of the review

It was not possible to integrate biomarker-related outcomes into the meta-analysis due to the large heterogeneity in the direction of effect for individual biomarkers. This is not surprising, as biomarkers are often indirect measures of a range of other functional, mechanical, structural or architectural outcomes (Capri et al., 2019). This does not mean biomarkers are not useful, as they can be an advantageous outcome measurement used to indirectly infer changes in astronaut health without direct contact with the astronaut population (Capri et al., 2019), which may be particularly useful for long distance spaceflight to Mars or beyond.

The ranking system is trialed for the first time in this chapter as no scoring tool pre-exists to rank the effectiveness of exercise countermeasures for use during spaceflight. The results of the ranking system may be skewed by interventions which have been studied more commonly than others, and therefore have a greater opportunity to gain points for the ranking system. While this chapter has been able to present findings based upon the currently available literature, more data is ultimately needed to provide firm conclusions on the most effective exercise countermeasure. The scores provided by this ranking system are therefore intended only as a broad overview of intervention effectiveness and are not intended to be a sole guide to the effectiveness of interventions for spaceflight. Operational decision makers and researchers should consider the individual outcome scores for each intervention alongside the overall rank of each intervention when determining an exercise device to implement during spaceflight.

4.4.8. Conclusions

The flywheel exercise device was found to be the most effective intervention overall for musculoskeletal and cardiovascular deconditioning, based upon terrestrial microgravity simulations. When considered within the context of the musculoskeletal and cardiovascular outcomes of greatest relevance to astronaut health and operational mission success that were identified in Chapter 3, the flywheel exercise device remains the most effective exercise countermeasure overall. The results of this meta-analysis provide some degree of support to NASA's decision to implement a flywheel

exercise device for future Orion missions. While NASA had decided to implement a flywheel exercise device for Orion there was no synthesis of the evidence base, until this review, to provide an evidence-based medical justification to the decision. However, it is still not yet clear if a flywheel device is suitable for use within the technical constraints of Orion identified in Chapter 2 as there is no publicly available information on the dimensions of NASA's intended flywheel countermeasure. When the domains of the muscular, skeletal, and cardiovascular systems are considered individually, the treadmill with LBNP and zero-gravity treadmill + cycle ergometer may be more effective interventions than the flywheel for skeletal and cardiovascular deconditioning, respectively. The low upload mass and volume constraints of Orion will likely prevent the implementation of more than one exercise device, and so a single flywheel device may remain the best solution. However, these findings should be considered within the wider context of this chapter's limitations, in particular the lack of consistency in how results from spaceflight studies have been reported across the evidence base. The uneven distribution of intervention studies, which may skew the results of the ranking systems presented in this review in favour of interventions which have been studied across a larger number of outcomes or in favour of interventions for which only a single, but large effect size, outcome exists, preventing a true reflection of the effectiveness of the identified countermeasures for musculoskeletal and cardiovascular deconditioning. Likewise, large variations in sample size, the length of spaceflight, and the pooling of data from spaceflights of different lengths and missions were common features of the evidence base which may obscure the true effectiveness of the exercise countermeasures identified and create difficulties in assessing causal effects of exercise prescriptions on health outcomes. The ranking system provided here should be considered within these limitations and used only as a general overview, with attention paid to the effectiveness of interventions upon individual outcomes for operational decision making and research purposes.

5. Chapter Five: Astronaut-reported operational considerations for the implementation of an exercise countermeasure device for use during spaceflight on-board the MPCV

5.1. Introduction

The systematic review in Chapter 4 evaluated the effectiveness of exercise countermeasures from simulated microgravity trials in relation to the priority musculoskeletal and cardiovascular outcomes identified in Chapter 3, identifying flywheel exercise as potentially the most effective overall countermeasure. This supports NASA's intended approach to use a flywheel-based exercise countermeasure for missions of up to 30 days on the Orion MPCV (M. Downs, personal communication, October 1, 2020). Whilst the flywheel device may be the most effective exercise countermeasure overall for reducing musculoskeletal and cardiovascular deconditioning, there remains concern that astronauts may become bored using only a single exercise countermeasure (M. Downs, personal communication, October 1, 2020).

Previous studies have indicated boredom may be a risk factor in failing to adhere to exercise prescriptions (Jekauc, 2015; Wolff, Bieleke, Martarelli, & Danckert, 2021), and poor adherence in space could result in health risks to the astronauts and risk mission failure (Moore et al., 2010). As such, it is important to determine whether astronauts would become bored using a single exercise countermeasure. Furthermore, it is unclear if astronauts would be comfortable with the prospect of using a single exercise countermeasure device, as previous exercise prescriptions during spaceflight have often involved a variety of exercise countermeasures (Loehr et al., 2015; Petersen et al., 2016).

The aim of this qualitative work was, therefore, to identify astronaut-reported operational considerations for the implementation of an exercise countermeasure device for use during spaceflight, and if current NASA plans for the implementation of a single flywheel exercise countermeasure device might affect astronaut adherence to exercise prescriptions.

5.2. Method

5.2.1. Approach

A qualitative survey was used to explore astronaut operational considerations and preferences for the design and development of exercise countermeasures for use during spaceflight beyond low-Earth orbit, including the use of a single exercise countermeasure device (flywheel) for use on-board the Orion MPCV.

5.2.2. Participants

Three male astronauts (mean age = 57.7±9.07 years) were recruited via purposive (purposive) sampling (Bhardwaj, 2019) to take part in this survey. All participants were required to currently be taking part in, or have previously taken part in, human spaceflight.

5.2.3. Materials/Equipment

An open-ended, six question survey was designed by and implemented using the online survey platform Qualtrics (Qualtrics, 2020). The questions aimed to elicit the preferences and considerations that astronauts believe to be most important for the development and implementation of an exercise countermeasure during long-duration spaceflight, and consisted of the following questions:

1: What factors would you consider most important to you for the design of an exercise countermeasure device for use during spaceflight, and why?

2: Would you prefer to use multiple exercise devices during spaceflight or a single exercise device? Why is this the case?

3: Would you feel bored using only a single exercise countermeasure device? If so, how do you think this boredom might impact you?

4: Would you feel less likely to engage fully with an exercise prescription during spaceflight if there was only a single exercise device? Why is this the case?

5: Thinking about your health and wellbeing, would you feel confident using only a flywheel exercise countermeasure device for a mission of 30 days or less beyond low Earth orbit? Why is this the case?

6: Is there anything else that you would like to add?

5.2.4. Protocol and procedure for analysis

Ethical approval was received for this study from Northumbria University's Health and Life Sciences Ethics Committee. All data were collected through the online survey platform Qualtrics, where participants were provided with an information sheet so that they could provide informed consent to take part in the survey. After providing informed consent, participants then answered the six open-ended questions. Upon completion of the survey, participants were provided with a debrief sheet detailing the nature of the study. In total, the study was estimated to take between 5 and 10 minutes to complete.

To analyse the data, the 6-step process of thematic analysis (Braun et al., 2006; Braun et al., 2019), described in detail in Chapter 2, was implemented. NVivo qualitative data analysis software (QSR NVivo 12, 2014) was used to code and analyse the data (Appendix D).

5.3. Results and Discussion

The main finding of this study was the grouping of astronaut preferences for an exercise device during spaceflight into three common themes:

- Exercise device ease of access: this refers to codes relating to the accessibility of the exercise device, including the set-up, take-down, and ease of use.
- Motivational and behavioural considerations: these are concerned with psychological factors that affect the behaviour of the crew in relation to exercise, including enjoyment, boredom, and psychosocial considerations.
- Operational and technical considerations: these are concerned with the structure, function, and effectiveness (both physical and psychological) of exercise countermeasures, and how the mission profile (e.g. long, or short-term spaceflight, type of spacecraft) may affect exercise use.

These themes and the codes they relate to are displayed in Figure 5.1.

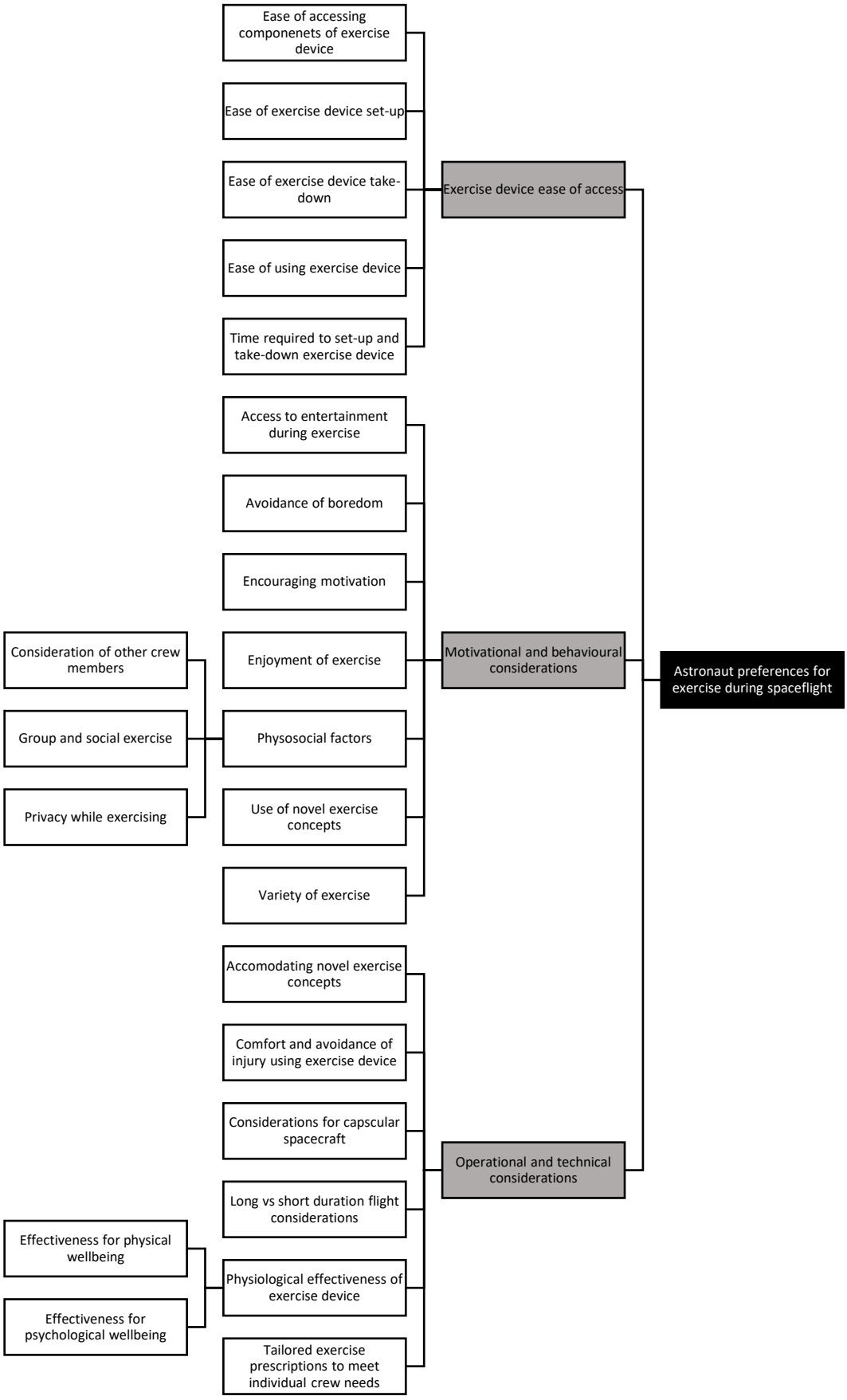

Figure 5.1 – Thematic map displaying codes and common themes related to astronaut preferences for exercise device considerations during spaceflight.

When asked what factors were most important for the design of an exercise countermeasure, ease of access requirements were common across all the astronauts, who suggested that "ease of use" (Participant 1), "ease of set-up" (Participant 2), and ease of setup and takedown" (Participant 3) were among the most important design considerations to them for the use of an exercise countermeasure during spaceflight. Participant 3 further suggested that ease of setup should be considered "in terms of time spent searching for parts", indicating that astronauts may prefer to have an exercise device that is either easy to assemble and disassemble, or remains fully assembled and in place. Participant 3 suggested that ease of access and use of the exercise device may be as or more important than the number of exercise devices chosen: "one device is fine, especially if it means that device can remain assembled in place, so it is easy to use", reflecting a common preference for the exercise device to be easily accessed and easy to use.

Ease of access for the exercise countermeasure was not the only factor considered among the most important to the astronauts. Several motivational and behavioural factors, and operational and technical factors were also identified. In terms of operational and technical considerations, the astronauts highlighted the need for the exercise countermeasure to be effective for relevant outcome measures. Participant 1 suggested that the exercise device should cover "a broad range of exercises", be "practical", and "appeal to a broad range of possible activities (both in terms of offering a full body workout and different types of exercise e.g HIT vs endurance) and crewmember preferences", and that the device should be "contributing to both physical and mental wellbeing". This indicates that one of the primary concerns for the astronauts is that the exercise countermeasure is effective for protecting relevant health outcomes, including both musculoskeletal and cardiovascular deconditioning, and psychological wellbeing during spaceflight. This sentiment was echoed by participant 2 who, in response to being asked what their most important considerations for the design of an exercise device was, said "replication of terrestrial loading, so as to avoid musculoskeletal deterioration during flight" and, when asked if they would prefer multiple exercise devices or a single exercise countermeasure, that the exercise countermeasure should include "multiple exercises for variety and to assure total body exercise". This both highlights the importance of the exercise countermeasure being effective for relevant health outcomes, and that a single exercise device may be suitable for use so long as it provides multiple exercises and variety.

The desire for "multiple exercises for variety" (participant 2) in the exercise prescription was a common outcome discussed by all three astronauts. For example, participant 1, echoing earlier statements from participant 2, suggested that if this variety in exercise is achieved it would potentially overcome the need to use multiple exercise devices:

> "Multiple devices currently offer a variety of different exercises and the ability for multiple crewmembers to train at the same time. However, this is not high on my priority list. If a new, single, device could offer a similar variety of exercises then a single device would suffice."

Participant 3 appeared more conflicted about the use of a single or multiple exercise countermeasures to achieve variety, as when they were asked if they would prefer to use multiple exercise devices or a single device they responded "multiple. Otherwise the exercise time can be tedious". However, when asked if they would fully engage with an exercise prescription using only a single exercise countermeasure, they suggested that "one device is fine, especially if it means that device can remain assembled in place, so it is easy to use. However, the routine should vary", echoing the calls of the other astronauts for a varied routine in their exercise prescriptions.

While the desire for variety could be seen as an operational and technical outcome to be achieved by using an exercise device with a varied exercise prescription, the underlying reason for this preference may be related to motivational and behavioural factors, particularly enjoyment of exercise and the reduction of boredom. For example, participant one argued that "exercise in space needs to be an activity that crew will enjoy, contributing to both physical and mental wellbeing. To that end, the device needs to appeal to a broad range of possible activities", suggesting an initial link between exercise and enjoyment. This sentiment was supported by participant 2 who, when asked if they would feel bored using only a single exercise countermeasure, replied "yes, most definitely" and that "boredom" would be partially responsible for failing to engage fully with an exercise prescription. Participant 3 also suggested that a "varied routines to reduce boredom" was among their most important considerations for exercise countermeasure design. These statements are reflected in terrestrial studies, in which boredom has been linked to lower performance and adherence to exercise prescriptions, for example through reducing motivation to exercise (Jekauc, 2015; Wolff et al., 2021).

Maintaining variety may overcome the challenge of using only a single exercise device, as participant 1 suggested that "if it is well designed it will offer something for everyone and enough range of possible exercises to allow sufficient variety for a week-long exercise programme" and, when asked if they would feel bored using a single exercise countermeasure, they went on to say "no - not if it offered a good variety and range of possible exercises", highlighting both the preference for variety to reduce boredom and echoing concerns about maintaining the effectiveness of the exercise countermeasure. Participant 2 held similar preferences, suggesting that "short duration, for which 30 days is at the upper limit, would probably be OK with a simple flywheel device. There are clever adaptations with a flywheel that could make exercise less boring, however (and more effective for total body resistance training)", further highlighting the preference to make exercise less boring while maintaining the effectiveness of exercise countermeasures.

The astronauts also suggested that other measures to reduce boredom that were not specific to the exercise device itself could be implemented, such as avoiding "boredom through VR/AR augmentation and/or Peloton-type motivation with virtual instructors" (participant 2). This was also highlighted in greater detail by participant 1:

> "Crew enjoyment during exercise often comes from listening to music/podcasts, watching TV etc. I enjoyed running and biking using a tablet app 'Run Social', which enabled me to immerse myself in an almost virtual environment (Swiss/Scottish mountains etc). I think entertainment during exercise is an extremely important element to consider for integration or at least compatibility with future countermeasure devices."

This indicates both the potential to implement entertainment alongside the exercise device, and a potential desire for a more social aspect to exercise using virtual instructors. While the use of virtual instructors during short-duration spaceflight may be possible, it could become more difficult during longer-duration spaceflight (such as to Mars) where communication delays (Kanas, 2013) or technical constraints such as a limited power supply (Sheehan et al., 2016) may prevent or reduce the effectiveness of such technologies. This could be overcome through pre-recorded video and audio exercise instructions, or more novel techniques could be implemented to generate power, as suggested by participant 3:

> "Power needed for biofeedback is minimal-- use a coin battery for example. Or use a fitbit or a cell phone with batteries. Or use a USB3 port on a laptop. If there is really no power, then use a hand generator (squeeze to turn a wheel that generates power) with a super capacitor and consider the power generation as part of the exercise routine (It's quantifiable and you need hand strength for EVA!)."

Participant 3 further suggested more novel methods of increasing enjoyment during exercise that could increase enjoyment of exercise, reduce boredom, and add a social aspect to the exercise prescriptions:

> "Exercise devices in flight have historically mimicked exercise devices on earth. There is a better way. [*Name and mission redacted for anonymity*] introduced to the crew some active exercises that were fun and engaging. For example, we pushed off a bulkhead with our feet, flew fast to the opposite bulkhead and pushed off that to return. At first, this is hard to do-- you don't fly straight. After just a few minutes, you improve a lot. After a while, everyone got really good and we were tumbling between the bulkheads and going very fast so that we got strength training, impact training to the long bones, coordination exercises, spatial orientation exercises, all at the same time, while having a lot of fun. We would go in pairs and eventually we could get four people going simultaneously, rushing past each other. We really learned to fly! We also played games for exercise. We played tag and king of the mountain. We played a

> form of Quidditch in an emptied supply module where we used a red rubber ball as the snitch and went after it, pushing and pulling each other all over the place. In the current ISS, you could do that in the airlock. I encourage you to find exercises that utilize the unique environment of spaceflight rather than just reproducing earth-based exercise devices."

These novel exercises that utilise the space environment could provide an alternative to the traditional exercise countermeasure suite, while also accommodating many of the astronaut preferences, including removing the need to setup and takedown the device (ease of access), increasing enjoyment while reducing boredom (motivational and behavioural considerations), and meeting operational requirements (operational and technical considerations). The use of these novel space-environment exercise countermeasures, which would not need to use restraint systems to attach the astronaut to an exercise device, may also lead to the "avoidance of "hot spots" and overuse injuries as a result of restraint systems", a concern highlighted by participant 2. However, the feasibility of such a novel exercise countermeasure approach, particularly within the constraints of capsular spacecraft such as the Orion MPCV (as identified in Chapter 2), and the impact these novel exercises may have on the spacecraft should be considered. For example, participant 3 recalled that during these novel exercises: "we did get a call from the ground during our high impact exercises that we were registering on the station accelerometers and to go look at the solar arrays which were indeed flapping". However, they also suggested solutions to limit the impact these exercises have upon the spacecraft, suggesting that "there are lots of ways around that issue, for example, install a springboard at the bulkhead that isolates the impact from the vehicle". This suggests that the spacecraft could potentially be modified to accommodate these novel exercises to overcome the impact they may have upon the vehicle. This would be similar to how many current ISS microgravity applications, including exercise countermeasures, are attached via a vibration isolation system (Grodsinsky & Whorton, 2000). Participant 3 also suggested that these novel exercises could still be implemented within the technical constraints of future capsular spacecraft, in which the volume of exercise space will be limited to an area of $5m^2$ (Sheehan et al., 2016): "I think there are plenty of exercises that could be done utilizing weightlessness within 5 cubic meters. For example, two crewmembers could simultaneously dribble each other off the walls like basketballs (that would be a hoot and a half!)." While these novel exercises may also allow for group and social exercise, participant 1 also highlighted that considerations should be made for astronauts that do not wish to be disturbed by the exercise prescriptions ("crew will want to exercise without being disturbed or disturbing other crew where possible" (participant 1)), however, this may be difficult to accomplish within the confines of the limited volume requirements of capsular spacecraft where most mission tasks, including exercise, will likely occur in the same space.

As NASA intends to implement a single exercise countermeasure, the flywheel exercise device, on-board the Orion spacecraft (M. Downs, personal communication, October 1, 2020), the findings

should also be considered within this context. All three astronauts indicated that they would feel bored using only a single exercise countermeasure, risking the possibility that "it would make me less likely to do the exercise and also less likely to do it well" (participant 3), unless it "offered a good variety and range of possible exercises" (participant 1), or boredom could be avoided "through VR/AR augmentation and/or Peloton-type motivation with virtual instructors" (participant 2). As it has been evidenced that moderate effects of muscle deterioration become apparent by seven days of simulated microgravity exposure (Winnard, Scott, et al., 2019) and that this deconditioning may affect crew performance and safety (Moore et al., 2010), it is vital that astronauts fully engage with the exercise countermeasures available. As suggested by the astronauts surveyed here, this may be achieved through variety in the exercise prescription, as well as implementing additional forms of entertainment, including virtual reality or augmented reality augmentation (participant 2), or access to music, podcasts, or television (participant 1). The astronauts also suggested concern that the use of only a flywheel exercise device may not be suitable for missions of longer than 30 days. For example, when asked if they would feel confident using only a flywheel exercise countermeasure for a mission of 30 days or less, participant 1 said "yes. For a mission of such short duration then a flywheel, although perhaps not able to fulfil the points raised above, would suffice", while participant 2 said "short duration, for which 30 days is at the upper limit, would probably be OK with a simple flywheel device. There are clever adaptations with a flywheel that could make exercise less boring, however (and more effective for total body resistance training)," and participant 3 suggested that "for 30 days or less, a simple flywheel is fine. It's not about the device, it is about the routine". This suggests that, so long as missions remain short in duration (less than 30 days) and there is enough variety in the flywheel exercise prescription to prevent boredom, then its use on-board the Orion MPCV may be acceptable to astronauts. Participant 2 reaffirmed the possibility for a varied exercise prescription with a flywheel exercise device by suggesting that "different modes of resistance and endurance training can easily be envisioned with a flywheel - so don't treat it as a single exercise device. Think about other adapters for different exercise modalities," echoing the statement from participant 3 that "it's not about the device, it is about the routine".

5.3.1. Limitations

While the data here present common preferences across three astronauts, this is a broad collection of preferences and should be used to supplement, not entirely inform, the development and use of future exercise countermeasures. Following the guidance from participant 1 that "the device needs to appeal to a broad range of possible activities… and crewmember preferences", the crewmembers chosen for future spaceflights should be asked for their own preferences for exercise device development and usage so that their preferences can be augmented into their own individual, tailored exercise prescriptions.

5.3.2. Conclusions

Astronaut preferences for the use of an exercise device during spaceflight may be categorised into three broad themes: exercise device ease of access (e.g. ease of setting up and using the device), motivational and behavioural considerations (e.g. enjoyment and boredom while exercising), and operational and technical considerations (e.g. effectiveness of the device for relevant health outcomes). The data presented here suggest that astronauts may consider a flywheel-based exercise device suitable as the sole exercise countermeasure on-board the Orion MPCV, and similar capsular spacecraft, so long as it engages astronauts in a varied exercise prescription that meet the physiological expectations required of exercise countermeasures for spaceflight deconditioning, is enjoyable and that measures are put in place to reduce boredom (achieved primarily through variety in exercise prescription), is easy to access in terms of both use and setup/takedown, and is used only as the sole exercise countermeasure for missions of 30 days or less. Individual crewmember preferences should be taken into consideration following crew selection to ensure the greatest adherence to the exercise programme.

6. Chapter Six: Conclusion

The aim of this thesis was to recommend exercise countermeasures for spaceflight musculoskeletal and cardiovascular deconditioning within the technical constraints of the Orion MPCV and transferable capsular spacecraft. To achieve this, the thesis first identified the technical constraints of the Orion MPCV and transferable capsular spacecraft that prevent the use of current ISS countermeasures (Chapter 2) to ensure that the final exercise recommendations were realistic. Next, it was necessary to identify the musculoskeletal and cardiovascular outcomes of greatest relevance to astronaut health and operational success (Chapter 3) to enable selection of exercise recommendations based on the highest priority space medical needs, and outcome groupings could be used to inform the meta-analysis in Chapter 4. Having identified both the technical constraints of the Orion MPCV and the most important outcomes, it was then possible to identify the most effective exercise countermeasures for space medicine priority outcomes (Chapter 4). To ensure a patient centred approach, self-reported outcomes from astronauts on their preferences for an exercise device during spaceflight were collected and analysed to provide additional context and input to help tailor final recommendations for astronaut needs and preferences (Chapter 5).

6.1. Original findings and implications

The findings of this thesis indicate that the flywheel may be the most effective single exercise countermeasure for use during spaceflight to reduce musculoskeletal and cardiovascular deconditioning, based upon the results of terrestrial microgravity simulation trials. In the context of the Orion MPCV and transferable capsular spacecraft, a lack of publicly available information prevents a clear determination of whether flywheel, or any of the other countermeasures studied, will meet the mass and volume constraints of Orion. It will be necessary for space agencies and commercial space entities to examine if any potential exercise device, including flywheel, are capable of meeting the technical constraints of the Orion MPCV identified in Chapter 2. Self-reported astronaut considerations, assessed in Chapter 5, have further suggested that the use of a flywheel exercise countermeasure will be acceptable for missions of up to 30 days. For longer duration mission of more than 30 days, such as to Mars, astronauts indicated a single flywheel exercise device might not be sufficient as limited options may induce boredom, reducing adherence to exercise prescriptions and risk their health and the chance of operational mission success. As a result, missions of longer than 30 days should consider implementing a larger spacecraft or deep-space habitat for use alongside the Orion MPCV in which the volume and mass constraints preventing the use of only a single exercise device can be negated. In both cases, considerations should be made for the entertainment of astronauts during exercise (such as access to podcasts, virtual reality) to prevent boredom and increase adherence to exercise. Additional social considerations, including the implementation of team exercises, or exercise that utilises the spaceflight environment might also be useful in increasing adherence to exercise. These recommendations provide medical-evidence-based support, to NASA's

operational decision to implement a flywheel-based exercise countermeasure on-board Orion for missions of less than 30 days (M. Downs, personal communication, October 1, 2020). As highlighted in Chapter 4, it will still be necessary for NASA to ensure that their flywheel-based countermeasure meets the constraints of the Orion MPCV identified in Chapter 2.

Chapter 2 identified the technical constraints of the Orion MPCV and similar capsular spacecraft that would prevent the implementation of current exercise countermeasures used on-board the ISS. Prior to the systematic review carried out in Chapter 2, there was no synthesis or single collection of this information available, and while some concerns regarding the limited volume and upload mass on-board these spacecraft had been published in peer-reviewed journals, there was no synthesis of information available regarding other constraints or their relationships with one another. Chapter 2 identified that the limited volume and upload mass of the Orion MPCV and similar capsular spacecraft present the most important challenges to the capability of astronauts to exercise effectively during spaceflight, with almost all other identified technical constraints resulting from these limitations. The chapter also led to the prediction of additional constraints based upon the small amount of quantitative data available. For example, it was possible to determine the total amount of time it would take for astronauts to complete a single day's exercise prescription (based on current ISS prescriptions) within the constraints of Orion's life support systems, which can be used to assist in exercise prescription plans. Chapter 2 also presented previously unpublished information obtained from personal communications with ESA staff (A. Frechette, personal communication, August 07, 2019), providing insights into the technical constraints of the Orion MPCV that were not previously in the public domain.

Chapter 3 identified 616 musculoskeletal and cardiovascular outcomes of relevance to astronaut health and operational mission success from spaceflight studies using a mixed-method systematic review. This review represents the largest, most comprehensive, synthesis of space medicine outcomes ever undertaken globally. In terms of primary outcomes, the review identified the outcomes, extracted quantitative information and converted them to effect sizes allowing for direct comparisons between studies. The chapter further extracted qualitative information in order to establish the relationships between, and common themes relevant to, the outcomes and rank them in terms of medical relevance and operational impact, with assistance from two medical doctors with space medicine backgrounds, in order to inform the methods of Chapter 4 and provide guidance to space medicine researchers on outcomes that should be prioritised for further research and study replication. For the muscle outcomes in Chapter 3, the main findings were that the most important outcome groups to astronaut health and operational success, in descending order of relevance, were functional and mechanical properties were the most relevant to astronaut health and mission success, followed by architectural and structural properties and then biomarkers of muscular deconditioning. For skeletal outcomes, the order of relevance were skeletal functional and mechanical properties, followed

by measures of volumetric bone mineral density; then biomarkers of bone remodelling, followed by measures of bone mineral density, and then skeletal architectural and structural properties. For cardiovascular outcomes, the order of relevance were hemodynamics and vascular function, cardiac muscle deconditioning, biomarkers of cardiovascular deconditioning, and then pulmonary ventilation and gas exchange.

Chapter 4 identified the most effective exercise countermeasure, from a pool of 13 devices studied in randomised and controlled trials during terrestrial microgravity simulations, that would be effective for the space medicine prioritised outcomes identified in Chapter 3. The main finding of this chapter was that flywheel was the most effective overall countermeasure to musculoskeletal and cardiovascular deconditioning. The findings of this meta-analysis provided support for, and were supported by, NASA's decision to implement a flywheel exercise device for future Orion missions (M. Downs, personal communication, October 1, 2020). While NASA had by this point decided to implement a flywheel exercise device there was no synthesis of the evidence base, until this review, to provide an evidence-based medical justification to the decision. The review also highlighted that there was little publicly available information on the dimensions of the potential exercise countermeasures, preventing direct comparisons with the technical constraints of Orion identified in Chapter 2. As such, the chapter recommended that NASA confirms that their flywheel-based device is capable of meeting the constraints of the Orion MPCV identified in Chapter 2.

Chapter 5 identified astronaut self-reported outcome preferences for the design and implementation of an exercise countermeasure, providing both novel primary data and additional context to the results of the meta-analysis from Chapter 4. This also provided an opportunity to ask astronauts directly about the use of flywheel as a sole exercise countermeasure for use on-board the Orion MPCV and similar capsular spacecraft. In doing so, Chapter 5 was able to highlight limitations to the use of flywheel and other exercise countermeasures during future space missions (such as being inappropriate to astronauts for missions of longer than 30 days, as it may result in boredom and a failure to adhere to exercise prescriptions), and additional considerations such as the provision of entertainment to increase adherence to exercise prescriptions during exercise and the possibility for novel exercise countermeasures that utilised the spaceflight environment rather than an exercise device. For example, one astronaut described a novel exercise that had been attempted on the ISS that utilised the spaceflight environment, where astronauts pushed off a bulkhead, floated to the opposite bulkhead and then pushed off to float back. Whilst Orion may be too small to carry out this type of movement/exercise, a key lesson learned was the importance of minimising the transfer of loads to the vehicle and the potential to utilise the spaceflight environment. Combined with the results from Chapter 4, this thesis was then able to provide clear recommendations on the most effective exercise countermeasure for musculoskeletal and cardiovascular deconditioning during spaceflight on-board the Orion MPCV and transferable capsular spacecraft.

6.2. Methodological contributions

Searching grey literature during systematic reviews is suggested by gold-standard systematic review method providers, such as Cochrane (Higgins et al., 2020), yet no tool for scoring their quality existed prior to Chapter 2. To assess the methodological quality of the included grey literature, a novel quality scoring tool was developed. The publication of the findings from Chapter 2 has led to the identified grey literature under-going peer-review scrutiny and the full collection of technical constraints being collated into a single published manuscript (Laws, Caplan, et al., 2020). The grey literature quality scoring tool was later used as part of a NASA systematic review assessing the impact of elevated ambient CO_2 in the atmosphere on pharmaceutical stability (Yuen et al., 2021).

In the process of developing a mixed-methods systematic review study protocol for Chapter 3, a wide number of methodological tools were developed and made publicly available, including: a quantitative (Winnard, Bruce-Martin, et al., 2020) and qualitative systematic review methods guide (Laws, Bruce-Martin, et al., 2020a); methodological guidance for implementing thematic analysis in systematic reviews (Laws et al., 2019a); guidance on the use of NVivo for the systematic review process (Laws, Bruce-Martin, & Winnard, 2020c); an aerospace medicine systematic review protocol template (Winnard & Laws, 2020); and a tool listing common sources of grey literature and useful space medicine databases for systematic searches (Winnard, Laws, & Swain, 2020). The systematic review and NVivo guides were later implemented as part of a NASA project investigating spaceflight medical evacuation risk assessment principles (Almand, Laws, Lehnhardt, & Easter, 2021a; Almand, Laws, Lehnhardt, & Easter, 2021b). These tools have been subject to peer-review scrutiny and presented in a peer-reviewed, published methods manuscript (Winnard et al., 2021).

6.3. Policy implications

Chapter 2 led to recommendations for changes to the ESA's current policy for exercise in the outer-space environment. Personal communications with ESA during this chapter indicated that ESA's current policy is that exercise is not necessary for short-duration missions of nine days or less (A. Frechette, personal communication, August 07, 2019). However, a recent systematic review (Winnard, Scott, et al., 2019) had found that moderate effects of muscle deconditioning during spaceflight simulation were observed after seven days when undertaking no exercise countermeasures. As such, it was recommended that the ESA amends policy to necessitate exercise for missions of seven days or more, rather than nine, and that the MPCV is not used for missions longer than seven days unless exercise countermeasures are available in order to reduce risk of injury to the crew involved.

Chapter 3 identified a large number of common limitations that were prevalent across the entire musculoskeletal field, including a lack of standardisation and the use of highly heterogenous outcomes, a common failure to report key outcome data (such as mean scores, standard deviations, and number of participants), and a severe lack of study replication. These limitations made it both difficult to compare results using standardised effect sizes and contributed to making gold-standard meta-analysis impossible. These findings represented a global problem for the space medicine field that can only be addressed at a sector level, and provide clear evidence that the current musculoskeletal and cardiovascular medical guidance for space medicine is not based upon the highest possible level of the evidence hierarchy (meta-analysis). To address these limitations, Chapter 3 recommended actions to space agencies, funders, and researchers that could be taken to remedy these limitations, including: the prioritisation of study replication that use relevant, pre-existing outcomes as identified in Chapter 3, reporting the pre- and post-flight data necessary to calculate standardised effect sizes, reporting the exercise countermeasures used during spaceflight, and not pooling data across spaceflights of different lengths. To initiate this process, the guidance from these chapters led to the development of peer-reviewed and published methodological guidance (Winnard et al., 2021) that provides an overview of these common limitations and suggests the need for a centralised methods group to direct the process of discussing and agreeing upon standardised outcomes and study protocols for use within space medicine.

6.4. Limitations

The thesis has made conclusions based upon a vast amount of data collected during multiple systematic reviews, and synthesis of 169 documents. Particularly in the case of quantitative synthesis, systematic reviews rely upon a comprehensive search strategy to ensure that as many relevant studies are included as possible. The Cochrane handbook recognises that it is possible studies may be missing from a review, which can occur because the data were never published, were published in obscure places, were inappropriately indexed in databases, or were rarely cited (Higgins et al., 2020). While every step, following both Cochrane and AMSRG guidelines, has been taken to reduce the risk of missing data, it should be acknowledged that the possibility of missing data exists.

The thesis also makes use of a number of methodological tools (e.g. ranking and scoring systems) which are trialled for the first time in this thesis. While many of these tools have passed the scrutiny of peer-review and have been included in a published manuscript (Laws, Caplan, et al., 2020; Winnard et al., 2021), the tools have not been formally tested for validity or reliability. The scoring tool presented in Chapter 3 to rank the effectiveness of musculoskeletal and cardiovascular deconditioning was developed with the input of two medical doctors with space medicine backgrounds. While this allowed for a qualitative assessment of the relative importance of each

outcome group to astronaut health and operational outcome success, it should be noted that given more time and resources additional content experts could have been used to enhance the reliability and trustworthiness of the ranking system. The scores and conclusions provided by the ranking system and the other tools are intended as a broad overview of the findings and are not intended to be taken as a sole guide for use in space medicine operational decision making. Operational decision makers and researchers should consider the individual outcome scores and effect sizes presented throughout the chapters of this thesis alongside any overall ranking or scoring system when undertaking the operational decision making processes. Likewise, the data presented in Chapter 5 represent the common preferences of only a small sample of the overall astronaut population and should be used to supplement, not entirely inform, the development and use of future exercise countermeasures. Ideally, the crewmembers chosen for future spaceflights should be asked for their own preferences for exercise countermeasure development so that their preferences can be augmented into their own individual, tailored exercise prescriptions.

Limitations of this thesis are not solely due to methodological reasons. Across the systematic reviews carried out in Chapters 2-4, it became clear that the conclusions of this thesis would be limited by poor-quality reporting within the space medicine evidence base. The evidence base examined in Chapter 2 consisted almost entirely of expert testimony and anecdotal evidence, leading to a lack of clear and detailed information. While this was not surprising during a synthesis of grey literature sources, a failure to clearly and accurately report information became far more concerning during Chapters 3 to 4, where peer-reviewed literature were collected for the data synthesis. Key outcome data, such as pre-flight scores, mean scores, standard deviations, and number of participants, were often unreported or unclear, preventing the calculation of standardised effect sizes and meta-analysis. In some cases, only figures were presented and no other quantitative data were presented at all. Data were sometimes pooled across multiple spaceflights, obscuring the length of time in which outcomes had been measured, or obscuring the countermeasures used during these spaceflights, creating difficulty in making inferences regarding long and short duration spaceflight differences and sources of heterogeneity. These issues were exacerbated by a severe lack of study replication that exists across the space medicine evidence base, evidenced by only 63 (~10%) of the 616 unique outcome measures identified in Chapter 3 having been reported in more than one study. This severe lack of study replication and highly heterogenous use of outcome measures represents a replication crisis within the musculoskeletal and cardiovascular sectors of the space medicine field that must be addressed for space medicine to become a truly evidence-based field.

6.5. Recommendations for future research

The limitations of the musculoskeletal and cardiovascular sectors of the space medicine evidence base identified within this thesis are expansive and must be addressed at the sector level. Researchers should discuss and agree upon a minimum set of reporting standards, such as the reporting of both pre- and post-spaceflight data, specifically the mean, standard deviation and number of participants, so that standardised effect size scores can be calculated and meta-analysis completed. Researchers should also report the exercise countermeasures used during spaceflight for each astronaut and report the number of days of spaceflight (for each flight, if multiple spaceflights are reported for a single astronaut) that each astronaut took part in. Standardised measurements, common outcome measures, and study protocols should also be agreed upon to reduce heterogeneity in the use of outcome measures. These recommendations will help to allow for comparisons using standardised effect sizes, and increase the statistical power of samples heterogeneous enough to be pooled from the evidence base. As these recommendations would require sector level implementation, it would be beneficial for researchers to discuss and agree upon standardised measurements, common outcome measures, and study protocols that can lead to more homogeneous outcome reporting. Winnard et al. (2021) has published an initial overview of the common limitations across spaceflight studies and the need for a centralized group to provide guidance and gap analysis to address them, as an initial starting point for this discussion. The synthesis of data within this thesis, such as the prioritisation of medical and operational rankings, could also be used as a basis for discussing and reaching consensus on which outcomes are most relevant to undergo study replication, given the inherent time and financial costs of spaceflight research.

This thesis has identified flywheel-based exercise as potentially the most effective single exercise countermeasure, based upon simulated microgravity trials, for musculoskeletal and cardiovascular deconditioning during spaceflight. Implementation of flywheel, or any other potential exercise countermeasure for Orion, should be done only with confirmation that they meet the technical limitations of Orion identified within this thesis. The astronaut-reported preferences for the development and implementation of an exercise device, examined in Chapter 5, have also highlighted the need to explore methods of increasing astronaut adherence to exercise on MPCV missions by reducing boredom. One avenue for doing so that was highlighted by the astronauts is the use of virtual or augmented reality technology. The use of these technologies could provide additional entertainment to the astronauts to help relieve boredom, reduce feelings of confinement, and increase positive affect whilst reducing negative affect (Anderson et al., 2017; Yeo et al., 2020). Therefore, future research should consider the potential of virtual reality technologies and other entertainment systems that could be implemented as part of astronaut exercise prescriptions. While the findings of this thesis may be useful for future spaceflight beyond low-Earth orbit (for example, to the Moon or Mars), it has not considered the effectiveness of exercise countermeasures in partial gravity once the

spacecraft reaches its destination. Future research should consider which exercise countermeasures will be most effective for maintaining astronaut health in these partial-gravity environments to provide a more complete understanding of the most effective exercise countermeasures for use during missions to the Moon, Mars, and beyond.

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Stemming from Chapter 2:

Laws, J.M., Caplan, N., Bruce, C., McGrogan, C., Lindsay, K., Wild, B., Debuse, D., Wotring, V., & Winnard, A. (2020). Systematic review of the technical and physiological constraints of the Orion Multi-Purpose Crew Vehicle that affect the capability of astronauts to exercise effectively during spaceflight. *Acta Astronautica*.

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Sandal, P. H., Kim, D., Fiebig, L., Winnard, A., Caplan, N., Green, D. A., & Weber, T. (2020). Effectiveness of nutritional countermeasures in microgravity and its ground-based analogues to ameliorate musculoskeletal and cardiopulmonary deconditioning–A Systematic Review. *PloS one*, *15*(6), e0234412.

Macaulay, T. R., Peters, B. T., Wood, S. J., Clément, G. R., Oddsson, L., & Bloomberg, J. J. (2021). Developing Proprioceptive Countermeasures to Mitigate Postural and Locomotor Control Deficits After Long-Duration Spaceflight. *Frontiers in Systems Neuroscience*, *15*, 37.

Swain, P., Laws, J. M., De Martino, E., Wotring, V., Caplan, N., & Winnard, A. (2021). Effectiveness of exercise countermeasures for the prevention of musculoskeletal deconditioning in simulated hypogravity: A systematic review. *Acta Astronautica*.

Yuen, A., Velho, R., **Laws, J.M.,** Stratton, E., Patel, K., Christensen, B., Demetres, M., Easter, B, Lehnhardt, K. (2021). A qualitative systematic review evaluating the impact of elevated ambient CO_2 in atmosphere on pharmaceutical stability. *Aerospace Medical Association's 91st Annual Scientific Meeting, Peppermill Resort Hotel, Reno, NV, May 23-27. Accepted December 2020.*

Stemming from Chapter 3:

Winnard, A., Caplan, N., Bruce-Martin, C., Swain, P., Velho, R., Meroni, R., Wotring, V., Damann, V., Weber, T., Evetts, S., **Laws, J.M.** *In Press* (2021). Developing and implementing novel

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Laws, J.M. & Winnard, A. (2019). Aerospace medicine systematic review group advice for embedding thematic analysis in systematic reviews. DOI: 10.13140/RG.2.2.30211.14888

Laws, J.M. & Winnard, A. (2019). AMSRG tool for scoring quality of non-empirical data sources. DOI: 10.13140/RG.2.2.18134.91207

Other Publications:

Swain, P., **Laws, J. M.**, De Martino, E., Wotring, V., Caplan, N., & Winnard, A. (2021). Effectiveness of exercise countermeasures for the prevention of musculoskeletal deconditioning in simulated hypogravity: A systematic review. *Acta Astronautica*.

Winnard, A., Bruce-Martin, C., **Laws, J.M.**, & Caplan, C. SpaceX: Will the average person need to exercise during a commercial spaceflight?

9.Appendices

9.1. Appendix A

Pre-scoping from Chapter 2.

A pre-scoping search was conducted to define the population, intervention, comparison, outcomes and types of studies (PICOS), inclusion criteria, and search strategy for the review (Higgins et al., 2011). The pre-scoping search of the literature was carried out using the NASA Technical Reports Server (NTRS), NASA Life Science Data Archive (LSDA), Google Scholar, PubMed/MEDLINE and the German Aerospace Centre Electronic Library (DLR elib) databases in October 2018. PubMed/MEDLINE and DLR elib were not used in the final review as pre-scoping found no relevant results in these databases.

Google Scholar was searched as part of pre-scoping in order to act as a safety net in case any other relevant documents had been missed. Though the limitations of Google Scholar (see section 2.4.7) make it difficult to use as a final search database, it is useful as a pre-scoping tool, as it is capable of searching multiple databases and has a high coverage of both research articles and grey literature (Gehanno, Rollin, & Darmoni, 2013; Giustini & Boulos, 2013). Google Scholar indicated a relevant paper in the Texas Digital Library (TDL) (TTU, 2019), which was then systematically searched for relevant documents. The final databases included in the review were NTRS, LSDA and TDL.

The EXCEL pre-scoping file can be found here: https://docs.google.com/spreadsheets/d/16PwDbQTgxcZw0jFXsvy0ZekyYI7L4_B3kIdGMFDLlog/edit?usp=sharing

9.2. Appendix B

Pre-scoping from Chapter 3.

A pre-scoping search of the literature was carried out using Cochrane Library, PubMed/MEDLINE, Science Direct, Web of Science, the NASA Technical Reports Server (NTRS) and Google Scholar (as a safety net), to determine the participants/population, interest/intervention, context/control and type of studies (PICOS (Higgins et al., 2011)) to be included in these reviews. Pre-scoping was further used to identify any relevant MeSH terms for use during the PubMed/MEDLINE search. The final databases used in these reviews include: Cochrane Library; PubMed/MEDLINE; Web of Science; and NTRS. Science direct was not used, as pre-scoping indicated that relevant results from this database could be obtained through already included databases. Google Scholar was searched as part of pre-scoping to act as a safety net in case any other relevant documents had been missed. Though the limitations of Google Scholar (see section 2.4.7) make it unsuitable to use as a final search database (Laws, Caplan, et al., 2020) it is useful as a pre-scoping tool, as it is capable of searching multiple databases and has a high coverage of both research articles and grey literature (Gehanno et al., 2013; Giustini et al., 2013). The search strategy for the databases were informed by pre-scoping. The final search terms were decided based upon pre-scoping and then confirmed through a meeting of experts within the Aerospace Medicine Systematic Review Group.

The EXCEL pre-scoping file can be found here: https://docs.google.com/spreadsheets/d/1zMil8hdgQxn5YeD9VGErWfT82-q8BxV-zLHj-AELr74/edit?usp=sharing

9.3. Appendix C

Muscle, skeletal, and cardiovascular outcome tables from chapter 3

Table 9.1 Physiological outcomes related to muscular health identified during the systematic search. Significant increase decrease or no change is reported where effect size data could not be extracted.

Outcome (Article cross reference number)	Theme	Days of Spaceflight	Effect size increase (↑), Decrease (↓) or No Change (NC) (with 95 Confidence Interval +/-) from prefight values (Article cross reference number)
Peak torque of knee extension* (20)	Isokinetic strength	First 10 years of ISS spaceflight	Significant ↓(20)
Peak torque of knee flexion* (20)	Isokinetic strength	First 10 years of ISS spaceflight	Significant ↓(20)
Peak torque of knee extension, total work* (20)	Isokinetic strength	First 10 years of ISS spaceflight	Significant ↓(20)
Peak torque of knee flexion, total work* (20)	Isokinetic strength	First 10 years of ISS spaceflight	Significant ↓(20)
Peak torque of concentric ankle extension* (20)	Isokinetic strength	First 10 years of ISS spaceflight	Significant ↓(20)
Peak torque of eccentric ankle extension* (20)	Isokinetic strength	First 10 years of ISS spaceflight	Significant ↓(20)
Peak torque of concentric ankle flexion* (20)	Isokinetic strength	First 10 years of ISS spaceflight	Significant ↓(20)
Peak torque of eccentric ankle flexion* (20)	Isokinetic strength	First 10 years of ISS spaceflight	Significant ↓(20)
Peak torque of trunk flexion* (20)	Isokinetic strength	First 10 years of ISS spaceflight	Significant ↓(20)
Peak torque of trunk extension* (20)	Isokinetic strength	First 10 years of ISS spaceflight	Significant ↓(20)
Plantarflexor torque* (76)	Isokinetic strength	N/A	N/A(76)
Dorsiflexor torque* (76)	Isokinetic strength	N/A	**NC**(76)
Triceps surae twitch peak torque of ankle joint angle*(75)	Isokinetic strength	17	N/A(75)
Force-velocity measurements at ankle angle, 30°/s(77)	Isokinetic strength	9	Significant ↓(77)
Force-velocity measurements at ankle angle, 60°/s(77)	Isokinetic strength	9	Significant ↓(77)
Force-velocity measurements at ankle angle, 120°/s(77)	Isokinetic strength	9	Significant ↓(77)
Force-velocity measurements at ankle angle, 180°/s(77)	Isokinetic strength	9	Significant ↓(77)
Force-velocity measurements at ankle angle, 240°/s(77)	Isokinetic strength	9	Significant ↓(77)
Force-velocity measurements at ankle angle, 300°/s(77)	Isokinetic strength	9	Significant ↓(77)
Maximal isometric strength at ankle angles of 80° (77)	Isometric strength	9	N/A(77)
Maximal isometric strength at ankle angles of 90° (77)	Isometric strength	9	N/A(77)
Maximal isometric strength at ankle angles of 100° (77)	Isometric strength	9	N/A(77)
Maximal voluntary isometric knee extensor force (63)	Isometric strength	16	0.50 (1.41) ↓(63)
Concentric knee extensor force (63)	Isometric strength	16	0.38 (1.40) ↓(63)
Eccentric knee extensor force (63)	Isometric strength	16	0.44 (1.40) ↓(63)
Mean force of lower limbs* (2)	Muscle maximal power	31	2.34 (1.80) ↓(2)
Maximal velocity of lower limbs* (2)	Muscle maximal power	31	1.78 (1.64) ↓(2)
Mean maximal power of lower limbs* (2)	Muscle maximal power	31	2.71 (1.92) ↓(2)

Outcome (Article cross reference number)	Theme	Days of Spaceflight	Effect size increase (↑), Decrease (↓) or No Change (NC) (with 95 Confidence Interval +/-) from prefight values (Article cross reference number)
Peak maximal power of lower limbs* (2)	Muscle maximal power	31	2.48 (1.84) ↓(2)
Maximal acceleration of lower limbs* (2)	Muscle maximal power	31	2.54 (1.86) ↓(2)
Overall mechanical work of lower limbs* (2)	Muscle maximal power	31	2.36 (1.80) ↓(2)
Peak mechanical power of lower limbs, during maximal explosive power test* (3)	Muscle maximal power	31-180	Significant ↓(3)
Mean mechanical power of lower limbs, during maximal explosive power test * (3)	Muscle maximal power	31-180	Significant ↓(3)
Peak mechanical power of lower limbs, during maximal cycling power test* (3)	Muscle maximal power	31-180	Significant ↓(3)
Mean mechanical power of lower limbs, during maximal cycling power test* (3)	Muscle maximal power	31-180	Significant ↓(3)
Maximal explosive power of the lower limbs (3)	Muscle maximal power	31-180	Significant ↓(3)
Maximal cycling power of the lower limbs (3)	Muscle maximal power	31-180	Significant ↓(3)
Sartorius muscle volume (1)	Muscle volume	9-16	Significant ↓(1)
Gracilis muscle volume (1)	Muscle volume	9-16	Significant ↓(1)
Quadriceps femoris muscle volume* (1, 34)	Muscle volume	9-16(1) 17-196(34)	Significant ↓(1) Significant ↓(34)
Hamstring muscles volume* (1, 34)	Muscle volume	9-16(1) 17-196(34)	Significant ↓(1) Significant ↓(34)
Triceps surae muscles volume* (1)	Muscle volume	9-16	Significant ↓(1)
Gastrocnemius muscle volume (34)	Muscle volume	17-196	Significant ↓(34)
Soleus muscle volume (34, 52, 78)	Muscle volume	17-196(34) 183(52) 9(77)	Significant ↓(34) Significant ↓(52) Significant ↓(77)
Gastrocnemius medial + lateral head muscle volume (77)	Muscle volume	9	Significant ↓(77)
Gastrocnemius + soleus muscle volume (77)	Muscle volume	9	Significant ↓(77)
Plantar flexor muscle volume* (78)	Muscle volume	30-138	N/A(78)
Calf muscle volume* (78)	Muscle volume	30-138	N/A(78)
Paraspinal muscles (erector spinae) volume* (38)	Muscle volume	121-183	Significant ↓(38)
Psoas muscle volume (34, 38)	Muscle volume	17-196(34) 121-183(38)	Significant ↓(34) **NC** (38)
Quadratus lumborum muscle volume (38)	Muscle volume	121-183	Significant ↓(38)
Anterior leg muscles volume* (34)	Muscle volume	17-196	Significant ↓(34)
Intrinsic back muscles volume* (34)	Muscle volume	17-196	Significant ↓(34)
Calf muscle transverse relaxation time (T2) (34)	Muscle volume	17-196	Significant ↑(34)
Femoral muscles volume* (40)	Muscle volume	8.9-14.7	Significant ↓(40)
Crural muscles volume* (40)	Muscle volume	8.9-14.7	Significant ↓(40)
Medial gastrocnemius muscle volume (52)	Muscle volume	183	N/A(52)
Erector spinae cross-sectional area (13)	Muscle cross-sectional area	121-213	0.40 (0.68) ↓(13)
Lumbar paraspinal muscle cross-sectional area (17)	Muscle cross-sectional area	117-213	0.14 (1.13) ↓(17)
Multifidus cross-sectional area (13)	Muscle cross-sectional area	121-213	0.39 (0.68) ↓(13)
Quadratus lumborum cross-sectional area (13)	Muscle cross-sectional area	121-213	0.48 (0.68) ↓(13)
Psoas cross-sectional area (13)	Muscle cross-sectional area	121-213	0.21 (0.67) ↓(13)

Outcome (Article cross reference number)	Theme	Days of Spaceflight	Effect size increase (↑), Decrease (↓) or No Change (NC) (with 95 Confidence Interval +/-) from prefight values (Article cross reference number)
Medial gastrocnemius muscle physiological cross-sectional area [52]	Muscle cross-sectional area	183	N/A[52]
Soleus muscle physiological cross-sectional area [52]	Muscle cross-sectional area	183	N/A[52]
Quadriceps muscles cross-sectional area* [63]	Muscle cross-sectional area	16	0.62 (1.42) ↓[63]
Gluteal muscles cross-sectional area* [63]	Muscle cross-sectional area	16	0.88 (1.45) ↓[63]
Hamstring muscles cross-sectional area* [63]	Muscle cross-sectional area	16	0.06 (1.39) ↓[63]
Calf muscle and bone cross-sectional area [75]	Muscle cross-sectional area	17	N/A[75]
Plantar flexor cross-sectional area [78]	Muscle cross-sectional area	30-138	N/A[78]
Erector spinae attenuation [13]	Muscle attenuation	121-213	0.83 (0.70) ↓[13]
Multifidus attenuation [13]	Muscle attenuation	121-213	0.76 (0.70) ↓[13]
Quadratus lumborum attenuation [13]	Muscle attenuation	121-213	0.79 (0.70) ↓[13]
Psoas attenuation [13]	Muscle attenuation	121-213	0.55 (0.68) ↓[13]
Medial gastrocnemius muscle fascicle length [52]	Gastrocnemius muscle fibre architectural and structural properties	183	N/A[52]
Diameter of the gastrocnemius slow red type I muscle fibre [21, 71]	Gastrocnemius muscle fibres architectural and structural properties	161-192[21] 17[71]	3.14 (1.31) ↓[21] 0.85 (1.45) ↓[71]
Cross-sectional area of the gastrocnemius slow red type I muscle fibre [21]	Gastrocnemius muscle fibres architectural and structural properties	161-192	0.81 (0.91) ↓[21]
Diameter of the gastrocnemius fast white type II muscle fibre [21]	Gastrocnemius muscle fibres architectural and structural properties	161-192	0.18 (0.88) ↓[21]
Cross-sectional area of the gastrocnemius fast white type II muscle fibre [21]	Gastrocnemius muscle fibres architectural and structural properties	161-192	0.34 (0.88) ↓[21]
Gastrocnemius fast white type IIa/IIx muscle fibre thin filament density [51]	Gastrocnemius muscle fibres architectural and structural properties	17	0.04 (1.39) ↓[51]
Gastrocnemius fast white type IIa muscle fibre thin filament density [51]	Gastrocnemius muscle fibres architectural and structural properties	17	0.10 (1.39) ↓[51]
Gastrocnemius slow red type I muscle fibre thin filament density [51]	Gastrocnemius muscle fibres architectural and structural properties	17	0.21 (1.39) ↓[51]
Gastrocnemius fast white type IIa/IIx muscle fibre thick filament density [51]	Gastrocnemius muscle fibres architectural and structural properties	17	0.02 (1.39) ↓[51]
Gastrocnemius fast white type IIa muscle fibre thick filament density [51]	Gastrocnemius muscle fibres architectural and structural properties	17	0.01 (1.39) ↑[51]
Gastrocnemius slow red type I muscle fibre thick filament density [51]	Gastrocnemius muscle fibres architectural and structural properties	17	0.11 (1.39) ↓[51]

Outcome (Article cross reference number)	Theme	Days of Spaceflight	Effect size increase (↑), Decrease (↓) or No Change (NC) (with 95 Confidence Interval +/-) from prefight values (Article cross reference number)
Percentage of gastrocnemius fast white type IIa/IIx muscle fibre short thin filaments [51]	Gastrocnemius muscle fibres architectural and structural properties	17	0.49 (1.41) ↓[51]
Percentage of gastrocnemius fast white type IIa muscle fibre short thin filaments [51]	Gastrocnemius muscle fibres architectural and structural properties	17	0.01 (1.39) ↑[51]
Percentage of gastrocnemius slow red type I muscle fibre short thin filaments [51]	Gastrocnemius muscle fibres architectural and structural properties	17	0.52 (1.41) ↑[51]
Gastrocnemius fast white type IIa/IIx muscle fibre thin filament spacing [51]	Gastrocnemius muscle fibres architectural and structural properties	17	N/A[51]
Gastrocnemius fast white type IIa muscle fibre thin filament spacing [51]	Gastrocnemius muscle fibres architectural and structural properties	17	N/A[51]
Gastrocnemius slow red type I muscle fibre thin filament spacing [51]	Gastrocnemius muscle fibres architectural and structural properties	17	N/A[51]
Gastrocnemius fast white type IIa/IIx muscle fibre thick filament spacing [51]	Gastrocnemius muscle fibres architectural and structural properties	17	N/A[51]
Gastrocnemius fast white type IIa muscle fibre thick filament spacing [51]	Gastrocnemius muscle fibres architectural and structural properties	17	N/A[51]
Gastrocnemius slow red type I muscle fibre thick filament spacing [51]	Gastrocnemius muscle fibres architectural and structural properties	17	N/A[51]
Gastrocnemius fast white type IIa muscle fibre diameter [71]	Gastrocnemius muscle fibres architectural and structural properties	17	0.00 (1.39) **NC** [71]
Gastrocnemius fast white type IIa/IIx muscle fibre diameter [71]	Gastrocnemius muscle fibres architectural and structural properties	17	0.14 (1.39) ↓[71]
Type I Gastrocnemius muscle fibre type distribution [77]	Gastrocnemius muscle fibres architectural and structural properties	9	1.92 (1.68) ↑[77]
Type I/IIa Gastrocnemius muscle fibre type distribution [77]	Gastrocnemius muscle fibres architectural and structural properties	9	1.84 (1.65) ↑[77]
Type IIa Gastrocnemius muscle fibre type distribution [77]	Gastrocnemius muscle fibres architectural and structural properties	9	1.77 (1.09) ↑[77]
Type IIa/IIx Gastrocnemius muscle fibre type distribution [77]	Gastrocnemius muscle fibres architectural and structural properties	9	1.11 (0.99) ↑[77]

Outcome (Article cross reference number)	Theme	Days of Spaceflight	Effect size increase (↑), Decrease (↓) or No Change (NC) (with 95 Confidence Interval +/-) from prefight values (Article cross reference number)
Type IIx Gastrocnemius muscle fibre type distribution (77)	Gastrocnemius muscle fibres architectural and structural properties	9	1.42 (1.03) ↑(77)
Type I/IIa/IIx Gastrocnemius muscle fibre type distribution (77)	Gastrocnemius muscle fibres architectural and structural properties	9	**NC**(77)
Hybrids Gastrocnemius muscle fibre type distribution (77)	Gastrocnemius muscle fibres architectural and structural properties	9	1.64 (1.07) ↑(77)
Soleus muscle fascicle length (52)	Soleus muscle fibre architectural and structural properties	183	N/A(52)
Soleus slow red type I relative content of the slow isoform of myosin heavy chain (52)	Soleus muscle fibres architectural and structural properties	17	N/A (52)
Actin sliding velocity of the soleus muscle fibres (52)	Soleus muscle fibres architectural and structural properties	17	N/A (52)
Diameter of the soleus slow red type I muscle fibre (21, 70)	Soleus muscle fibres architectural and structural properties	161-192(21) 17(70)	3.14 (1.31) ↓(21)
Cross-sectional area of the soleus slow red type I muscle fibre (21, 52)	Soleus muscle fibres architectural and structural properties	161-192(21) 17(52)	N/A (52)
Diameter of the soleus fast white type II muscle fibre (21)	Soleus muscle fibres architectural and structural properties	161-192	1.48 (0.99) ↓(21)
Cross-sectional area of the soleus fast white type II muscle fibre (21)	Soleus muscle fibres architectural and structural properties	161-192	1.81 (1.04) ↓(21)
Soleus muscle fibre thick filament density (50)	Soleus muscle fibres architectural and structural properties	17	0.59 (1.42) ↓(50)
Soleus muscle fibre thin filament density (50)	Soleus muscle fibres architectural and structural properties	17	0.91 (1.46) ↓(50)
Soleus muscle fibre thick filament spacing (50)	Soleus muscle fibres architectural and structural properties	17	0.46 (1.40) ↓(50)
Soleus muscle fibre thin filament spacing (50)	Soleus muscle fibres architectural and structural properties	17	N/A(50)
Percentage of soleus muscle fibre short thin filaments (50)	Soleus muscle fibres architectural and structural properties	17	Significant ↓(50)
Percentage of soleus muscle fibre filament loss (50)	Soleus muscle fibres architectural and structural properties	17	Significant ↓(50)
Soleus slow red type I muscle fibre thin filament density (51)	Soleus muscle fibres architectural and structural properties	17	0.91 (1.46) ↓(51)
Soleus slow red type I muscle fibre thick filament density (51)	Soleus muscle fibres architectural and structural properties	17	0.56 (1.41) ↓(51)
Percentage of soleus slow red type I muscle fibre short thin filaments (51)	Soleus muscle fibres architectural and structural properties	17	1.25 (1.52) ↑(51)
Soleus slow red type I muscle fibre thin filament spacing (51)	Soleus muscle fibres architectural and structural properties	17	N/A(51)
Soleus slow red type I muscle fibre thick filament spacing (51)	Soleus muscle fibres architectural and structural properties	17	N/A(51)
Soleus slow red type I muscle fibre myosin heavy chain composition (70)	Soleus muscle fibres architectural and structural properties	17	N/A(70)

Outcome (Article cross reference number)	Theme	Days of Spaceflight	Effect size increase (↑), Decrease (↓) or No Change (NC) (with 95 Confidence Interval +/-) from prefight values (Article cross reference number)
Soleus fast white type IIa muscle fibre myosin heavy chain composition [70]	Soleus muscle fibres architectural and structural properties	17	N/A[70]
Type I Soleus muscle fibre type distribution [77]	Soleus muscle fibres architectural and structural properties	9	3.66 (1.51) ↑[77]
Type I/IIa Soleus muscle fibre type distribution [77]	Soleus muscle fibres architectural and structural properties	9	0.76 (0.96) ↓[77]
Type IIa Soleus muscle fibre type distribution [77]	Soleus muscle fibres architectural and structural properties	9	0.90 (0.97) ↑[77]
Type IIa/IIx Soleus muscle fibre type distribution [77]	Soleus muscle fibres architectural and structural properties	9	0.55 (0.94) ↑[77]
Type IIx Soleus muscle fibre type distribution [77]	Soleus muscle fibres architectural and structural properties	9	**NC**[77]
Type I/IIa/IIx Soleus muscle fibre type distribution [77]	Soleus muscle fibres architectural and structural properties	9	**NC**[77]
Hybrids Soleus muscle fibre type distribution [77]	Soleus muscle fibres architectural and structural properties	9	1.44 (1.04) ↑[77]
Meta-vinculin alterations [52]	Skeletal muscle anaerobic metabolism protein alterations	183	N/A[52]
Tenascin-C alterations [52]	Skeletal muscle anaerobic metabolism protein alterations	183	N/A[52]
FAK-pY397 alterations [52]	Skeletal muscle anaerobic metabolism protein alterations	183	N/A[52]
FAk alterations [52]	Skeletal muscle anaerobic metabolism protein alterations	183	N/A[52]
FRNK alterations [52]	Skeletal muscle anaerobic metabolism protein alterations	183	N/A[52]
Gamma-vinculin alterations [52]	Skeletal muscle anaerobic metabolism protein alterations	183	N/A[52]
PYGM anaerobic metabolism protein alterations [52]	Skeletal muscle anaerobic metabolism protein alterations	183	N/A[52]
GPD1 anaerobic metabolism protein alterations [52]	Skeletal muscle anaerobic metabolism protein alterations	183	N/A[52]
ALDOA anaerobic metabolism protein alterations [52]	Skeletal muscle anaerobic metabolism protein alterations	183	N/A[52]
GAPDH anaerobic metabolism protein alterations [52]	Skeletal muscle anaerobic metabolism protein alterations	183	N/A[52]
PGAM2 anaerobic metabolism protein alterations [52]	Skeletal muscle anaerobic metabolism protein alterations	183	N/A[52]
ENO1 anaerobic metabolism protein alterations [52]	Skeletal muscle anaerobic metabolism protein alterations	183	N/A[52]
ENO3 anaerobic metabolism protein alterations [52]	Skeletal muscle anaerobic metabolism protein alterations	183	N/A[52]
PKM anaerobic metabolism protein alterations [52]	Skeletal muscle anaerobic metabolism protein alterations	183	N/A[52]
LDHA anaerobic metabolism protein alterations [52]	Skeletal muscle anaerobic metabolism protein alterations	183	N/A[52]

Outcome (Article cross reference number)	Theme	Days of Spaceflight	Effect size increase (↑), Decrease (↓) or No Change (NC) (with 95 Confidence Interval +/-) from prefight values (Article cross reference number)
ACO2 anaerobic metabolism protein alterations (52)	Skeletal muscle anaerobic metabolism protein alterations	183	N/A(52)
IDH2 anaerobic metabolism protein alterations (52)	Skeletal muscle anaerobic metabolism protein alterations	183	N/A(52)
OGDH anaerobic metabolism protein alterations (52)	Skeletal muscle anaerobic metabolism protein alterations	183	N/A(52)
DLD anaerobic metabolism protein alterations (52)	Skeletal muscle anaerobic metabolism protein alterations	183	N/A(52)
SUCLA2 anaerobic metabolism protein alterations (52)	Skeletal muscle anaerobic metabolism protein alterations	183	N/A(52)
SDHA anaerobic metabolism protein alterations (52)	Skeletal muscle anaerobic metabolism protein alterations	183	N/A(52)
MDH1 anaerobic metabolism protein alterations (52)	Skeletal muscle anaerobic metabolism protein alterations	183	N/A(52)
GOT1 anaerobic metabolism protein alterations (52)	Skeletal muscle anaerobic metabolism protein alterations	183	N/A(52)
GOT2 anaerobic metabolism protein alterations (52)	Skeletal muscle anaerobic metabolism protein alterations	183	N/A(52)
NDUFS3 anaerobic metabolism protein alterations (52)	Skeletal muscle anaerobic metabolism protein alterations	183	N/A(52)
NDUFV1 anaerobic metabolism protein alterations (52)	Skeletal muscle anaerobic metabolism protein alterations	183	N/A(52)
UQCRC1 anaerobic metabolism protein alterations (52)	Skeletal muscle anaerobic metabolism protein alterations	183	N/A(52)
ATP5A1 anaerobic metabolism protein alterations (52)	Skeletal muscle anaerobic metabolism protein alterations	183	N/A(52)
ATP5B anaerobic metabolism protein alterations (52)	Skeletal muscle anaerobic metabolism protein alterations	183	N/A(52)
ATP5H anaerobic metabolism protein alterations (52)	Skeletal muscle anaerobic metabolism protein alterations	183	N/A(52)
ETFB anaerobic metabolism protein alterations (52)	Skeletal muscle anaerobic metabolism protein alterations	183	N/A(52)
ACADVL anaerobic metabolism protein alterations (52)	Skeletal muscle anaerobic metabolism protein alterations	183	N/A(52)
ACADS anaerobic metabolism protein alterations (52)	Skeletal muscle anaerobic metabolism protein alterations	183	N/A(52)
ECI1 anaerobic metabolism protein alterations (52)	Skeletal muscle anaerobic metabolism protein alterations	183	N/A(52)
ECH1 anaerobic metabolism protein alterations (52)	Skeletal muscle anaerobic metabolism protein alterations	183	N/A(52)
CKM anaerobic metabolism protein alterations (52)	Skeletal muscle anaerobic metabolism protein alterations	183	N/A(52)
CKMT2 anaerobic metabolism protein alterations (52)	Skeletal muscle anaerobic metabolism protein alterations	183	N/A(52)
AK1 anaerobic metabolism protein alterations (52)	Skeletal muscle anaerobic metabolism protein alterations	183	N/A(52)

Outcome (Article cross reference number)	Theme	Days of Spaceflight	Effect size increase (↑), Decrease (↓) or No Change (NC) (with 95 Confidence Interval +/-) from preflight values (Article cross reference number)
ACTA1 contractile protein alterations [52]	Skeletal muscle contractile protein alterations	183	N/A[52]
TNNI2 contractile protein alterations [52]	Skeletal muscle contractile protein alterations	183	N/A[52]
TNNT1 contractile protein alterations [52]	Skeletal muscle contractile protein alterations	183	N/A[52]
TNNT3 contractile protein alterations [52]	Skeletal muscle contractile protein alterations	183	N/A[52]
TPM1 contractile protein alterations [52]	Skeletal muscle contractile protein alterations	183	N/A[52]
TPM2 contractile protein alterations [52]	Skeletal muscle contractile protein alterations	183	N/A[52]
Heat shock protein beta-1 [16]	Protein biomarkers of muscular deconditioning	183	N/A[16]
60 kDa heat shock protein, mitochondrial [16]	Protein biomarkers of muscular deconditioning	183	N/A[16]
Heat shock–related 70 kDa protein 2 [16]	Protein biomarkers of muscular deconditioning	183	N/A[16]
Endoplasmic reticulum chaperone BiP [16]	Protein biomarkers of muscular deconditioning	183	N/A[16]
Annexin A2 [16]	Protein biomarkers of muscular deconditioning	183	N/A[16]
a-1-antitrypsina [16]	Protein biomarkers of muscular deconditioning	183	N/A[16]
Peroxiredoxin-2 [16]	Protein biomarkers of muscular deconditioning	183	N/A[16]
Peroxiredoxin-6 [16]	Protein biomarkers of muscular deconditioning	183	N/A[16]
Tripartite motif-containing protein 72 [16]	Protein biomarkers of muscular deconditioning	183	N/A[16]
Superoxide dismutase [16]	Enzyme biomarkers of muscular deconditioning	183	N/A[16]
Catalase [16]	Enzyme biomarkers of muscular deconditioning	183	N/A[16]
Glutathione S-transferase Mu 2 [16]	Enzyme biomarkers of muscular deconditioning	183	N/A[16]
Protein/nucleic acid deglycase DJ-1 [16]	Enzyme biomarkers of muscular deconditioning	183	N/A[16]
miR-206 [16]	Blood c-markers	183	N/A[16]
miR-133a-3p [16]	Blood c-markers	183	N/A[16]
miR-146a-5p [16]	Blood c-markers	183	N/A[16]
c-proteasome [16]	Blood c-markers	183	N/A[16]
Leptin [16]	Blood c-markers	183	N/A[16]
mtDNA [16]	Blood c-markers	183	N/A[16]
miR-363-3p [16]	Blood c-markers	183	N/A[16]
miR-122-5p [16]	Blood c-markers	183	N/A[16]
miR-145-5p [16]	Blood c-markers	183	N/A[16]

Outcome (Article cross reference number)	Theme	Days of Spaceflight	Effect size increase (↑), Decrease (↓) or No Change (NC) (with 95 Confidence Interval +/-) from preflight values (Article cross reference number)
miR-126-3p [16]	Blood c-markers	183	N/A[16]
miR-21-5p [16]	Blood c-markers	183	N/A[16]
IL-6 [16]	Blood c-markers	183	N/A[16]
TGF-b1 [16]	Blood c-markers	183	N/A[16]
Alanine aminoacid metabolism alterations [52]	Plasma metabolomic alterations	183	N/A[52]
Isoleucine aminoacid metabolism alterations [52]	Plasma metabolomic alterations	183	N/A[52]
Phenylalanine aminoacid metabolism alterations [52]	Plasma metabolomic alterations	183	N/A[52]
Tyrosine aminoacid metabolism alterations [52]	Plasma metabolomic alterations	183	N/A[52]
Glucose energetic metabolism alterations [52]	Plasma metabolomic alterations	183	N/A[52]
Lactate energetic metabolism alterations [52]	Plasma metabolomic alterations	183	N/A[52]
Pyruvate energetic metabolism alterations [52]	Plasma metabolomic alterations	183	N/A[52]
Pyruvate-lactate ratio energetic metabolism alterations [52]	Plasma metabolomic alterations	183	N/A[52]
Medial gastrocnemius muscle pennation angle [52]	Functional and mechanical properties of the gastrocnemius muscle	183	N/A[52]
Maximal voluntary contraction of the lateral gastrocnemius [29]	Functional and mechanical properties of the gastrocnemius muscle	115-380	N/A[29]
Tetanic tension of the lateral gastrocnemius [29]	Functional and mechanical properties of the gastrocnemius muscle	115-380	N/A[29]
Voluntary contraction time of the lateral gastrocnemius [29]	Functional and mechanical properties of the gastrocnemius muscle	115-380	N/A[29]
Electrically evoked contraction time of the lateral gastrocnemius [29]	Functional and mechanical properties of the gastrocnemius muscle	115-380	N/A[29]
Force deficiency of the lateral gastrocnemius [29]	Functional and mechanical properties of the gastrocnemius muscle	115-380	N/A[29]
Maximal voluntary contraction of the medial gastrocnemius [29]	Functional and mechanical properties of the gastrocnemius muscle	115-380	N/A[29]
Tetanic tension of the medial gastrocnemius [29]	Functional and mechanical properties of the gastrocnemius muscle	115-380	N/A[29]
Voluntary contraction time of the medial gastrocnemius [29]	Functional and mechanical properties of the gastrocnemius muscle	115-380	N/A[29]
Electrically evoked contraction time of the medial gastrocnemius [29]	Functional and mechanical properties of the gastrocnemius muscle	115-380	N/A[29]
Force deficiency of the medial gastrocnemius [29]	Functional and mechanical properties of the gastrocnemius muscle	115-380	N/A[29]

Outcome (Article cross reference number)	Theme	Days of Spaceflight	Effect size increase (↑), Decrease (↓) or No Change (NC) (with 95 Confidence Interval +/-) from prefight values (Article cross reference number)
Maximal isometric torque of the gastrocnemius muscle (31)	Functional and mechanical properties of the gastrocnemius muscle	90-180	N/A(31)
Maximal shortening velocity of the gastrocnemius muscle (31)	Functional and mechanical properties of the gastrocnemius muscle	90-180	N/A(31)
Maximal muscle activation of the gastrocnemius muscle (31)	Functional and mechanical properties of the gastrocnemius muscle	90-180	N/A(31)
Musculotendinous stiffness of the gastrocnemius muscle (31)	Functional and mechanical properties of the gastrocnemius muscle	90-180	N/A(31)
Whole joint stiffness of the gastrocnemius muscle (31)	Functional and mechanical properties of the gastrocnemius muscle	90-180	N/A(31)
Hoffman's reflex of the lateral gastrocnemius (30)	Functional and mechanical properties of the gastrocnemius muscle	90-180	N/A(30)
Tendon reflex of the lateral gastrocnemius (30)	Functional and mechanical properties of the gastrocnemius muscle	90-180	N/A(30)
Musculotendinous stiffness of the lateral gastrocnemius (30)	Functional and mechanical properties of the gastrocnemius muscle	90-180	N/A(30)
Musculoarticular stiffness of the lateral gastrocnemius (30)	Functional and mechanical properties of the gastrocnemius muscle	90-180	N/A(30)
Hoffman's reflex of the medial gastrocnemius (30)	Functional and mechanical properties of the gastrocnemius muscle	90-180	N/A(30)
Tendon reflex of the medial gastrocnemius (30)	Functional and mechanical properties of the gastrocnemius muscle	90-180	N/A(30)
Musculotendinous stiffness of the medial gastrocnemius (30)	Functional and mechanical properties of the gastrocnemius muscle	90-180	N/A(30)
Medial gastrocnemius muscle mean integrated electromyography activity (76)	Functional and mechanical properties of the gastrocnemius muscle	N/A	N/A(76)
Medial gastrocnemius muscle electromyography amplitude during dorsiflexion (76)	Functional and mechanical properties of the gastrocnemius muscle	N/A	N/A(76)

Outcome (Article cross reference number)	Theme	Days of Spaceflight	Effect size increase (↑), Decrease (↓) or No Change (NC) (with 95 Confidence Interval +/-) from prefight values (Article cross reference number)
Triceps surae tetanic torque [75]	Functional and mechanical properties of the gastrocnemius muscle.	17	N/A[75]
Triceps surae fatigability [75]	Functional and mechanical properties of the gastrocnemius muscle.	17	N/A[75]
Soleus muscle pennation angle [52]	Functional and mechanical properties of the soleus muscle	183	N/A[52]
Maximal voluntary contraction of the lateral soleus [29]	Functional and mechanical properties of the soleus muscle	115-380	N/A[29]
Tetanic tension of the lateral soleus [29]	Functional and mechanical properties of the soleus muscle	115-380	N/A[29]
Voluntary contraction time of the lateral soleus [29]	Functional and mechanical properties of the soleus muscle	115-380	N/A[29]
Electrically evoked contraction time of the lateral soleus [29]	Functional and mechanical properties of the soleus muscle	115-380	N/A[29]
Force deficiency of the lateral soleus [29]	Functional and mechanical properties of the soleus muscle	115-380	N/A[29]
Maximal voluntary contraction of the medial soleus [29]	Functional and mechanical properties of the soleus muscle	115-380	N/A[29]
Tetanic tension of the medial soleus [29]	Functional and mechanical properties of the soleus muscle	115-380	N/A[29]
Voluntary contraction time of the medial soleus [29]	Functional and mechanical properties of the soleus muscle	115-380	N/A[29]
Electrically evoked contraction time of the medial soleus [29]	Functional and mechanical properties of the soleus muscle	115-380	N/A[29]
Force deficiency of the medial soleus [29]	Functional and mechanical properties of the soleus muscle	115-380	N/A[29]
Maximal isometric torque of the soleus muscle [31]	Functional and mechanical properties of the soleus muscle	90-180	N/A[31]
Maximal shortening velocity of the soleus muscle [31]	Functional and mechanical properties of the soleus muscle	90-180	N/A[31]
Maximal muscle activation of the soleus muscle [31]	Functional and mechanical properties of the soleus muscle	90-180	N/A[31]
Musculotendinous stiffness of the soleus muscle [30, 31]	Functional and mechanical properties of the soleus muscle	90-180[30] 90-180[31]	N/A[30] N/A[31]
Whole joint stiffness of the soleus muscle [31]	Functional and mechanical properties of the soleus muscle	90-180	N/A[31]
Hoffman's reflex of the soleus muscle [30]	Functional and mechanical properties of the soleus muscle	90-180	N/A[30]
Tendon reflex of the soleus muscle [30]	Functional and mechanical properties of the soleus muscle	90-180	N/A[30]

Outcome [Article cross reference number]	Theme	Days of Spaceflight	Effect size increase (↑), Decrease (↓) or No Change (NC) (with 95 Confidence Interval +/-) from prefight values [Article cross reference number]
Musculoarticular stiffness of the soleus muscle [30]	Functional and mechanical properties of the soleus muscle	90-180	N/A[30]
Soleus muscle mean integrated electromyography activity [76]	Functional and mechanical properties of the soleus muscle	N/A	Significant ↓[76]
Soleus muscle electromyography amplitude during dorsiflexion [76]	Functional and mechanical properties of the soleus muscle	N/A	N/A[76]
Soleus slow red type I muscle fibre peak force per fibre cross-sectional area [70]	Gastrocnemius muscle fibres functional and mechanical properties	17	N/A[70]
Peak force of the gastrocnemius slow red type I muscle fibre [21, 71]	Gastrocnemius muscle fibres functional and mechanical properties	161-192[21] 17[71]	2.71 (1.21) ↓[21] 0.56 (1.41) ↓[71]
Maximum shortening velocity of the gastrocnemius slow red type I muscle fibre [21, 71]	Gastrocnemius muscle fibres functional and mechanical properties	161-192[21] 17[71]	2.00 (1.07) ↓[21] 1.13 (1.49) ↑[71]
Peak stiffness ratio of the gastrocnemius slow red type I muscle fibre [21]	Gastrocnemius muscle fibres functional and mechanical properties	161-192	1.09 (0.94) ↑[21]
Rate constant of tension redevelopment of the gastrocnemius slow red type I muscle fibre [21]	Gastrocnemius muscle fibres functional and mechanical properties	161-192	1.33 (0.97) ↓[21]
Peak power of the gastrocnemius slow red type I muscle fibre [21, 71]	Gastrocnemius muscle fibres functional and mechanical properties	161-192[21] 17[71]	3.76 (1.46) ↓[21] 0.42 (0.79) ↓[71]
Peak force of the gastrocnemius fast white type II muscle fibre [21]	Gastrocnemius muscle fibres functional and mechanical properties	161-192	0.56 (0.89) ↓[21]
Maximal shortening velocity of the gastrocnemius fast white type II muscle fibre [21]	Gastrocnemius muscle fibres functional and mechanical properties	161-192	1.68 (1.02) ↓[21]
Gastrocnemius fast white type IIa muscle fibre peak force [71]	Gastrocnemius muscle fibres functional and mechanical properties	17	0.44 (1.40) ↓[71]
Gastrocnemius fast white type IIa/IIx muscle fibre peak force [71]	Gastrocnemius muscle fibres functional and mechanical properties	17	0.14 (1.39) ↑[71]
Gastrocnemius slow red type I muscle fibre unloaded shortening velocity [71]	Gastrocnemius muscle fibres functional and mechanical properties	17	1.77 (1.64) ↑[71]
Gastrocnemius fast white type IIa muscle fibre unloaded shortening velocity [71]	Gastrocnemius muscle fibres functional and mechanical properties	17	1.03 (1.48) ↑[71]
Gastrocnemius fast white type IIa/IIx muscle fibre unloaded shortening velocity [71]	Gastrocnemius muscle fibres functional and mechanical properties	17	0.49 (1.41) ↑[71]

Outcome (Article cross reference number)	Theme	Days of Spaceflight	Effect size increase (↑), Decrease (↓) or No Change (NC) (with 95 Confidence Interval +/-) from prefight values (Article cross reference number)
Gastrocnemius slow red type I muscle fibre peak activated force (71)	Gastrocnemius muscle fibres functional and mechanical properties	17	0.71 (1.43) ↓(71)
Gastrocnemius fast white type IIa muscle fibre peak activated force (71)	Gastrocnemius muscle fibres functional and mechanical properties	17	1.33 (1.53) ↓(71)
Gastrocnemius fast white type IIa/IIx muscle fibre peak activated force (71)	Gastrocnemius muscle fibres functional and mechanical properties	17	0.88 (1.45) ↓(71)
Gastrocnemius slow red type I muscle fibre peak stiffness (71)	Gastrocnemius muscle fibres functional and mechanical properties	17	0.80 (1.44) ↓(71)
Gastrocnemius fast white type IIa muscle fibre peak stiffness (71)	Gastrocnemius muscle fibres functional and mechanical properties	17	0.75 (1.43) ↓(71)
Gastrocnemius fast white type IIa/IIx muscle fibre peak stiffness (71)	Gastrocnemius muscle fibres functional and mechanical properties	17	0.52 (1.41) ↑(71)
Gastrocnemius slow red type I muscle fibre peak stiffness/peak force ratio (71)	Gastrocnemius muscle fibres functional and mechanical properties	17	1.13 (1.49) ↓(71)
Gastrocnemius fast white type IIa muscle fibre peak stiffness/peak force ratio (71)	Gastrocnemius muscle fibres functional and mechanical properties	17	0.62 (1.42) ↓(71)
Gastrocnemius fast white type IIa muscle fibre maximum shortening velocity (71)	Gastrocnemius muscle fibres functional and mechanical properties	17	0.62 (1.42) ↑(71)
Gastrocnemius fast white type IIa/IIx muscle fibre maximum shortening velocity (71)	Gastrocnemius muscle fibres functional and mechanical properties	17	0.00 (1.39) **NC**(71)
Gastrocnemius fast white type IIa muscle fibre peak power (71)	Gastrocnemius muscle fibres functional and mechanical properties	17	0.54 (1.41) ↓(71)
Gastrocnemius fast white type IIa/IIx muscle fibre peak power (71)	Gastrocnemius muscle fibres functional and mechanical properties	17	0.45 (1.40) ↓(71)
Gastrocnemius slow red type I muscle fibre force constant (71)	Gastrocnemius muscle fibres functional and mechanical properties	17	0.38 (1.40) ↓(71)
Gastrocnemius fast white type IIa muscle fibre force constant (71)	Gastrocnemius muscle fibres functional and mechanical properties	17	0.12 (1.39) ↑(71)
Gastrocnemius fast white type IIa/IIx muscle fibre force constant (71)	Gastrocnemius muscle fibres functional and mechanical properties	17	0.36 (1.40) ↑(71)
Unloaded shortening velocity of the soleus muscle fibres (52)	Soleus muscle fibres functional and mechanical properties	183	N/A(52)

Outcome (Article cross reference number)	Theme	Days of Spaceflight	Effect size increase (↑), Decrease (↓) or No Change (NC) (with 95 Confidence Interval +/-) from prefight values (Article cross reference number)
Peak force of the soleus slow red type I muscle fibre (21)	Soleus muscle fibres functional and mechanical properties	161-192	8.56 (2.79) ↓(21)
Maximal shortening velocity of the soleus slow red type I muscle fibre (21)	Soleus muscle fibres functional and mechanical properties	161-192	3.07 (1.29) ↓(21)
Peak stiffness ratio of the soleus slow red type I muscle fibre (21)	Soleus muscle fibres functional and mechanical properties	161-192	1.10 (0.94) ↑(21)
Rate constant of tension redevelopment of the soleus slow red type I muscle fibre (21)	Soleus muscle fibres functional and mechanical properties	161-192	1.51 (0.99)↓(21)
Peak force of the soleus fast white type II muscle fibre (21)	Soleus muscle fibres functional and mechanical properties	161-192	1.80 (1.04) ↓(21)
Maximal shortening velocity of the soleus fast white type II muscle fibre (21)	Soleus muscle fibres functional and mechanical properties	161-192	0.52 (0.89) ↑(21)
Specific isometric force of the soleus muscle fibres (52)	Soleus muscle fibres functional and mechanical properties	183	N/A(52)
Soleus slow red type I muscle fibre peak activated force (70)	Soleus muscle fibres functional and mechanical properties	17	2.32 (1.79) ↓(70)
Soleus slow red type I muscle fibre peak stiffness (70)	Soleus muscle fibres functional and mechanical properties	17	N/A(70)
Soleus slow red type I muscle fibre peak stiffness/peak force ratio (70)	Soleus muscle fibres functional and mechanical properties	17	N/A(70)
Soleus slow red type I muscle fibre unloaded shortening velocity (70)	Soleus muscle fibres functional and mechanical properties	17	N/A(70)
Soleus slow red type I muscle fibre shortening velocity at peak power (70)	Soleus muscle fibres functional and mechanical properties	17	N/A(70)
Soleus slow red type I muscle fibre force at peak power output (70)	Soleus muscle fibres functional and mechanical properties	17	N/A(70)
Soleus slow red type I muscle fibre peak power (70)	Soleus muscle fibres functional and mechanical properties	17	N/A(70)
Tibialis anterior muscle mean integrated electromyography activity (76)	Functional and Mechanical Properties of the Tibialis Anterior Muscles	N/A	Significant ↓(76)
Tibialis anterior muscle electromyography amplitude during plantarflexion (76)	Functional and Mechanical Properties of the Tibialis Anterior Muscles	N/A	Significant ↑(76)
Tibialis anterior muscle electromyography amplitude during dorsiflexion (76)	Functional and Mechanical Properties of the Tibialis Anterior Muscles	N/A	**NC**(76)

*Indicates that while this outcome was reported in the article, it can be split up into multiple outcomes. For example, "triceps surae" refers to both "gastrocnemius" and "soleus", although the article may have only reported the term "triceps surae" without indicating if it looked at both gastrocnemius and soleus, or only one of the muscles. In the results column, data was converted to Hedge's *g* effect size decrease (↓), increase (↑), or no change (**NC**) where possible. If a paper did not report data that could be used to calculate effect sizes then significant decrease (↓), increase (↑), or no change (**NC**) from baseline was reported instead. **N/A** is used for outcomes where the study did not report the data necessary to calculate effect size changes and did not report if changes were statistically significant or not.

Table 9.2 Physiological outcomes related to skeletal health identified during the systematic search. Significant increase decrease or no change is reported where effect size data could not be extracted.

Outcome (Article cross reference number)	**Theme**	**Days of Spaceflight**	**Effect Size Increase (↑), Decrease (↓) or No Change (NC) (with 95 Confidence Interval +/-) from prefight values** (Article cross reference number)
Parathyroid hormone (PTH) (14,40, 61, 62)	Biomarkers of bone formation	180(14), 8.9-14.7 (40), 48-215 (61), 49-215 (62)	N/A(14), **NC** (40), **NC** (61), N/A (62)
Osteocalcin (BGP for bone gla protein) (14, 15, 18, 60, 61)	Biomarkers of bone formation	180(14), 21(15), 28-183(18), 121-183(60), 48-215(61)	N/A(14), N/A(15), N/A(18), 0.09 (0.77) ↓ (60), 0.00 (1.24) **NC**(61)
Intact osteocalcin (iBGP) (14)	Biomarkers of bone formation	180	N/A
Bone alkaline phosphatase (BAP) (14, 15, 18, 61)	Biomarkers of bone formation	180(14), 21 (15), 28-183 (18), 48-215 (61)	N/A(14), Significant ↓(15), N/A(18), 0.61 (1.27) ↑(61)
Carboxyl-terminal propeptide of human type 1 procollagen (PICP) (14, 15, 18)	Biomarkers of bone formation	180(14), 21 (15), 28-183 (18)	N/A(14), Significant ↓(15), N/A (18)
25-hydroxyvitamin D (25(OH)D) (60, 61, 62)	Biomarkers of bone formation	121-183 (60), 48-215 (61), 49-215 (62)	0.41 (0.78) ↓(60), 0.59 (1.27) ↓(61), N/A (62)
1,25-dihydroxyvitamin D ($1,25(OH)_2D$) (60, 61, 62)	Biomarkers of bone formation	121-183 (60), 48-215 (61), 49-215 (62)	0.41 (0.78) ↓(60), 0.16 (1.27) ↑(61), N/A (62)
Parathyroid intact molecule (PTH intact molecule) (60)	Biomarkers of bone formation	121-183	0.16 (0.77)↑
Parathyroid mid-molecule (PTH mid molecule) (60)	Biomarkers of bone formation	121-183	0.26 (0.77)↑
Bone specific alkaline phosphatase (60)	Biomarkers of bone formation	121-183	0.24 (0.77)↑
pH (60, 62)	Biomarkers of bone formation	121-183 (60), 49-215 (62)	0.32 (0.77)↓(60), N/A(62)

Outcome (Article cross reference number)	Theme	Days of Spaceflight	Effect Size Increase (↑), Decrease (↓) or No Change (NC) (with 95 Confidence Interval +/-) from preflight values (Article cross reference number)
Bone calcium deposition (60)	Biomarkers of bone formation	121-183	0.50 (1.15)↑
Alkaline phosphatase (60)	Biomarkers of bone formation	121-183	0.70 (0.79)↑
Free D-Pyridinoline (FD-Pyr) (14)	Biomarkers of bone resorption	180	N/A
Total D-Pyridinoline (Total D-Pyr) (14)	Biomarkers of bone resorption	180	N/A
Pyridinoline (Pyr; PYD) (14, 15, 18, 60)	Biomarkers of bone resorption	180(14), 21 (15), 28-183 (18), 121-183 (60)	N/A(14), N/A (15), N/A (18), 0.78 (0.80) ↑(60)
C-telopeptide (CTX) (14, 61, 62)	Biomarkers of bone resorption	180(14), 48-215 (61), 49-215 (62)	N/A(14), 1.14 (1.34) ↑(61), N/A(62)
Free Deoxypyridinoline (F-Dpd) (15)	Biomarkers of bone resorption	21	N/A
N-telopeptide of type 1 collagen (NTX) (15, 60, 61, 62)	Biomarkers of bone resorption	21 (15), 121-183 (60), 48-215 (61), 49-215 (62)	N/A(15), 1.64 (0.89) ↑(60), 1.05 (1.32) ↑(61), N/A (62)
Urinary C-telopeptide (Urinary CTX) (15)	Biomarkers of bone resorption	21	N/A
Serum C-telopeptide (Serum CTX) (15)	Biomarkers of bone resorption	21	N/A
Deoxypyridinoline (DPD; D.Pyr) (18, 60, 61)	Biomarkers of bone resorption	28-183(18), 121-183 (60), 48-215 (61)	N/A(18), 1.52 (0.87) ↑(60), 1.48 (1.40) ↑(61)
Fractional excretion of calcium (40)	Biomarkers of bone resorption	8.9-14	Significant ↑
Urinary calcium (60)	Biomarkers of bone resorption	121-183	0.43 (1.14)↓
Endogenous excretion of calcium (60)	Biomarkers of bone resorption	121-183	0.43 (1.14)↑

Outcome (Article cross reference number)	Theme	Days of Spaceflight	Effect Size Increase (↑), Decrease (↓) or No Change (NC) (with 95 Confidence Interval +/-) from prefight values (Article cross reference number)
Fecal excretion of calcium (60)	Biomarkers of bone resorption	121-183	0.56 (1.15)↑
Bone calcium resorption (60)	Biomarkers of bone resorption	121-183	0.61 (1.16)↑
Pyridinium crosslinks (61)	Biomarkers of bone resorption	48-215	1.45 (1.39)↑
Serum ferritin (74)	Biomarkers of bone resorption	50-247	0.40 (1.16)↑
Transferrin (74)	Biomarkers of bone resorption	50-247	0.41 (1.16)↓
Transferrin receptors (74)	Biomarkers of bone resorption	50-247	0.90 (1.20)↓
Iron (74)	Biomarkers of bone resorption	50-247	1.44 (1.28)↓
Lumbar bone mineral density (37)	Measures of bone mineral density	20-180	**NC**
Non-dominant tibia cancellous bone mineral density (67)	Measures of bone mineral density	30-183	0.22 (0.90)↓
Non-dominant radius cancellous bone mineral density (67)	Measures of bone mineral density	30-183	0.02 (0.90)↓
Non-dominant tibia cortical bone mineral density (67)	Measures of bone mineral density	30-183	0.19 (0.90)↓
Non-dominant radius cortical bone mineral density (67)	Measures of bone mineral density	30-183	0.01 (0.90)↑
Whole body bone mineral density (37, 61, 62)	Measures of bone mineral density	20-180(37), 48-215(61), 49-215(62)	**NC**(37), 0.01 (1.24) ↑(61), N/A(62)

Outcome (Article cross reference number)	**Theme**	**Days of Spaceflight**	**Effect Size Increase (↑), Decrease (↓) or No Change (NC) (with 95 Confidence Interval +/-) from preflight values** (Article cross reference number)
Skull (head) bone mineral density (37, 40)	Measures of bone mineral density	20-180(37), 8.9-14.7(40)	**NC**(37), Significant ↑(40)
Calcaneus bone mineral density (23, 37, 57, 58, 59)	Measures of bone mineral density	152(23), 20-180(37), 121-183(57), 121-183(58), 126-438(59)	N/A(23), **NC**(37), Significant ↓(57), N/A(58), Significant ↓(59)
Distal tibia bone mineral density (37)	Measures of bone mineral density	20-180	**NC**
Proximal femur bone mineral density (37)	Measures of bone mineral density	20-180	**NC**
Lumbar spine bone mineral density (40, 57, 58, 59 61, 62, 80)	Measures of bone mineral density	8.9-14.7(40), 121-183(57), 121-183(58), 126-438(59), 48-215(61), 49-215(62), 136-189(80)	Significant ↓(40), Significant ↓(57), N/A(58), Significant ↓(59), 0.03 (1.24) ↓(61), N/A(62), Significant ↓(80)
Femoral neck bone mineral density (23, 57, 58, 59, 62, 79, 80)	Measures of bone mineral density	152(23), 121-183(57), 121-183(58), 126-438(59), 49-215(62), 136-189(79), 136-183(80)	N/A(23), Significant ↓(57), N/A(58), Significant ↓(59), N/A(62), Significant ↓(79), 0.61 (0.71) ↓(80)
Ribs bone mineral density (37)	Measures of bone mineral density	20-180	**NC**
Arms bone mineral density (37)	Measures of bone mineral density	20-180	**NC**
Pelvis bone mineral density (40, 58, 59, 61, 80)	Measures of bone mineral density	8.9-14.7(40), 121-183(58), 126-438(59), 48-215(61), 136-189(80)	**NC**(40), N/A(58), Significant ↓(59), 0.09 (1.24)↓(61), Significant ↓(80)
Trochanter bone mineral density (57, 58, 59, 80)	Measures of bone mineral density	121-183(57), 121-183(58), 126-438(59), 136-189(80)	Significant ↓(57), N/A(58), Significant ↓(59), Significant ↓(80)
Left hip neck bone mineral density (61)	Measures of bone mineral density	48-215	0.12 (1.24)↓
Right hip neck bone mineral density (61)	Measures of bone mineral density	48-215	0.06 (1.24)↓

Outcome (Article cross reference number)	Theme	Days of Spaceflight	Effect Size Increase (↑), Decrease (↓) or No Change (NC) (with 95 Confidence Interval +/-) from prefight values (Article cross reference number)
Left hip trochanter bone mineral density (61)	Measures of bone mineral density	48-215	0.10 (1.24)↓
Right hip trochanter bone mineral density (61)	Measures of bone mineral density	48-215	0.13 (1.24)↓
Hip trochanter bone mineral density (62)	Measures of bone mineral density	49-215	N/A
Total left hip bone mineral density (61)	Measures of bone mineral density	48-215	0.12 (1.24)↓
Total right hip bone mineral density (61)	Measures of bone mineral density	48-215	0.13 (1.24)↓
Total hip bone mineral density (62, 80)	Measures of bone mineral density	49-215(62), 136-189(80)	N/A(62), Significant ↓(80)
Calcaneal areal bone mineral density (32)	Measures of bone mineral density	131-198	0.18 (0.74) ↓
Femoral neck integral bone mineral content (32)	Measures of bone mineral density	131-198	0.56 (0.76)↓
Trochanter integral bone mineral content (32)	Measures of bone mineral density	131-198	0.52 (0.75)↓
Overall proximal femur integral bone mineral content (32)	Measures of bone mineral density	131-198	0.56 (0.76)↓
Femoral neck cortical bone mineral content (32)	Measures of bone mineral density	131-198	0.50 (0.75)↓
Trochanter cortical bone mineral content (32)	Measures of bone mineral density	131-198	0.52 (0.75)↓

Outcome (Article cross reference number)	Theme	Days of Spaceflight	Effect Size Increase (↑), Decrease (↓) or No Change (NC) (with 95 Confidence Interval +/-) from prefight values (Article cross reference number)
Overall proximal femur cortical bone mineral content (32)	Measures of bone mineral density	131-198	0.55 (0.75)↓
Femoral neck trabecular bone mineral content (32)	Measures of bone mineral density	131-198	0.61 (0.76)↓
Trochanter trabecular bone mineral content (32)	Measures of bone mineral density	131-198	0.58 (0.76)↓
Overall proximal femur trabecular bone mineral content (32)	Measures of bone mineral density	131-198	0.63 (0.76)↓
Whole body bone mineral content (34, 37, 61)	Measures of bone mineral density	17, 112-196(34), 20-180(37), 48-215(61)	0.25 (0.74)↓(34), **NC**(37), 0.02 (1.24)↓(61)
Lumbar spine bone mineral content (61)	Measures of bone mineral density	48-215	0.32 (1.25)↓
Pelvis bone mineral content (61)	Measures of bone mineral density	48-215	0.03 (1.24)↓
Femoral neck trabecular volumetric bone mineral density (32, 79, 81)	Measures of volumetric bone mineral density	131-198(32), 136-189(79), 136-183(80)	0.88 (0.78)↓(32), 0.56 (1.07)↓(79), 0.71 (0.71)↓(80)
Femoral neck integral volumetric bone mineral density (32, 80)	Measures of volumetric bone mineral density	131-198(32), 136-189(80)	0.46 (0.75)↓(32), 0.55 (1.07)↓(80)
Trochanter integral volumetric bone mineral density (32, 80)	Measures of volumetric bone mineral density	131-198(32), 136-189(80)	0.76 (0.77)↓(32), 0.71 (1.08)↓(80)
Overall proximal femur integral	Measures of volumetric bone mineral density	131-198	0.70 (0.76)↓

Outcome (Article cross reference number)	Theme	Days of Spaceflight	Effect Size Increase (↑), Decrease (↓) or No Change (NC) (with 95 Confidence Interval +/-) from prefight values (Article cross reference number)
volumetric bone mineral density [32]			
Femoral neck cortical volumetric bone mineral density [32, 79, 80]	Measures of volumetric bone mineral density	131-198[32], 136-189[79], 136-183[80]	0.22 (0.74)↓[32], 0.52 (1.07)↓[79], 0.44 (0.70) ↓[80]
Trochanter cortical volumetric bone mineral density [32, 80]	Measures of volumetric bone mineral density	131-198[32], 136-189[80]	0.39 (0.75)↓[32], 0.50 (1.06)↓[80]
Overall proximal femur cortical volumetric bone mineral density [32]	Measures of volumetric bone mineral density	131-198	0.31 (0.75)↓
Trochanter trabecular volumetric bone mineral density [32, 80]	Measures of volumetric bone mineral density	131-198[32], 136-189[80]	0.72 (0.76)↓[32], 0.48 (1.06)↓[80]
Overall proximal femur trabecular volumetric bone mineral density [32]	Measures of volumetric bone mineral density	131-198	0.72 (0.76)↓
Total femur volumetric bone mineral density [80]	Measures of volumetric bone mineral density	136-183	N/A
Femur trabecular volumetric bone mineral density [80]	Measures of volumetric bone mineral density	136-183	0.75 (0.72)↓
Femur cortical volumetric bone mineral density [80]	Measures of volumetric bone mineral density	136-183	0.47 (0.70)↓
Total hip trabecular volumetric bone mineral density [79]	Measures of volumetric bone mineral density	136-189	0.56 (1.07)↓

Outcome (Article cross reference number)	Theme	Days of Spaceflight	Effect Size Increase (↑), Decrease (↓) or No Change (NC) (with 95 Confidence Interval +/-) from prefight values (Article cross reference number)
Total hip cortical volumetric bone mineral density (79)	Measures of volumetric bone mineral density	136-189	0.43 (1.06)↓
Total hip integral volumetric bone mineral density (79)	Measures of volumetric bone mineral density	136-189	0.67 (1.08)↓
Femoral neck trabecular volumetric bone mineral content (79)	Measures of volumetric bone mineral density	136-189	0.43 (1.06)↓
Trochanter trabecular volumetric bone mineral content (79)	Measures of volumetric bone mineral density	136-189	0.48 (1.06)↓
Total hip trabecular volumetric bone mineral content (79)	Measures of volumetric bone mineral density	136-189	0.52 (1.06)↓
Femoral neck cortical volumetric bone mineral content (79)	Measures of volumetric bone mineral density	136-189	0.52 (1.07)↓
Trochanter cortical volumetric bone mineral content (79)	Measures of volumetric bone mineral density	136-189	0.52 (1.06)↓
Total hip cortical volumetric bone mineral content (79)	Measures of volumetric bone mineral density	136-189	0.46 (1.06)↓
Femoral neck integral volumetric bone mineral content (79)	Measures of volumetric bone mineral density	136-189	0.54 (1.07)↓
Trochanter integral volumetric bone mineral content (79)	Measures of volumetric bone mineral density	136-189	0.51 (1.06)↓

Outcome (Article cross reference number)	Theme	Days of Spaceflight	Effect Size Increase (↑), Decrease (↓) or No Change (NC) (with 95 Confidence Interval +/-) from prefight values (Article cross reference number)
Total hip integral volumetric bone mineral content (79)	Measures of volumetric bone mineral density	136-189	0.54 (1.07)↓
Intervertebral disc height (17)	Skeletal architectural and structural properties	117-213	0.75 (1.17)↓
Non-dominant radius cortical bone mass (18)	Skeletal architectural and structural properties	28-183	N/A
Non-dominant radius trabecular bone mass (18)	Skeletal architectural and structural properties	28-183	N/A
Non-dominant tibia cortical bone mass (18)	Skeletal architectural and structural properties	28-183	N/A
Non-dominant tibia trabecular bone mass (18)	Skeletal architectural and structural properties	28-183	N/A
Total femoral neck mass (80)	Skeletal architectural and structural properties	136-183	0.67 (0.71)↓
Total femur mass (80)	Skeletal architectural and structural properties	136-183	0.68 (0.71)↓
Total femoral neck cortical mass (80)	Skeletal architectural and structural properties	136-183	0.64 (0.71)↓
Total femur cortical mass (80)	Skeletal architectural and structural properties	136-183	0.69 (0.71)↓
Femoral neck integral volume (32)	Skeletal architectural and structural properties	131-198	0.20 (0.74)↓
Femoral neck cortical volume (32, 80)	Skeletal architectural and structural properties	131-198(32), 136-183(80)	0.51 (0.75)↓(32), 0.59 (0.71)↓(80)
Total femur cortical volume (80)	Skeletal architectural and structural properties	136-183	0.66 (0.71)↓

Outcome (Article cross reference number)	Theme	Days of Spaceflight	Effect Size Increase (↑), Decrease (↓) or No Change (NC) (with 95 Confidence Interval +/-) from prefight values (Article cross reference number)
Total femoral neck volume (80)	Skeletal architectural and structural properties	136-183	0.15 (0.69)↓
Total femur volume (80)	Skeletal architectural and structural properties	136-183	0.11 (0.69)↓
Trochanter integral volume (32)	Skeletal architectural and structural properties	131-198	0.07 (0.74)↓
Trochanter cortical volume (32)	Skeletal architectural and structural properties	131-198	0.48 (0.75)↓
Overall proximal femur integral volume (32)	Skeletal architectural and structural properties	131-198	0.14 (0.74)↓
Overall proximal femur cortical volume (32)	Skeletal architectural and structural properties	131-198	0.55 (0.75)↓
Femoral neck cross-section of minimal area (MNCS) (80)	Skeletal architectural and structural properties	136-183	0.06 (0.69)↑
Cross-sectional area of the femoral neck (32)	Skeletal architectural and structural properties	131-198	0.00 (0.74)**NC**
Cross-sectional area of the mid-trochanter (32)	Skeletal architectural and structural properties	131-198	0.09 (0.74)↑
Cross-sectional area of the mid-vertebrae (32)	Skeletal architectural and structural properties	131-198	0.04 (0.74)↓
L3 bone marrow functional cellular fraction (33)	Skeletal architectural and structural properties	17	**NC**
Transverse relaxation time of L3 bone	Skeletal architectural and structural properties	17	Significant ↑

Outcome (Article cross reference number)	Theme	Days of Spaceflight	Effect Size Increase (↑), Decrease (↓) or No Change (NC) (with 95 Confidence Interval +/-) from prefight values (Article cross reference number)
marrow functional cellular fraction (33)			
Proximal femur strength (28)	Skeletal functional and mechanical properties	131-198	N/A
Femoral neck bending/torsional strength index (NBSI) (80)	Skeletal functional and mechanical properties	136-183	0.47 (0.70)↓
Femoral neck compressive strength index (NCSI) (80)	Skeletal functional and mechanical properties	136-183	0.65 (0.71)↓
Cortisol (14)	Unspecified biomarkers of bone remodelling	180	N/A
Somatomedin (IGF-1) (14)	Unspecified biomarkers of bone remodelling	180	N/A
Serum calcium (14, 40)	Unspecified biomarkers of bone remodelling	180(14), 8.9-14.7(40)	N/A(14), **NC**(40)
Type 1 procollagen propeptide (14)	Unspecified biomarkers of bone remodelling	180	N/A
Creatinine (18, 60, 61)	Unspecified biomarkers of bone remodelling	28-183(18), 121-183 (60), 48-215 (61)	N/A(18), 0.70 (0.79) ↑(60), 0.24 (1.24) ↑(61)
Calcium (60, 61, 62)	Unspecified biomarkers of bone remodelling	121-183 (60), 48-215 (61), 49-215 (62)	0.36 (0.78) ↑(60), 7.24 (3.40) ↓(61), N/A (62)
Calcitonin (60)	Unspecified biomarkers of bone remodelling	121-183	0.33 (0.77)↓
Ionized calcium (60, 61)	Unspecified biomarkers of bone remodelling	121-183 (60), 48-215 (61)	0.26 (0.77)↓(60), 0.61 (1.27)↓(61)
Phosphorus (60)	Unspecified biomarkers of bone remodelling	121-183	1.45 (0.86)↓

Outcome (Article cross reference number)	Theme	Days of Spaceflight	Effect Size Increase (↑), Decrease (↓) or No Change (NC) (with 95 Confidence Interval +/-) from prefight values (Article cross reference number)
Calcium intake (60)	Unspecified biomarkers of bone remodelling	121-183	0.40 (1.14)↑
Calcium absorption (60)	Unspecified biomarkers of bone remodelling	121-183	0.14 (1.13)↓
Fractional calcium absorption (60)	Unspecified biomarkers of bone remodelling	121-183	1.84 (1.35)↓
Bone calcium balance (60)	Unspecified biomarkers of bone remodelling	121-183	0.08 (1.13)↓
Helical peptide (HP) (61, 74)	Unspecified biomarkers of bone remodelling	48-215 (61), 50-247(74)	1.25 (1.36)↑(61), N/A(74)
24-h volume (62)	Unspecified biomarkers of bone remodelling	49-215	N/A
Oxalate (62)	Unspecified biomarkers of bone remodelling	49-215	N/A
Sodium (62)	Unspecified biomarkers of bone remodelling	49-215	N/A
CaOx supersaturation (62)	Unspecified biomarkers of bone remodelling	49-215	N/A
Brushite supersaturation (62)	Unspecified biomarkers of bone remodelling	49-215	N/A
Na urate supersaturation (62)	Unspecified biomarkers of bone remodelling	49-215	N/A
Struvite supersaturation (62)	Unspecified biomarkers of bone remodelling	49-215	N/A
Uric acid supersaturation (62)	Unspecified biomarkers of bone remodelling	49-215	N/A
Whole-blood haematocrit (74)	Unspecified biomarkers of bone remodelling	50-247	0.66 (1.08)↓

Outcome (Article cross reference number)	Theme	Days of Spaceflight	Effect Size Increase (↑), Decrease (↓) or No Change (NC) (with 95 Confidence Interval +/-) from prefight values (Article cross reference number)
Haemoglobin (74)	Unspecified biomarkers of bone remodelling	50-247	0.84 (1.09)↓
Superoxide dismutase (74)	Unspecified biomarkers of bone remodelling	50-247	N/A
Plasma lipid peroxides (74)	Unspecified biomarkers of bone remodelling	50-247	N/A
Urinary 8-hydroxy-2'-deoxyguanosine (8OHdG) (74)	Unspecified biomarkers of bone remodelling	50-247	N/A
Prostaglandin F2a (PGF2a) (74)	Unspecified biomarkers of bone remodelling	50-247	N/A
Heme (74)	Unspecified biomarkers of bone remodelling	50-247	0.33 (1.16)↓

In the results column, data were converted to Hedge's *g* effect size decrease (↓), increase (↑), or no change (**NC**) where possible. If a paper did not report data that could be used to calculate effect sizes then significant decrease (↓), increase (↑), or no change (**NC**) from baseline was reported instead. **N/A** is used for outcomes where the study did not report the data necessary to calculate effect size changes and did not report if changes were statistically significant or not

Table 9.3 Physiological outcomes related to cardiovascular health identified during the systematic search. Significant increase decrease or no change is reported where effect size data could not be extracted.

Outcome (Article cross reference number)	Theme	Days of Spaceflight	Increase (↑), Decrease (↓) or No Change (NC) (with 95 Confidence Interval +/-) from prefight values (Article cross reference number)
Left ventricle volume (4)	Cardiac architectural and structural properties	14	N/A
Left ventricular end-diastolic internal dimension (11)	Cardiac architectural and structural properties	N/A	N/A
Left ventricular internal dimension systole (11)	Cardiac architectural and structural properties	N/A	N/A
Left atrial diameter (11)	Cardiac architectural and structural properties	N/A	N/A

Outcome (Article cross reference number)	**Theme**	**Days of Spaceflight**	**Increase (↑), Decrease (↓) or No Change (NC) (with 95 Confidence Interval +/-) from prefight values** (Article cross reference number)
Left ventricular end-diastolic volume (24)	Cardiac architectural and structural properties	8-438	N/A
Left atrial maximal volume (84)	Cardiac architectural and structural properties	13	N/A
Right atrial area (84)	Cardiac architectural and structural properties	13	N/A
Right atrial longitudinal diameter (84)	Cardiac architectural and structural properties	13	N/A
Right atrial transversal diameter (84)	Cardiac architectural and structural properties	13	N/A
Left ventricular atrioventricular plane displacement (84)	Cardiac architectural and structural properties	13	N/A
Right ventricular atrioventricular plane displacement (84)	Cardiac architectural and structural properties	13	N/A
Cardiac output (4, 11, 12, 25, 48, 54, 56, 65, 69)	Cardiac functional and mechanical properties	14(4), N/A(11), 9-14**(12)**, 153-180**(25)**, 9(48), N/A(54), 9-15(56), 10(65), 5-16(69)	N/A(4), 0.01 (0.74)↓(11), 0.68 (0.79)↓**(12)**, 0.58 (1.16)↑**(25)**, N/A(48), N/A(54), N/A(56), N/A(65), N/A(69)
Heart rate (4, 5, 7, 8, 10, 11, 12, 19, 22, 24, 25, 27, 35, 36, 39, 41, 46, 53, 54, 55, 56, 65, 66, 69, 72, 82, 83)	Cardiac functional and mechanical properties	14(4), 10-15(5), 152-182(7), 38(8), 10-30(10), N/A(11), 9-14(12), 16(19), 16(22), 8-438(24), 153-180(25), 16(27), 16(35), 15(36), 16(39), 127-188(41), 130-196↑(46), N/A(53), N/A(54), 183(55), 9-15(56), 10(65), 10-11(66), 5-16(69), 52-199(72) 26(82), 13(83)	N/A(4), Significant ↑(5)*, N/A(7), 0.04 (1.13)↑(8)*, 2.37 (1.62)↑(10), 0.62 (0.74)↑(11), 1.78 (0.88)↑(12), N/A(19), 0.22 (1.24)↓(22), N/A(24), 0.43 (1.14)↑(25), N/A(27), 2.12 (1.14)↑(35), N/A(36), 0.59 (1.42)↑(39), 0.68 (1.16)↑(41), 0.62 (0.90)↑(46), N/A(53), N/A(54), 0.83 (1.45)↑(55), N/A(56), N/A(65), 0.68 (1.28)↑(66), N/A(69), 0.65 (1.08)↑(72), N/A(82), N/A(83)
Heart rate variability (RRI/R-R Interval) (5, 6, 7, 9, 19, 25, 26, 39, 42, 43, 64, 72, 73, 81)	Cardiac functional and mechanical properties	10-15(5), 162-196(6), 152-182(7), 10-30(9), 16(19), 153-180(25), 16(26), 16(39), 172.6 ± 14.6 (42), 171.8 ± 14.4 (43), 10-183(64), 52-199(72), 163-199(73), 274(81)	N/A(5), **N/C**(6), N/A(7), 0.07 (1.24)↓(9), N/A(19), N/A(25), N/A(26), N/A(39), N/A(42), N/A(43), N/A(64), N/A(72), N/A(73), N/A(81)
Heart rate amplitude (36)	Cardiac functional and mechanical properties	15	N/A

Outcome (Article cross reference number)	Theme	Days of Spaceflight	Increase (↑), Decrease (↓) or No Change (NC) (with 95 Confidence Interval +/-) from prefight values (Article cross reference number)
Maximum heart rate (36)	Cardiac functional and mechanical properties	15	N/A
Minimum heart rate (36)	Cardiac functional and mechanical properties	15	N/A
Velocity of circumferential shortening (11)	Cardiac functional and mechanical properties	N/A	N/A
Left-ventricular ejection time index (25)	Cardiac functional and mechanical properties	153-180	0.15 (1.13) ↓
Respiratory sinus arrhythmia (39)	Cardiac functional and mechanical properties	16	0.78 (1.44) ↓
Supraventricular beats (84)	Cardiac functional and mechanical properties	13	0.25 (0.77)
ECG p-wave duration (84)	Cardiac functional and mechanical properties	13	0.22 (0.77)
ECG filtered p-wave duration (84)	Cardiac functional and mechanical properties	13	-0.10 (0.77)
ECG RMS20 (84)	Cardiac functional and mechanical properties	13	0.12 (0.77
ECG P-wave amplitude I (84)	Cardiac functional and mechanical properties	13	0.00 (0.77)
ECG P-wave amplitude II (84)	Cardiac functional and mechanical properties	13	-0.31 (0.77)
ECG P-wave amplitude III (84)	Cardiac functional and mechanical properties	13	-0.26 (0.77)
ECG P-wave amplitude aVr (84)	Cardiac functional and mechanical properties	13	-0.47 (0.78)
ECG P-wave amplitude aVL (84)	Cardiac functional and mechanical properties	13	-0.47 (0.78)
ECG P-wave amplitude aVF (84)	Cardiac functional and mechanical properties	13	-0.26 (0.77)

Outcome (Article cross reference number)	Theme	Days of Spaceflight	Increase (↑), Decrease (↓) or No Change (NC) (with 95 Confidence Interval +/-) from prefight values (Article cross reference number)
ECG P-wave amplitude V1 (84)	Cardiac functional and mechanical properties	13	-0.47 (0.78)
ECG P-wave amplitude V2 (84)	Cardiac functional and mechanical properties	13	-2.85 (1.09)
ECG P-wave amplitude V3 (84)	Cardiac functional and mechanical properties	13	-0.73 (0.79)
ECG P-wave amplitude V4 (84)	Cardiac functional and mechanical properties	13	-0.93 (0.81)
ECG P-wave amplitude V5 (84)	Cardiac functional and mechanical properties	13	-0.47 (0.78)
ECG P-wave amplitude V6 (84)	Cardiac functional and mechanical properties	13	-0.47 (0.78)
Total peripheral resistance (8, 12, 35, 53, 54, 56, 69)	Hemodynamics and vascular function	38 (8), 9-14 (12), 16(35), N/A(53), N/A(54), 9-15(56), 5-16(69)	0.18 (1.13) ↓ (8)*, 0.65 (0.79) ↑ (12), 0.53 (1.15) ↑ (35)*, N/A(53), N/A(54), N/A(56), N/A(69)
Circulation in the femoral artery (24)	Hemodynamics and vascular function	8-438	N/A
Femoral artery volumetric blood flow (24)	Hemodynamics and vascular function	8-438	N/A
Stroke volume (4, 8, 11, 12, 24, 25, 35, 48, 53, 54, 56, 65, 69)	Hemodynamics and vascular function	14(4), 38(8), N/A(11), 9-14(12), 8-438(24), 153-180(25), 16(35), 9(48), N/A(53), N/A(54), 9-15(56), 10(65), 5-16(69)	N/A(4), 0.15 (1.13) ↑ (8)*, 0.82 (0.77) ↓ (11), 1.96 (0.94) ↓ (12), N/A(24), 0.24 (1.14) ↑ (25), 2.37 (1.48) ↓ (35)*, 1.26 (1.52) ↓ (48), N/A(53), N/A(54), N/A(56), N/A(65), N/A(69)
Central venous pressure (4, 11)	Hemodynamics and vascular function	14(4), N/A(11)	N/A(4), N/A (8)
Renal vascular resistance (4)	Hemodynamics and vascular function	14	N/A
Mesenteric vascular resistance (4)	Hemodynamics and vascular function	14	N/A
Splanchnic vascular resistance (4)	Hemodynamics and vascular function	14	N/A

Outcome (Article cross reference number)	Theme	Days of Spaceflight	Increase (↑), Decrease (↓) or No Change (NC) (with 95 Confidence Interval +/-) from prefight values (Article cross reference number)
Cerebral flow volume [4]	Hemodynamics and vascular function	14	N/A
Femoral flow volume [4]	Hemodynamics and vascular function	14	N/A
Cerebral flow resistance [4]	Hemodynamics and vascular function	14	N/A
Femoral flow resistance [4]	Hemodynamics and vascular function	14	N/A
Blood pressure [4, 5, 7, 8, 10, 12, 24, 41, 56]	Hemodynamics and vascular function	14[4], 10-15[5], 152-182[7], 38[8], 10-30[10], 9-14[12], 8-438[24], 127-188[41], 9-15[56]	N/A[4], N/A[5], N/A[7], 0.12 (1.13) ↑[8]*, N/A[10], 0.14 (0.74) ↑[12], N/A[24], N/A[41], 0.65 (1.16) ↑[56]
Blood pressure variability [10]	Hemodynamics and vascular function	10-30	N/A
Systolic blood pressure [5, 8, 12, 22, 25, 26, 41, 55, 82, 83]	Hemodynamics and vascular function	10-15[5], 38[8], 9-14[12], 16[22], 153-180[25], 16[26], 127-188[41], 183[55] 26[82], 13[83]	**NC**[5]*, 0.23 ↓ (1.14)[8]*, 0.09 (0.74) ↑[12], 0.05 (1.24) ↓[22], 0.15 (1.13) ↓[25], 0.06 (1.39) ↑[26], 0.67 (1.16) ↑[41], 2.14 (1.74) ↑[55], N/A[82], N/A[83]
Diastolic blood pressure [5, 7, 8, 12, 22, 25, 26, 41, 55, 82, 83]	Hemodynamics and vascular function	10-15[5], 152-182[7], 38[8], 9-14[12], 16[22], 153-180[25], 16[26], 127-188[41], 183[55], 26[82], 13[83]	**NC** [5]*, N/A[7], 0.02 (1.13) ↓[8]*, 0.18 (0.74) ↑[12], 0.64 (1.27) ↑[22], 0.32 (1.14) ↓[25], 0.29 (1.39) ↑[26], 0.47 (1.15) ↑[41], 0.28 (1.39) ↑[55] , N/A[82], N/A[83]
Pulse pressure [25, 66, 83]	Hemodynamics and vascular function	16[22], 10-11[66], 13[83]	0.37 (1.14) ↑[25], 0.17 (1.24) ↓[66] , N/A[83]
Diastolic volume [11]	Hemodynamics and vascular function	N/A	N/A
Systolic volume [11]	Hemodynamics and vascular function	N/A	N/A
Calf blood volume* [4]	Hemodynamics and vascular function	14	N/A
Leg blood volume* [12]	Hemodynamics and vascular function	9-14	0.58 (0.77) ↓

Outcome (Article cross reference number)	Theme	Days of Spaceflight	Increase (↑), Decrease (↓) or No Change (NC) (with 95 Confidence Interval +/-) from prefight values (Article cross reference number)
Spontaneous baroreflex sensitivity (19)	Hemodynamics and vascular function	16	N/A
Baroreflex sensitivity (26)	Hemodynamics and vascular function	16	0.59 (1.42) ↑
Baroreflex scope (81)	Hemodynamics and vascular function	274	N/A
Mean arterial pressure (22, 27, 35, 54, 56, 66, 69, 83)	Hemodynamics and vascular function	16(22), 16(27), 16(35), N/A(54), 9-15(56), 10-11(66), 5-16(69), 13(83)	0.39 (1.25) ↑ (22), N/A(27), N/A(35), N/A(54), N/A(56), 0.26 (1.24) ↑ (66), N/A(69), N/A(83)
Systolic arterial pressure (27, 66, 81)	Hemodynamics and vascular function	16(27), 10-11(66), 274(81)	N/A (27), 0.22 (1.24) ↑ (66), N/A(81)
Diastolic arterial pressure (27, 66, 81)	Hemodynamics and vascular function	16(27), 10-11(66), 274(81)	N/A (27), 0.23 (1.24) ↑ (66), N/A(81)
Muscle sympathetic nerve activity (22, 35)	Hemodynamics and vascular function	16(22), 16(35)	0.32 (1.25) ↑ (22), 1.03 (1.20) ↑ (35)*
Femoral vein cross-sectional area (24)	Hemodynamics and vascular function	8-438	N/A
Changes in femoral artery resistance index (24)	Hemodynamics and vascular function	8-438	N/A
Cross-sectional area of the right jugular vein (24)	Hemodynamics and vascular function	8-438	N/A
Vascular compliance in the legs (24)	Hemodynamics and vascular function	8-438	N/A
Changes in cerebral flow deficit index (24)	Hemodynamics and vascular function	8-438	N/A
Circulation in the aorta (24)	Hemodynamics and vascular function	8-438	N/A
Circulation in the medial cerebral artery (24)	Hemodynamics and vascular function	8-438	N/A
Medial cerebral artery volumetric blood flow (24)	Hemodynamics and vascular function	8-438	N/A

Outcome (Article cross reference number)	Theme	Days of Spaceflight	Increase (↑), Decrease (↓) or No Change (NC) (with 95 Confidence Interval +/-) from prefight values (Article cross reference number)
Maximum rate of change in arterial pressure (25)	Hemodynamics and vascular function	153-180	0.29 (1.14) ↑
Systemic vascular resistance (25)	Hemodynamics and vascular function	153-180	0.76 (1.17) ↓
Postexercise circulatory occlusion (26)	Hemodynamics and vascular function	16	N/A
Plasma norepinephrine levels (53, 54)	Hemodynamics and vascular function	N/A(53), N/A(54)	N/A(53), N/A(54)
Plasma epinephrine levels (54)	Hemodynamics and vascular function	N/A	N/A
Plasma volume (54)	Hemodynamics and vascular function	N/A	N/A
Cardiovascular index of deconditioning (delta HR - delta SBP + delta DBP) (82)	Hemodynamics and vascular function	26 (24, with 2 flying twice)	N/A
Albumin (44)	Biomarkers of cardiovascular deconditioning	169-199	N/A
Ceruloplasmin (44)	Biomarkers of cardiovascular deconditioning	169-199	N/A
Cystatin C (44)	Biomarkers of cardiovascular deconditioning	169-199	N/A
Endothelial cell protein C receptor (44)	Biomarkers of cardiovascular deconditioning	169-199	N/A
Kallikrein 1 (44)	Biomarkers of cardiovascular deconditioning	169-199	N/A
Kininogen-1 (44)	Biomarkers of cardiovascular deconditioning	169-199	N/A
Osteopontin (44)	Biomarkers of cardiovascular deconditioning	169-199	N/A
Prostaglandin-H2 D-isomerase (44)	Biomarkers of cardiovascular deconditioning	169-199	N/A

Outcome (Article cross reference number)	Theme	Days of Spaceflight	Increase (↑), Decrease (↓) or No Change (NC) (with 95 Confidence Interval +/-) from prefight values (Article cross reference number)
Non-secretory ribonuclease (44)	Biomarkers of cardiovascular deconditioning	169-199	N/A
Annexin A5 (44)	Biomarkers of cardiovascular deconditioning	169-199	N/A
Transthyretin (44)	Biomarkers of cardiovascular deconditioning	169-199	N/A
Prostate specific antigen (44)	Biomarkers of cardiovascular deconditioning	169-199	N/A
Cadherin-2 (44)	Biomarkers of cardiovascular deconditioning	169-199	N/A
Alpha-2-HS-glycoprotein (44)	Biomarkers of cardiovascular deconditioning	169-199	N/A
Urokinase plasminogen activator (44)	Biomarkers of cardiovascular deconditioning	169-199	N/A
Vitamin D-binding protein (44)	Biomarkers of cardiovascular deconditioning	169-199	N/A
Neprilysin (44)	Biomarkers of cardiovascular deconditioning	169-199	N/A
Gamma-glutamyl transpeptidase 1 (44)	Biomarkers of cardiovascular deconditioning	169-199	N/A
Thioredoxin (44)	Biomarkers of cardiovascular deconditioning	169-199	N/A
Apolipoprotein A-I (44)	Biomarkers of cardiovascular deconditioning	169-199	N/A
Total lung capacity (46)	Pulmonary architectural and structural properties	130-196	N/A
Lung tissue volume (Pulmonary tissue volume) (65)	Pulmonary architectural and structural properties	10	Significant ↓
Abdominal volume (68)	Pulmonary architectural and structural properties	10-11	N/A

Outcome (Article cross reference number)	Theme	Days of Spaceflight	Increase (↑), Decrease (↓) or No Change (NC) (with 95 Confidence Interval +/-) from prefight values (Article cross reference number)
Respiratory frequency [6, 10, 72]	Pulmonary functional and mechanical properties	8[6], 5[10] 52-199 [72]	Significant ↓ [6], N/A[10], 1.12 (1.13) ↑ [72]
Sympathovagal balance [39]	Pulmonary functional and mechanical properties	16	0.47 (1.15) ↑
Cardiogenic oscillation size [45, 47]	Pulmonary functional and mechanical properties	9-14[45], 9 [47]	**NC**[45], 3.57 (2.23) ↓ [47]
Height of phase IV [45, 47]	Pulmonary functional and mechanical properties	9-14[45], 9 [47]	**NC**[45], Significant ↓ [47]
Inspiratory time as a function of total breath time [45]	Pulmonary functional and mechanical properties	9-14	**NC**
Inspiratory time as a function of average inspiratory flow rate [45]	Pulmonary functional and mechanical properties	9-14	**NC**
End-tidal partial pressure of oxygen in blood [45]	Pulmonary functional and mechanical properties	9-14	**NC**
Oxygen uptake [45]	Pulmonary functional and mechanical properties	9-14	**NC**
Carbon dioxide output [45]	Pulmonary functional and mechanical properties	9-14	**NC**
Oxygen consumption [46]	Pulmonary functional and mechanical properties	130-196	0.67 (0.90) ↑
Maximal oxygen consumption [56]	Pulmonary functional and mechanical properties	9-15	N/A
Carbon dioxide production [46]	Pulmonary functional and mechanical properties	130-196	0.46 (0.89) ↑
Respiratory rate [45]	Pulmonary functional and mechanical properties	9-14	**NC**
Total ventilation [45, 46]	Pulmonary functional and mechanical properties	9-14 [45], 130-196 [46]	Significant ↑ [45], 0.67 (0.90) ↑ [46]
Alveolar ventilation [45, 46]	Pulmonary functional and mechanical properties	9-14 [45], 130-196 [46]	Significant ↑ [45], 0.59 (0.90) ↑ [46]

Outcome (Article cross reference number)	Theme	Days of Spaceflight	Increase (↑), Decrease (↓) or No Change (NC) (with 95 Confidence Interval +/-) from prefight values (Article cross reference number)
Breathing frequency (46)	Pulmonary functional and mechanical properties	130-196	0.55 (0.89) ↑
End-tidal partial pressure of carbon dioxide (45, 46)	Pulmonary functional and mechanical properties	9-14 (45), 130-196 (46)	**NC**(45), 0.27 (0.88) ↓ (46)
Respiratory exchange ratio (46)	Pulmonary functional and mechanical properties	130-196	0.66 (0.88) ↑
Hyperventilation breathhold cardiogenic oscillation size (46)	Pulmonary functional and mechanical properties	130-196	0.29 (0.88) ↓
Hyperventilation-breath-hold vertical height of phase IV (46)	Pulmonary functional and mechanical properties	130-196	0.13 (0.88) ↓
Carbon dioxide concentration (47)	Pulmonary functional and mechanical properties	9	N/A
Diffusing capacity for carbon monoxide (48)	Pulmonary functional and mechanical properties	9	0.72 (1.43) ↓
Diffusing capacity per unit alveolar volume (48)	Pulmonary functional and mechanical properties	9	2.67 (1.91) ↑
Alveolar volume (48)	Pulmonary functional and mechanical properties	9	0.50 (1.41) ↓
Pulmonary capillary blood volume (48)	Pulmonary functional and mechanical properties	9	1.11 (1.49) ↓
Membrane diffusing capacity (48)	Pulmonary functional and mechanical properties	9	0.39 (1.40) ↓
Pulmonary capillary blood flow (48)	Pulmonary functional and mechanical properties	9	N/A
Diffusing capacity per unit lung volume (48)	Pulmonary functional and mechanical properties	9	N/A
Specific ventilation flow (49)	Pulmonary functional and mechanical properties	9	N/A
Specific ventilation volume (49)	Pulmonary functional and mechanical properties	9	N/A

Outcome (Article cross reference number)	Theme	Days of Spaceflight	Increase (↑), Decrease (↓) or No Change (NC) (with 95 Confidence Interval +/-) from prefight values (Article cross reference number)
Specific ventilation (mean) (49)	Pulmonary functional and mechanical properties	9	N/A
Slope ratio of mixed-expired washouts (49)	Pulmonary functional and mechanical properties	9	0.04 (1.39) ↓
Normalised phase III slope as a function of breath number (49)	Pulmonary functional and mechanical properties	9	N/A
Arteriovenous oxygen difference (56)	Pulmonary functional and mechanical properties	9-15	N/A
Respiratory quotient (56)	Pulmonary functional and mechanical properties	9-15	N/A
Minute ventilation (56)	Pulmonary functional and mechanical properties	9-15	N/A
Lung CO-diffusing capacity (65)	Pulmonary functional and mechanical properties	10	N/A
Lung CO-diffusing capacity per unit volume (65)	Pulmonary functional and mechanical properties	10	N/A
Forced vital capacity (45, 46)	Pulmonary vital capacity	9-14 (45), 130-196 (46)	**NC**(45), 0.34 (0.88) ↓ (46)
Expired vital capacity (45)	Pulmonary vital capacity	9-14	**NC**
Vital capacity (45)	Pulmonary vital capacity	9-14	**NC**
Tidal volume (45, 46, 56, 68)	Chest wall mechanics	9-14 (45), 130-196 (46), 9-15 (56), 10 (68)	**NC** (45), 0.00 (0.88)(46), N/A(56), N/A(68)
Abdominal component of total respiratory system compliance (68)	Chest wall mechanics	10	N/A
Rib cage component of total respiratory system compliance (68)	Chest wall mechanics	10	N/A
Range of ventilation-perfusion ratio over phase III (45)	Pulmonary perfusion ratio	9-14	**NC**
Range of ventilation-perfusion ratio over phase IV (45)	Pulmonary perfusion ratio	9-14	**NC**

Outcome (Article cross reference number)	Theme	Days of Spaceflight	Increase (↑), Decrease (↓) or No Change (NC) (with 95 Confidence Interval +/-) from prefight values (Article cross reference number)
Slope of intrabreath ventilation perfusion ratio vs volume over first half of phase III [46]	Pulmonary perfusion ratio	130-196	0.56 (0.89) ↑
Slope of intrabreath ventilation perfusion ratio range over phase IV [46]	Pulmonary perfusion ratio	130-196	9.00 (0.88) ↑
Forced expiratory volume in 1 second [45, 46]	Spirometry	9-14 [45], 130-196 [46]	**NC** [45], 0.29 (0.88) ↓ [46]
Forced expiratory flow after exhalation of 50% vital capacity [46]	Spirometry	130-196	0.25 (0.88) ↑
Forced expiratory flow at 25-75% vital capacity [46]	Spirometry	130-196	0.20 (0.88) ↑
Peak expiratory flow rate [46]	Spirometry	130-196	0.82 (0.91) ↑
Forced expiratory flow rate at 50% of inspired volume [46]	Spirometry	130-196	0.42 (0.89) ↑
Forced inspiratory flow at 25-75% of vital capacity [46]	Spirometry	130-196	0.32 (0.88) ↑
Peak inspiratory flow rate [46]	Spirometry	130-196	0.48 (0.89) ↑
Maximum inspiratory pressure [46]	Respiratory pressure	130-196	0.35 (0.88) ↓
Maximum expiratory pressure [46]	Respiratory pressure	130-196	0.01 (0.88) ↓
Functional residual capacity [46, 56, 65]	Respiratory pressure	9-14 [45], 130-196 [46], 10 [65]	N/A[46], N/A[56], N/A[65]
Residual volume [46]	Respiratory pressure	130-196	N/A
Anatomic dead space [45]	Pulmonary dead space	9-14	**NC**
Physiologic dead space [45]	Pulmonary dead space	9-14	**NC**
Alveolar dead space [45, 46]	Pulmonary dead space	9-14 [45], 130-196 [46]	N/A[45], N/A[46],
Anatomic dead space as a function of breath number [49]	Pulmonary dead space	9	N/A

Outcome (Article cross reference number)	Theme	Days of Spaceflight	Increase (↑), Decrease (↓) or No Change (NC) (with 95 Confidence Interval +/-) from prefight values (Article cross reference number)
Bohr dead space as a function of breath number (49)	Pulmonary dead space	9	N/A

In the results column, data was converted to Hedge's *g* effect size decrease (↓), increase (↑), or no change (**NC**) where possible. If a paper did not report data that could be used to calculate effect sizes then significant decrease (↓), increase (↑), or no change (**NC**) from baseline was reported instead. **N/A** is used for outcomes where the study did not report the data necessary to calculate effect size changes and did not report if changes were statistically significant or not. *Denotes data were collected during exercise or a functional task. All other data were collected during rest

9.4. Appendix D

Pre-scoping from Chapter 4.

The EXCEL pre-scoping file can be found here:
https://docs.google.com/spreadsheets/d/1YEIKvTqQwhH5npWxOSEQdjH1puBA0C-a5QD3-V668Ew/edit?usp=sharing

9.5. Appendix E

Chapter 4 figures displaying effect size differences between experimental and control group post-intervention scores

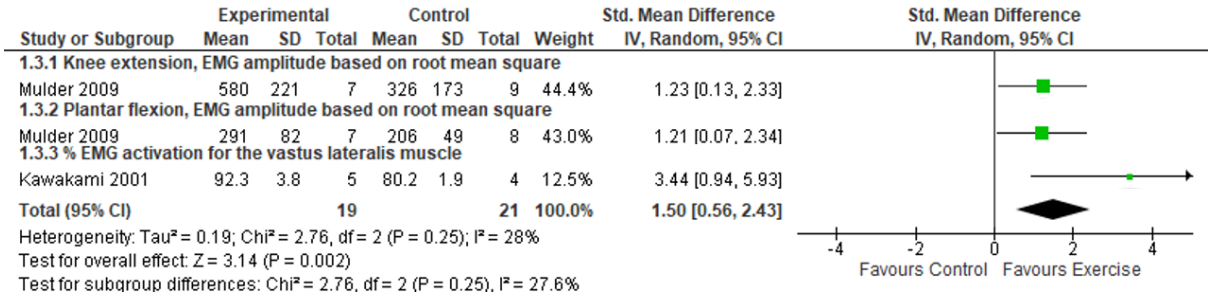

Figure 9.1 Forest plot of EMG activity effect size differences for the resistive exercise intervention

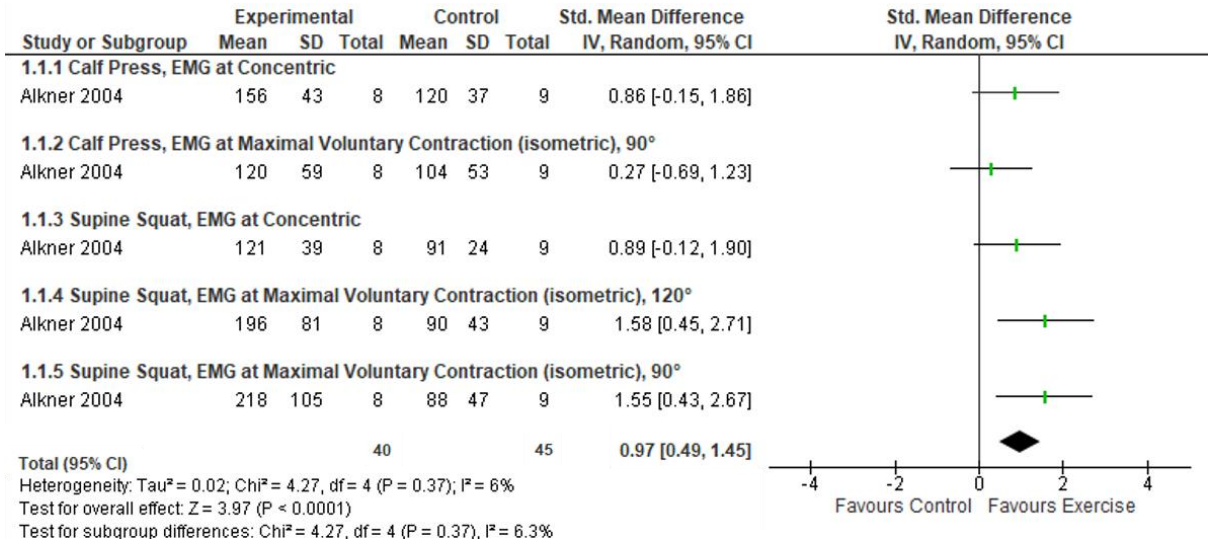

Figure 9.2 Forest plot of EMG activity effect size differences for the flywheel intervention

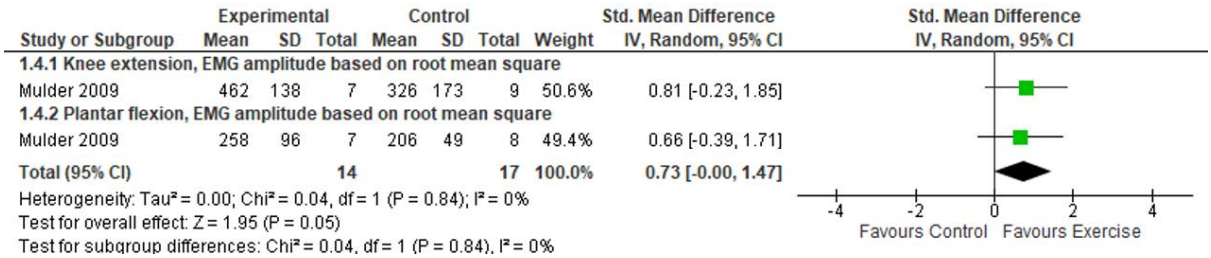

Figure 9.3 Forest plot of EMG activity effect size differences for the resistive vibration exercise intervention

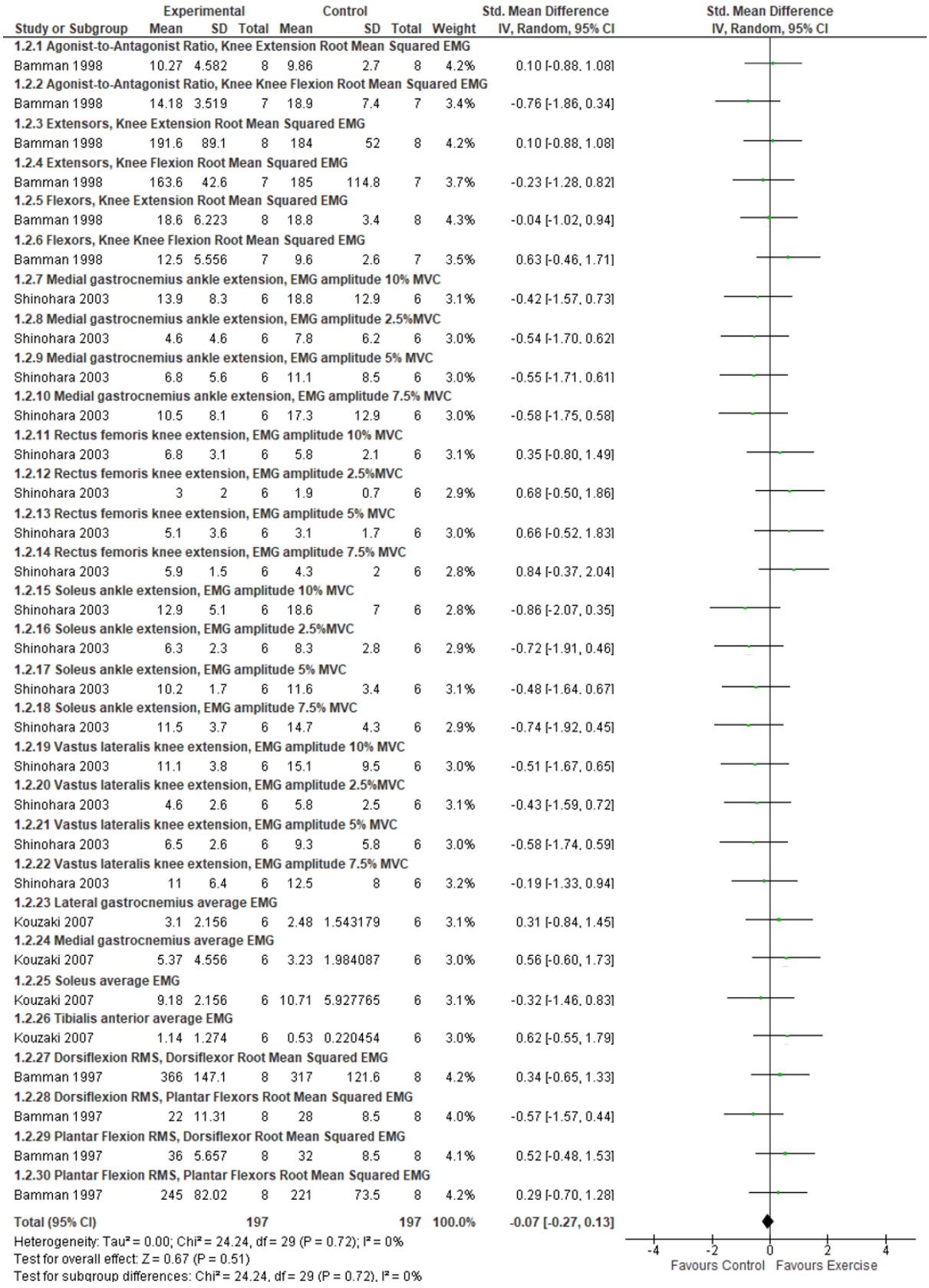

Figure 9.4 Forest plot of EMG activity effect size differences for the horizontal leg press intervention

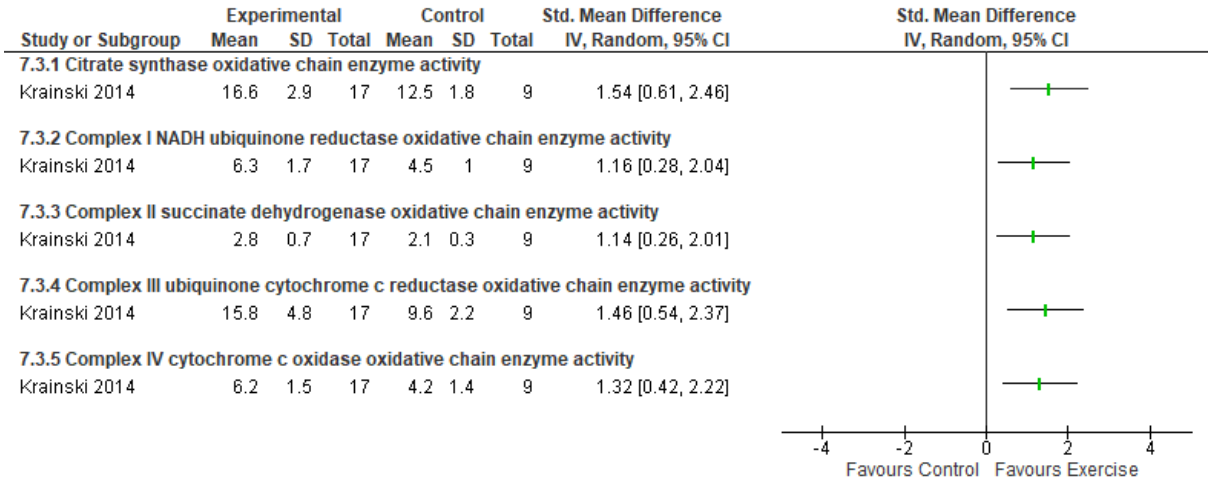

Figure 9.5 Forest plot of muscle biomarker effect size differences for the rowing ergometer + resistive exercise intervention

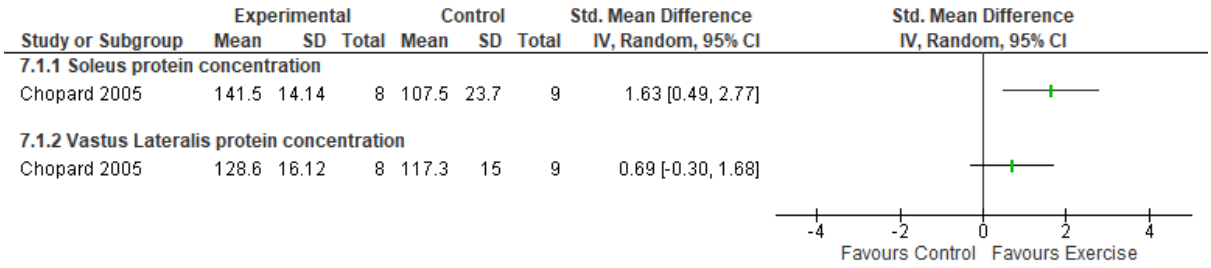

Figure 9.6 Forest plot of muscle biomarker effect size differences for the flywheel intervention

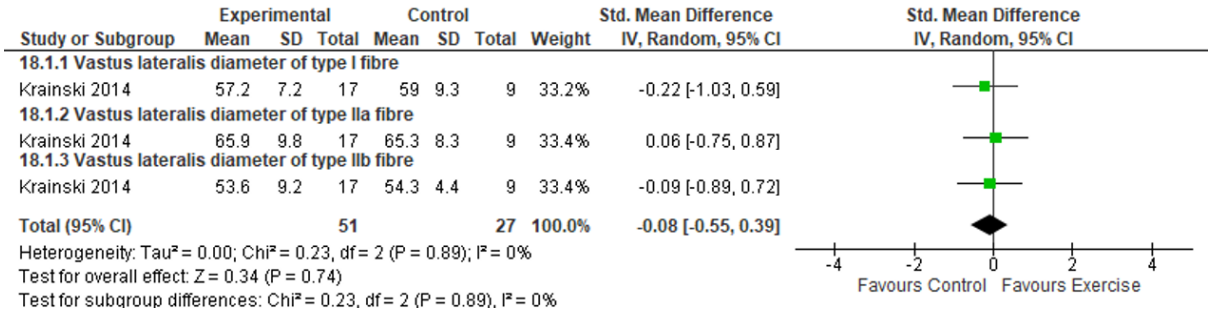

Figure 9.7 Forest plot of fibre diameter effect size differences for the rowing ergometer + resistive exercise intervention

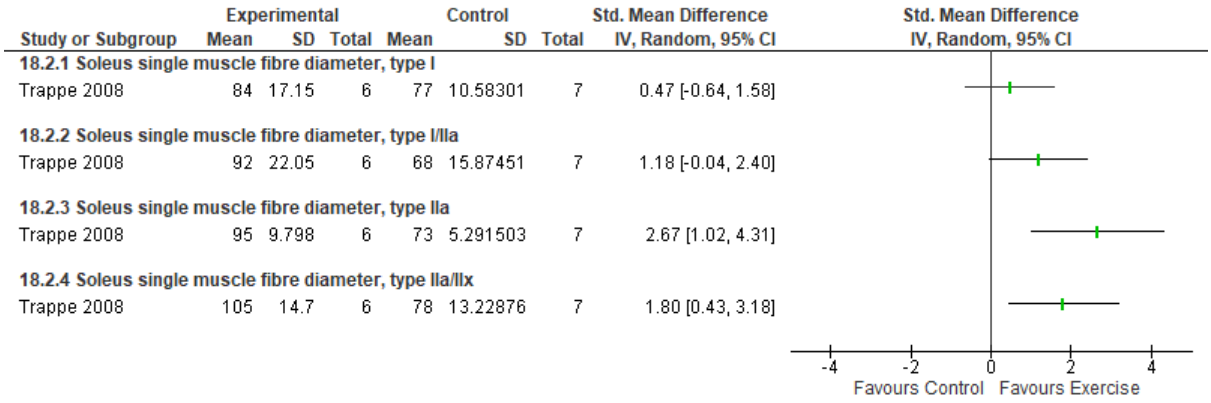

Figure 9.8 Forest plot of fibre diameter effect size differences for the resistive vibration exercise intervention

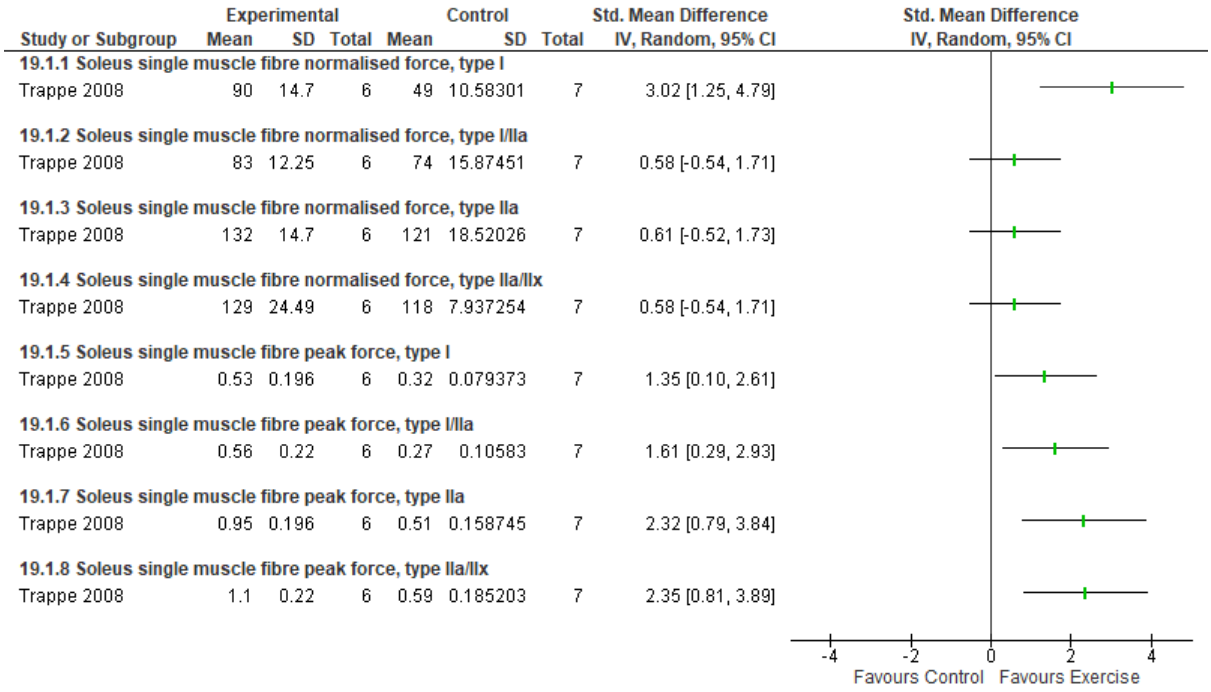

Figure 9.9 Forest plot of fibre force effect size differences for the resistive vibration exercise intervention

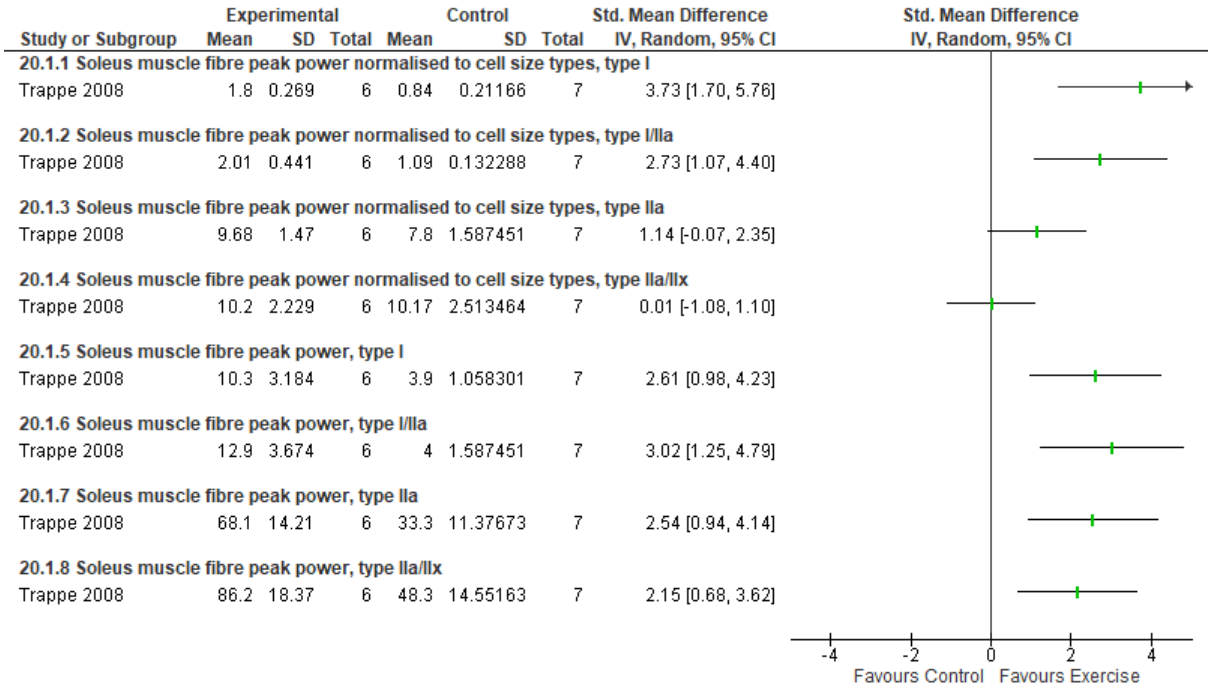

Figure 9.10 Forest plot of fibre power effect size differences for the resistive vibration exercise intervention

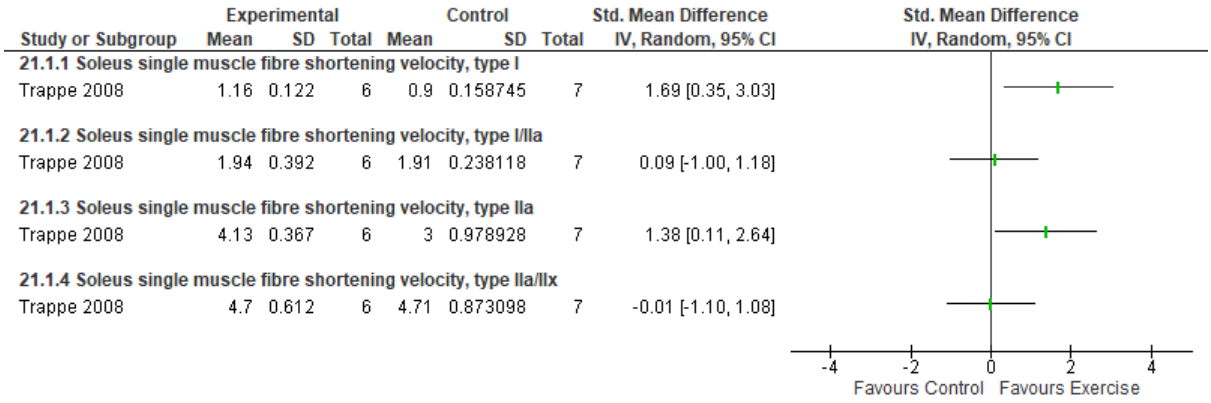

Figure 9.11 Forest plot of fibre shortening velocity effect size differences for the resistive vibration exercise intervention

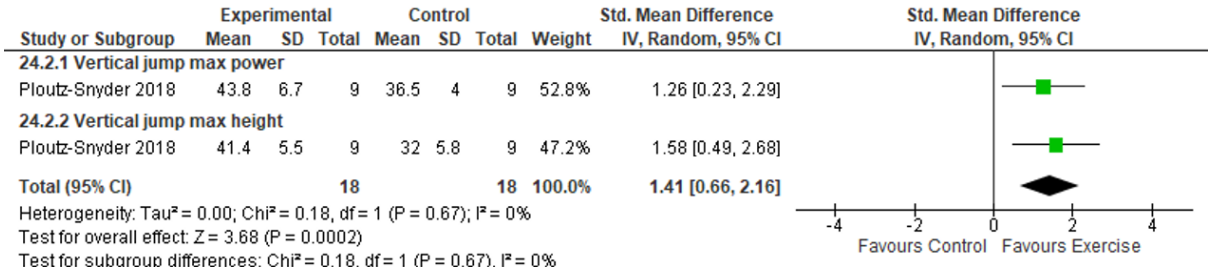

Figure 9.12 Forest plot of jump height and power effect size differences for the zero-gravity treadmill + cycle ergometer intervention

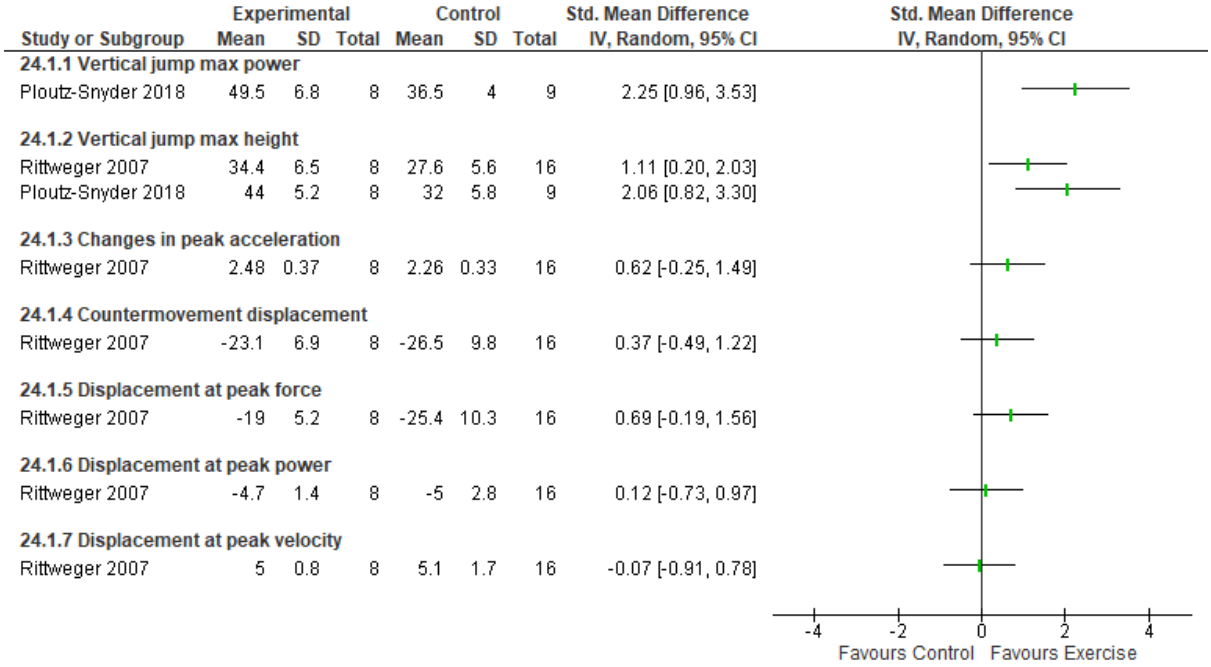

Figure 9.13 Forest plot of jump height and power effect size differences for the flywheel intervention

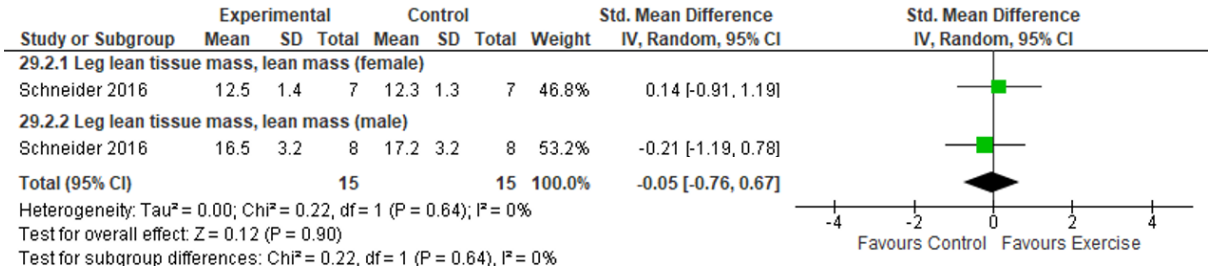

Figure 9.14 Forest plot of muscle mass effect size differences for the treadmill LBNP intervention

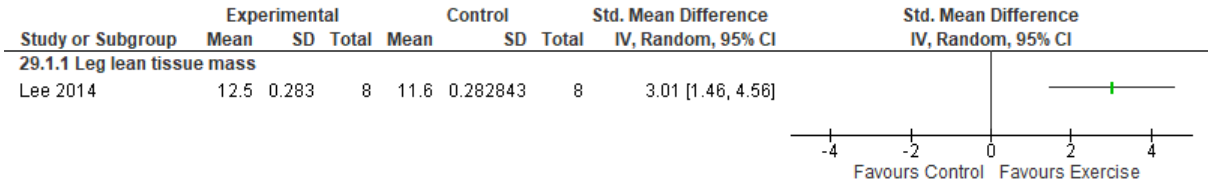

Figure 9.15 Forest plot of muscle mass effect size differences for the flywheel + treadmill LBNP intervention

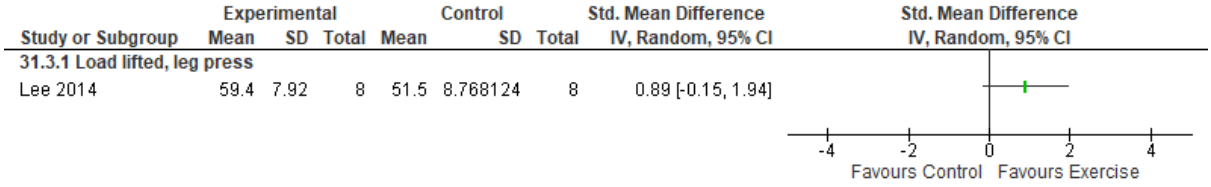

Figure 9.16 Forest plot of muscle strength effect size differences for the flywheel + treadmill LBNP intervention

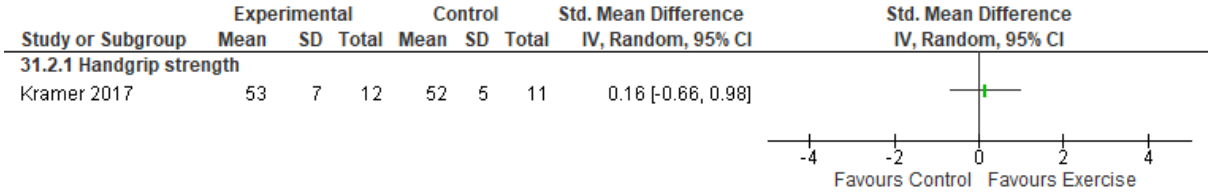

Figure 9.17 Forest plot of muscle strength effect size differences for horizontal sledge jump system intervention

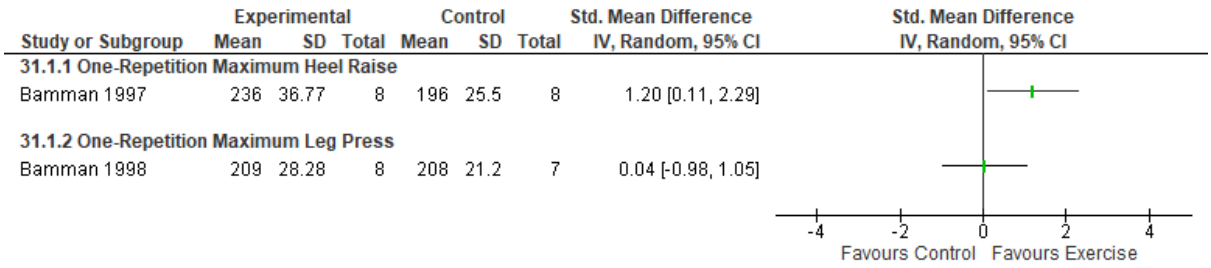

Figure 9.18 Forest plot of muscle strength effect size differences for the horizontal leg press intervention

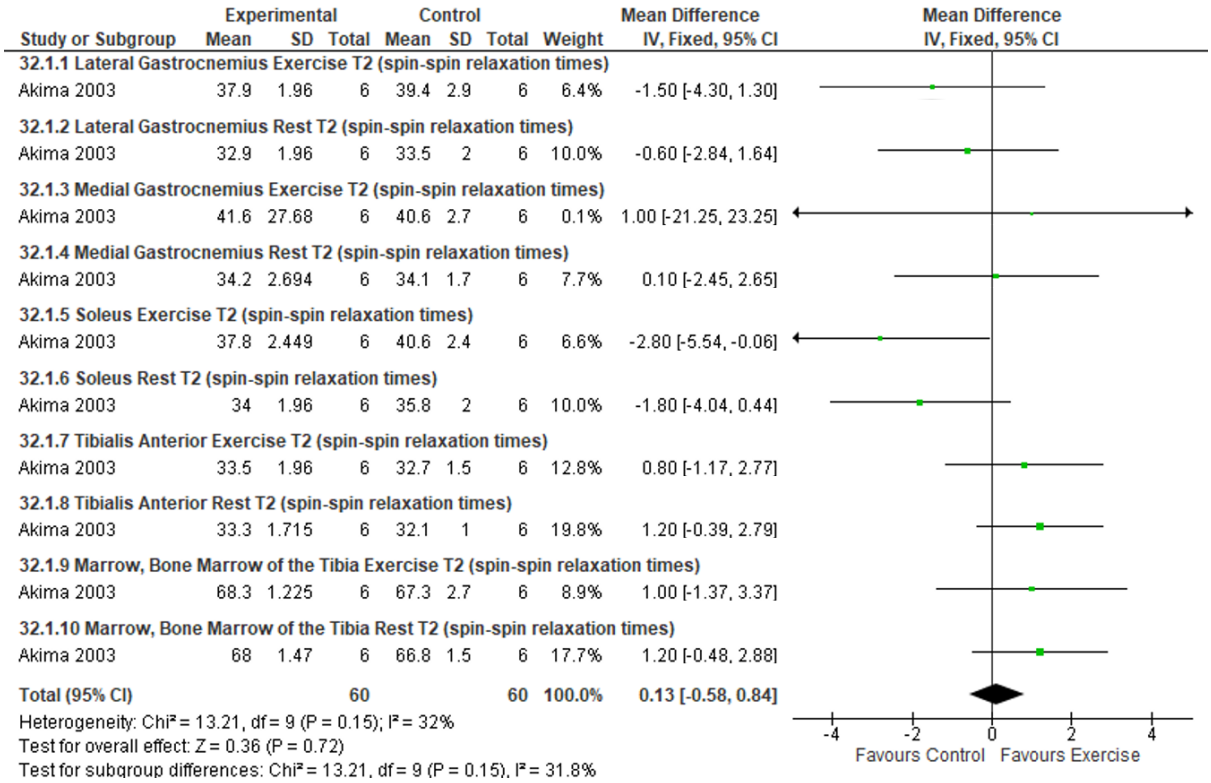

Figure 9.19 Forest plot of T2 relaxation effect size differences for the horizontal leg press intervention

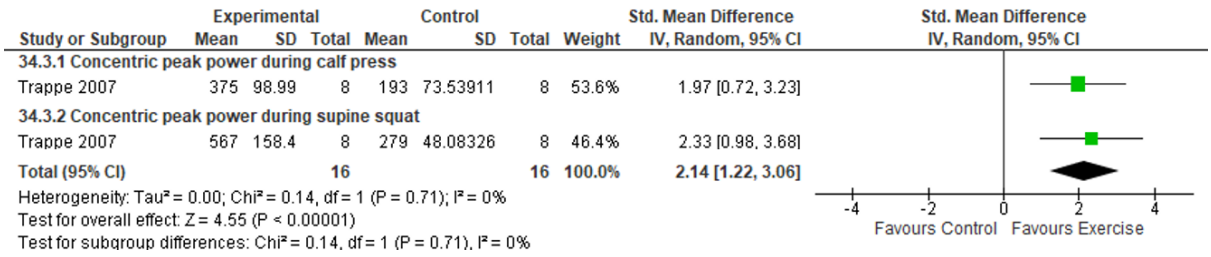

Figure 9.20 Forest plot of muscle power effect size differences for the gravity-independent inertial ergometer intervention

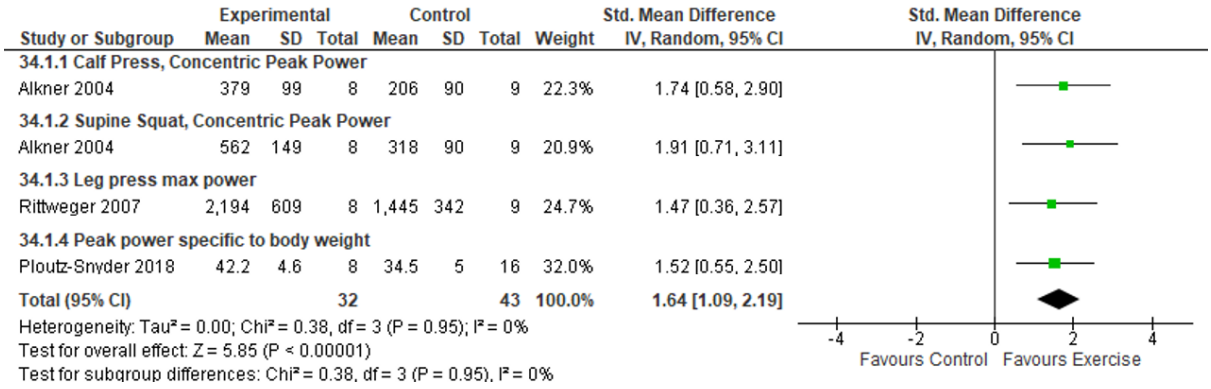

Figure 9.21 Forest plot of muscle power effect size differences for the flywheel intervention

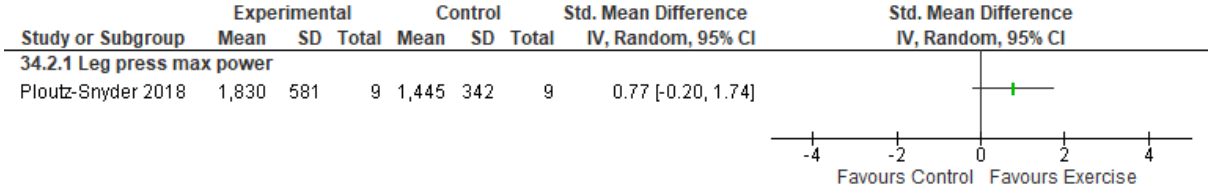

Figure 9.22 Forest plot of muscle power effect size differences for the zero-gravity treadmill + cycle ergometer intervention

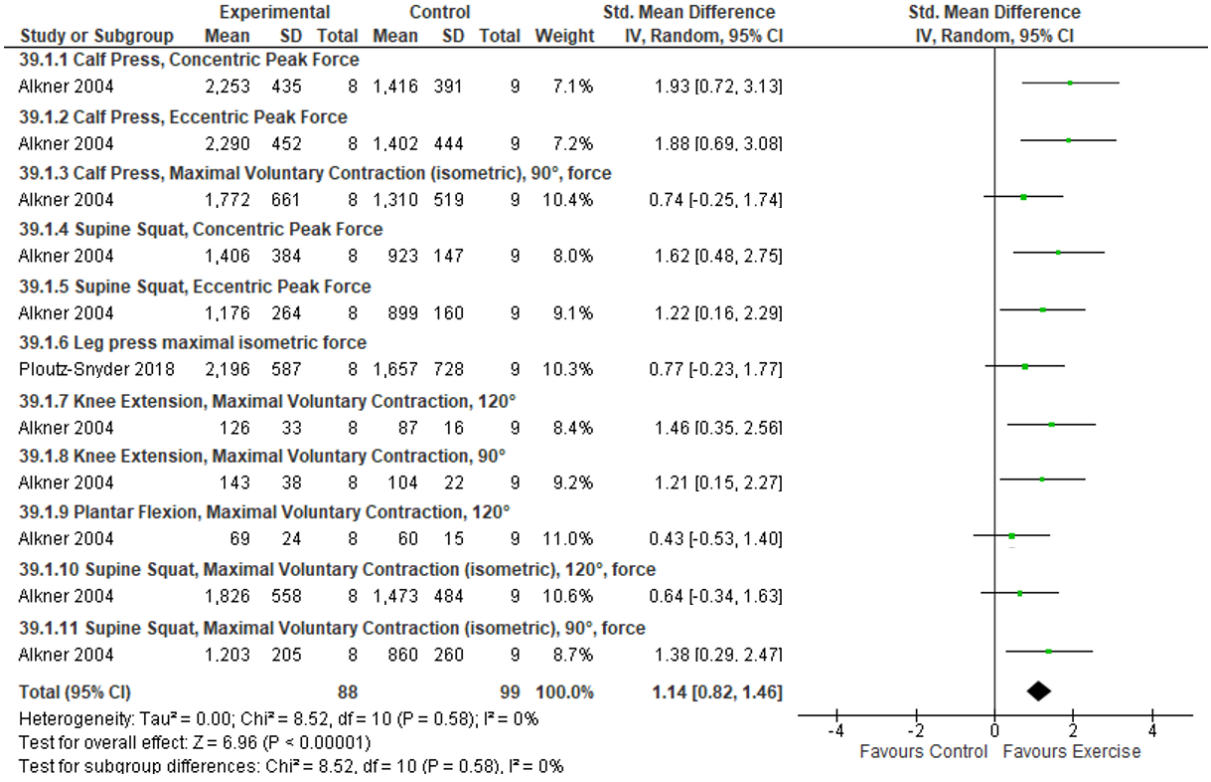

Figure 9.23 Forest plot of maximal voluntary contraction/muscle force effect size differences for the flywheel intervention

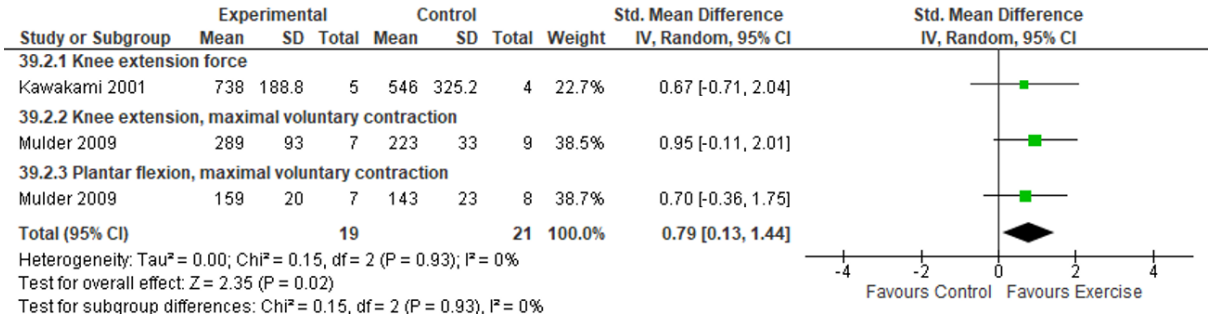

Figure 9.24 Forest plot of maximal voluntary contraction/muscle force effect size differences for the resistive exercise intervention

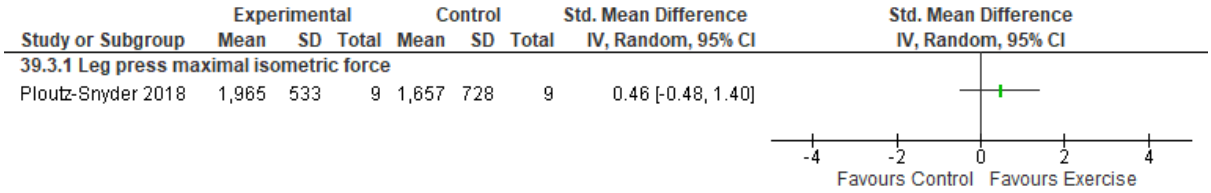

Figure 9.25 Forest plot of maximal voluntary contraction/muscle force effect size differences for the zero-gravity treadmill + cycle ergometer intervention

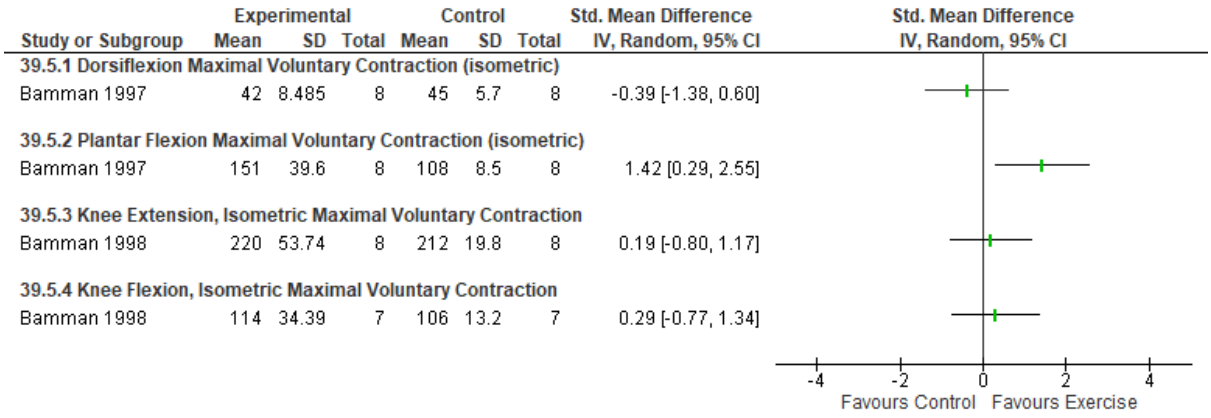

Figure 9.26 Forest plot of maximal voluntary contraction/muscle force effect size differences for the horizontal leg press intervention

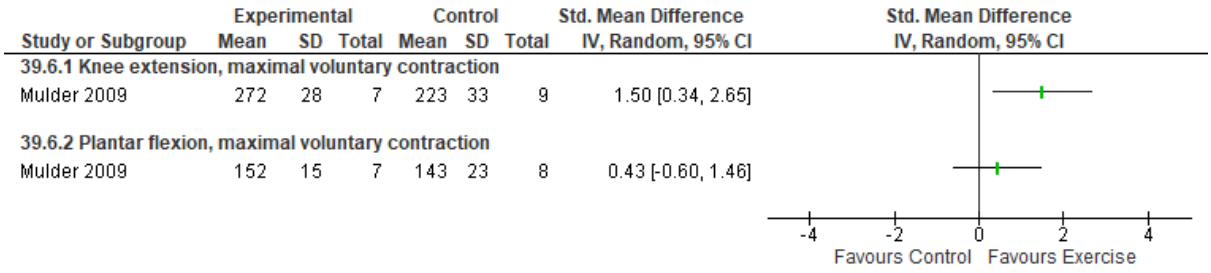

Figure 9.27 Forest plot of maximal voluntary contraction/muscle force effect size differences for the resistive vibration exercise intervention

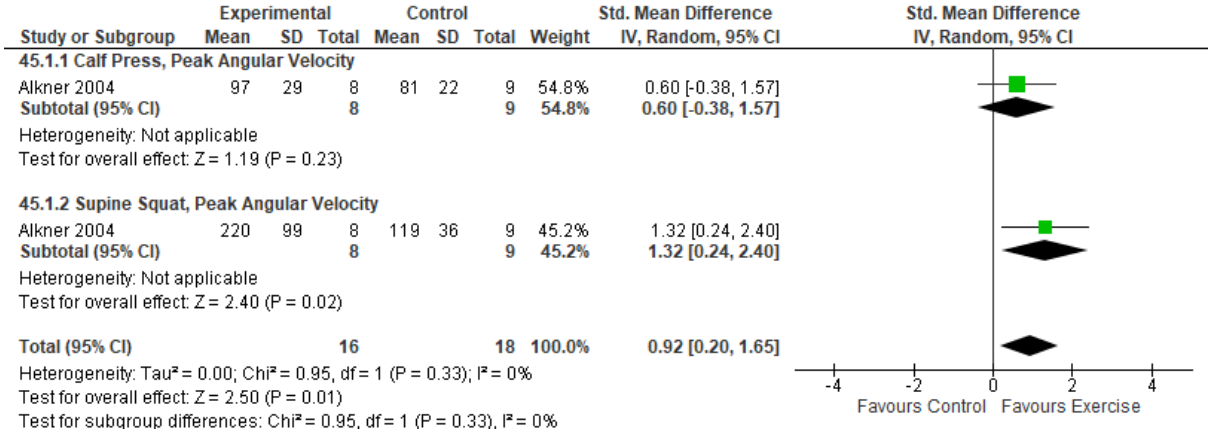

Figure 9.28 Forest plot of muscle velocity effect size differences for the flywheel intervention

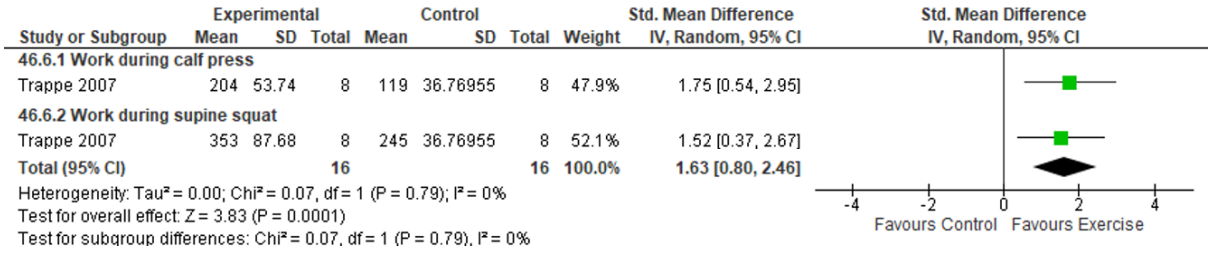

Figure 9.29 Forest plot of muscle work effect size differences for the gravity-independent inertial ergometer intervention

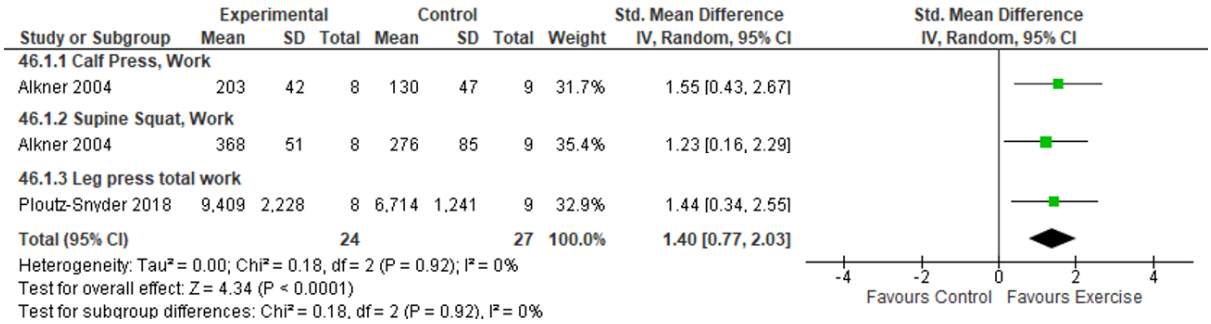

Figure 9.30 Forest plot of muscle work effect size differences for the flywheel intervention

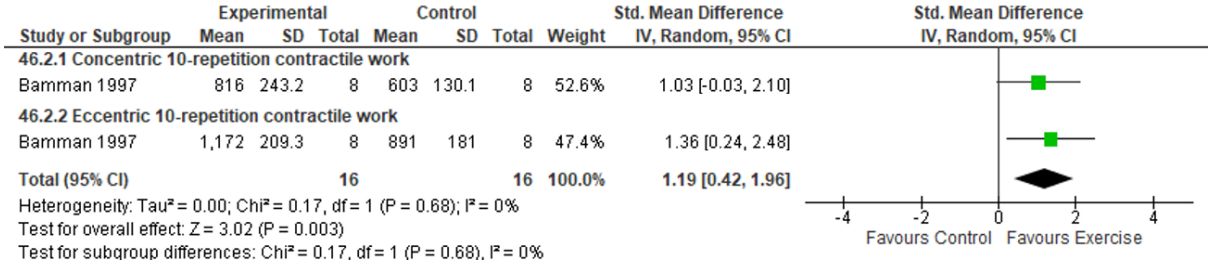

Figure 9.31 Forest plot of muscle work effect size differences for the horizontal leg press intervention

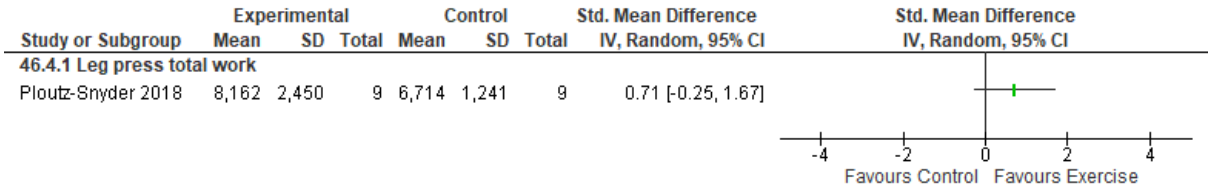

Figure 9.32 Forest plot of muscle work effect size differences for the zero-gravity treadmill + cycle ergometer

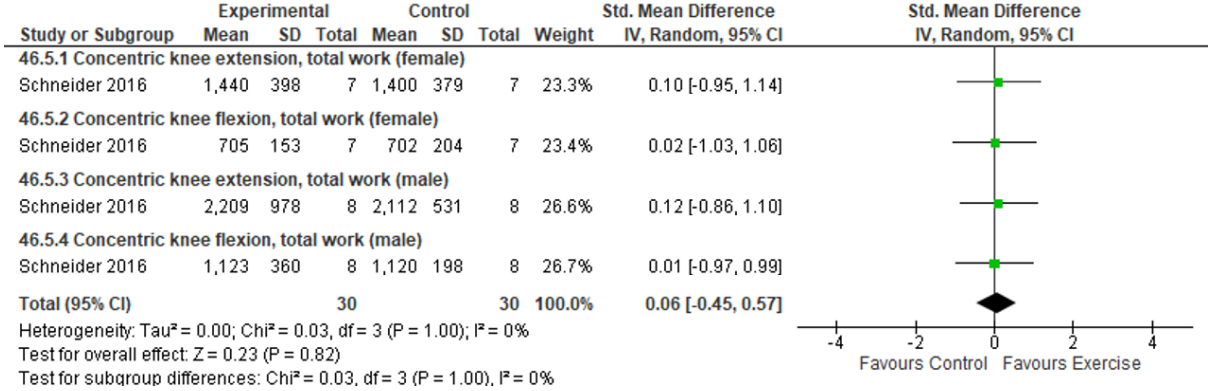

Figure 9.33 Forest plot of muscle work effect size differences for the treadmill LBNP intervention

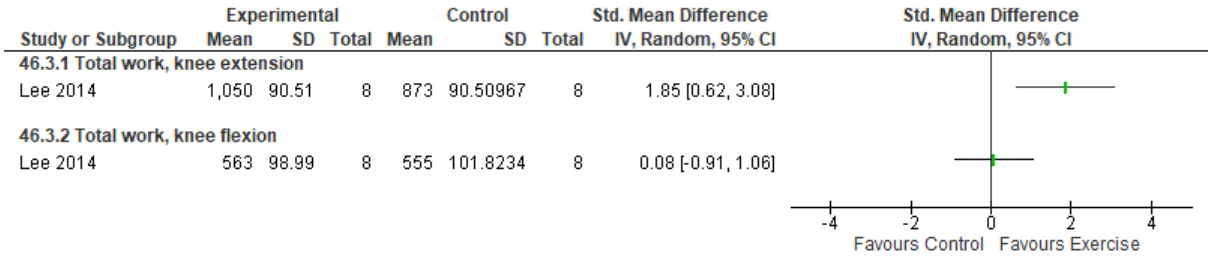

Figure 9.34 Forest plot of muscle work effect size differences for the Flywheel + Treadmill LBNP intervention

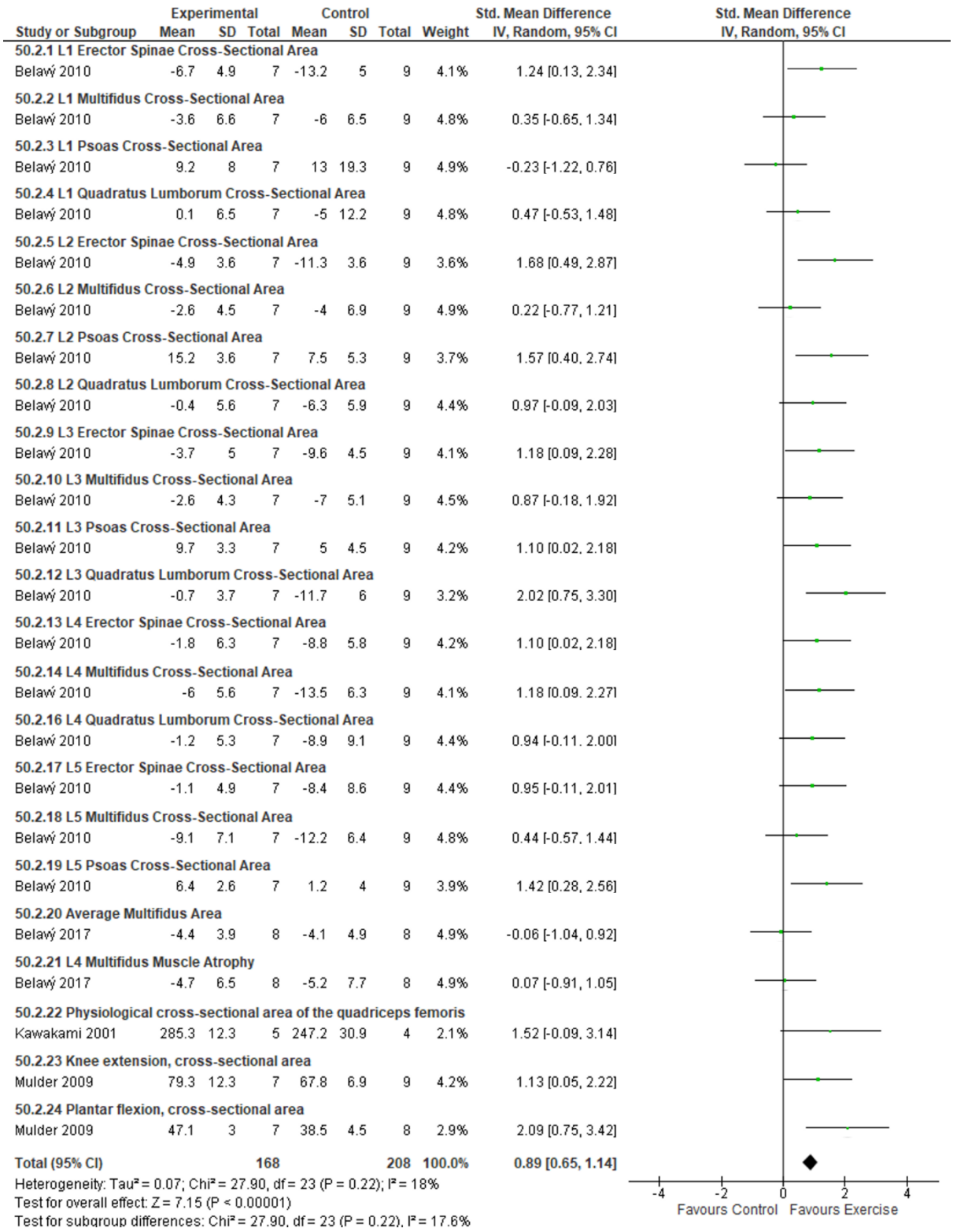

Figure 9.35 Forest plot of muscle CSA effect size differences for the resistive exercise intervention

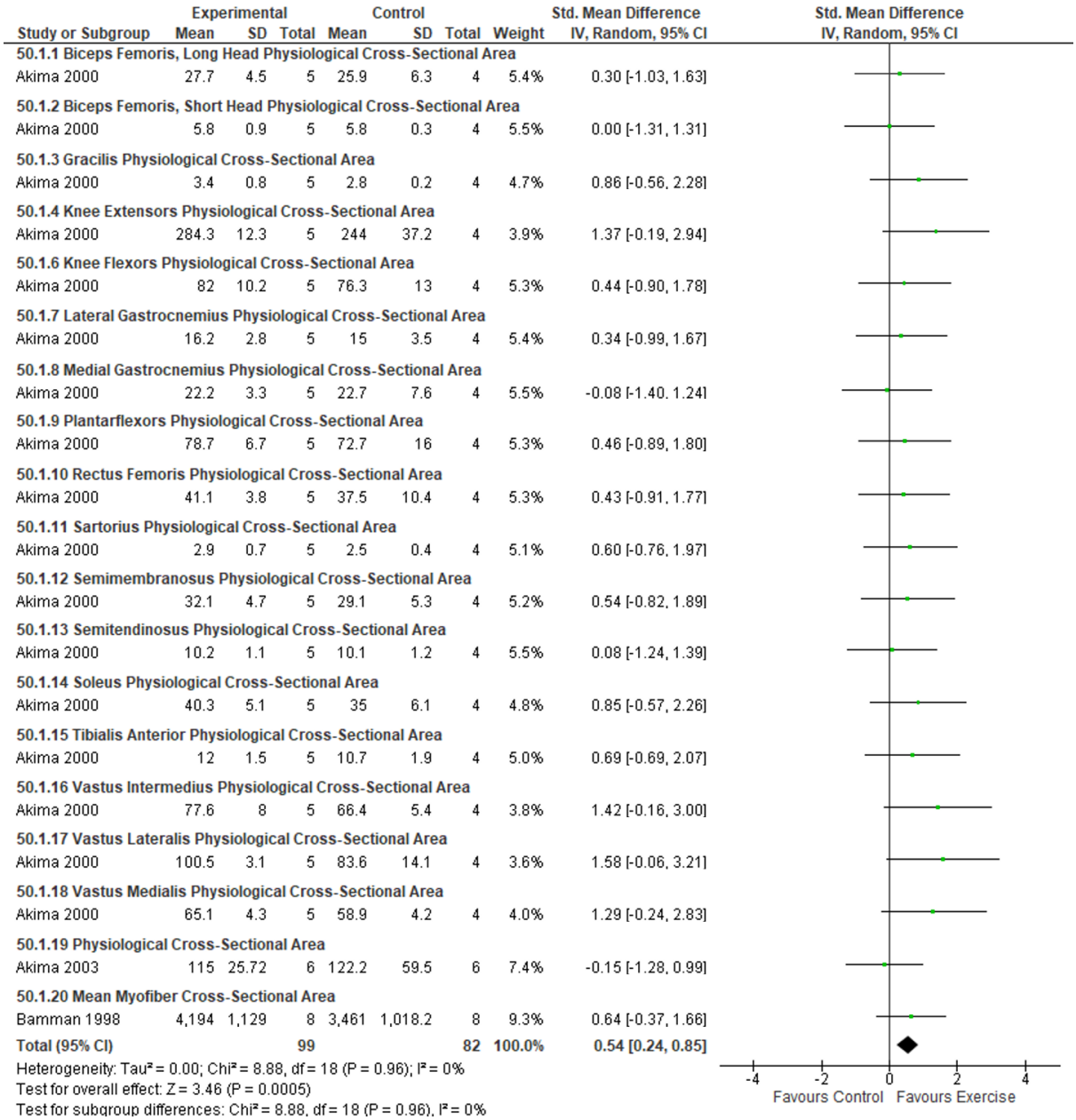

Figure 9.36 Forest plot of muscle CSA effect size differences for the horizontal leg press intervention

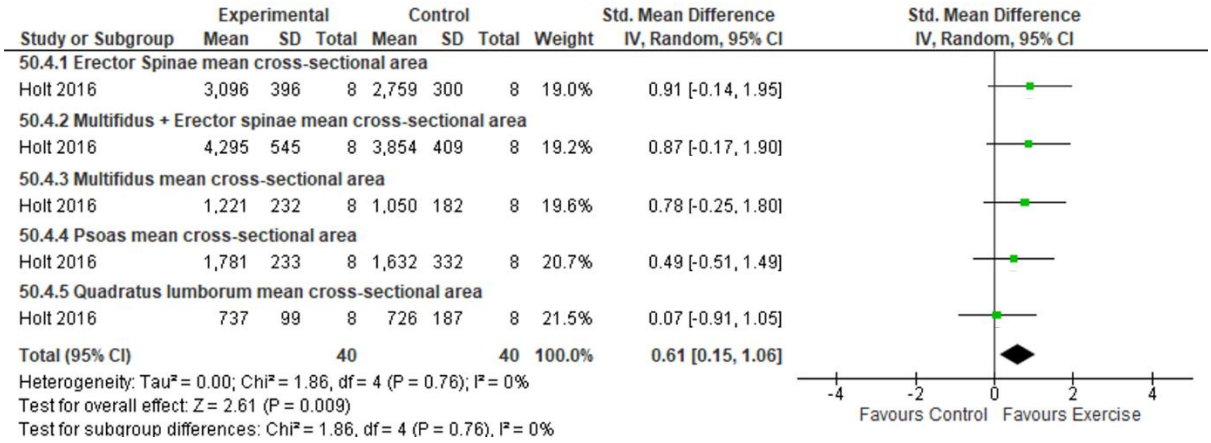

Figure 9.37 Forest plot of muscle CSA effect size differences for the flywheel + treadmill LBNP intervention

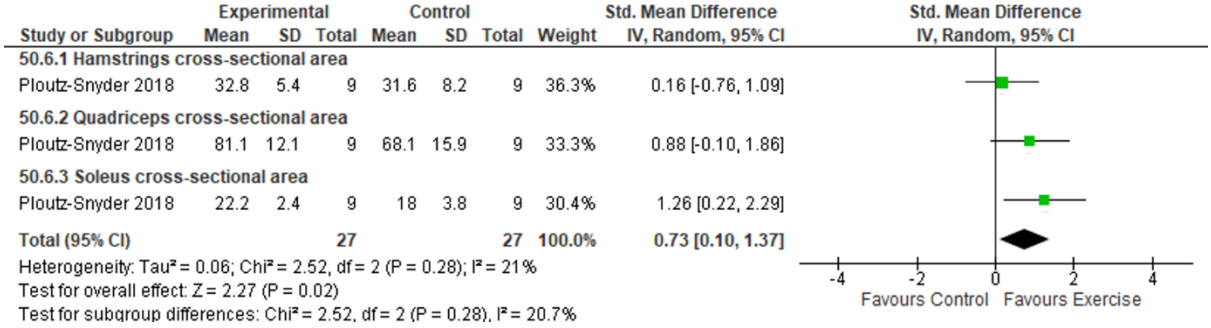

Figure 9.38 Forest plot of muscle CSA effect size differences for the zero-gravity treadmill + cycle ergometer intervention

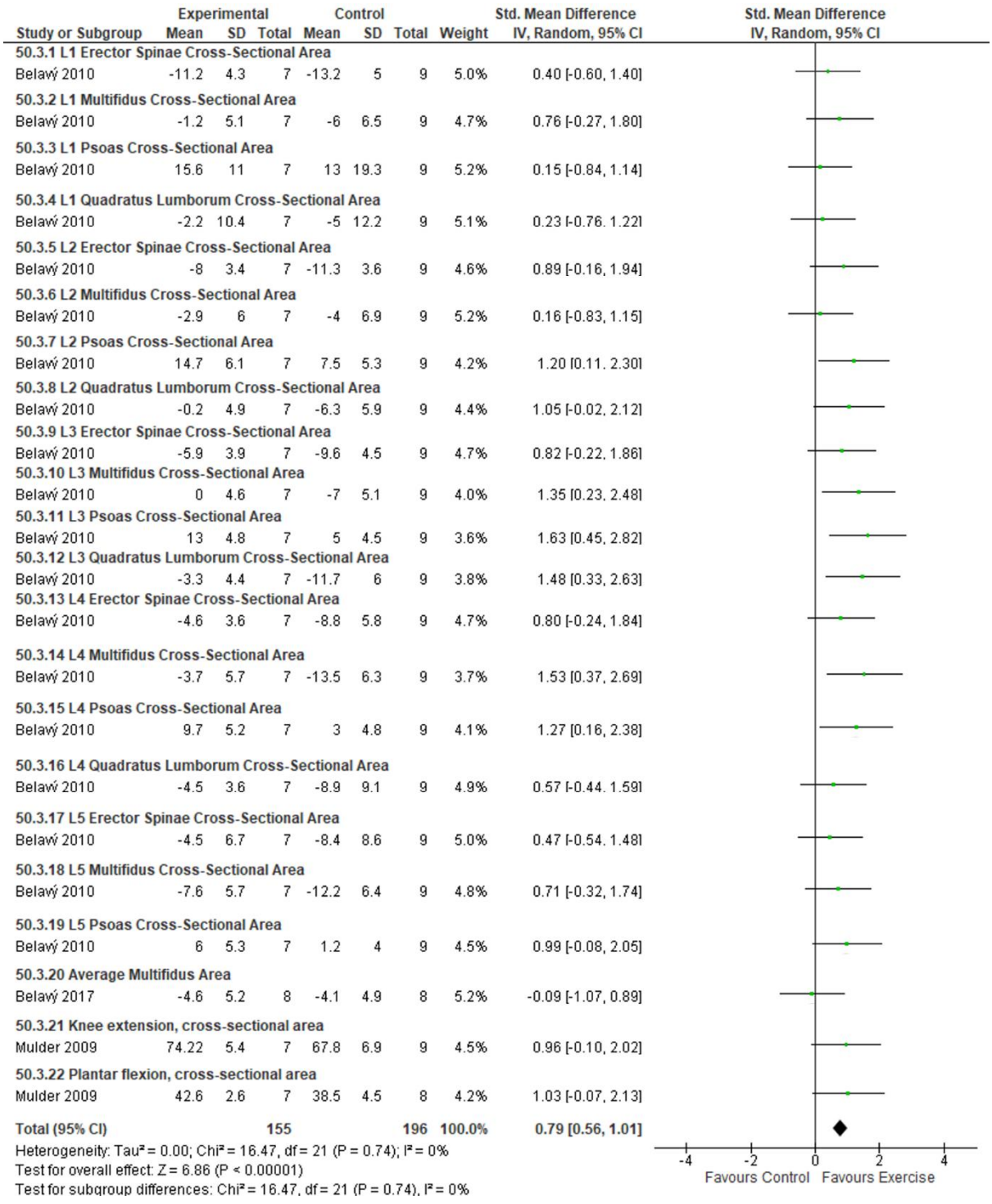

Figure 9.39 Forest plot of muscle CSA effect size differences for the resistive vibration exercise intervention

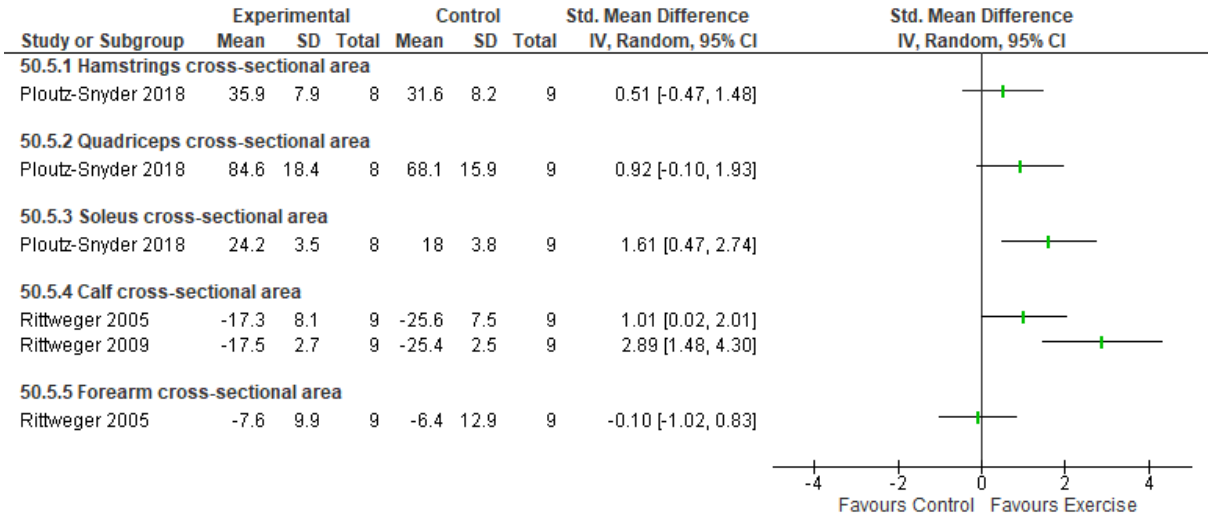

Figure 9.40 Forest plot of muscle CSA effect size differences for the flywheel intervention

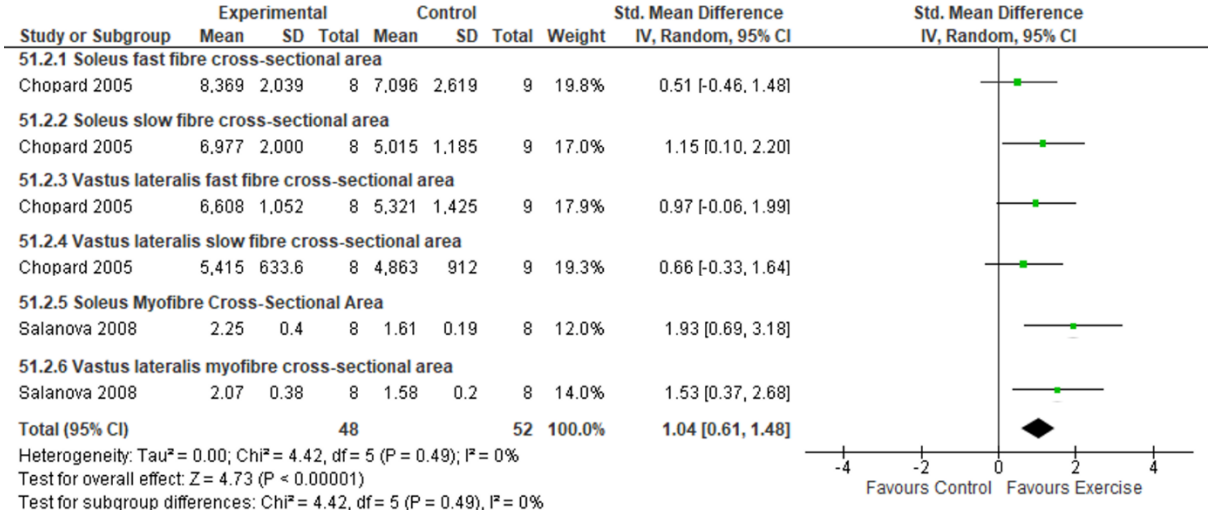

Figure 9.41 Forest plot of fibre CSA effect size differences for the flywheel intervention

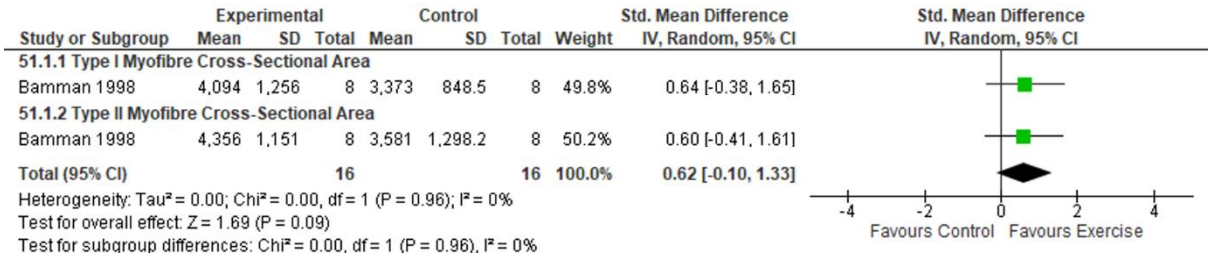

Figure 9.42 Forest plot of fibre CSA effect size differences for the horizontal leg press intervention

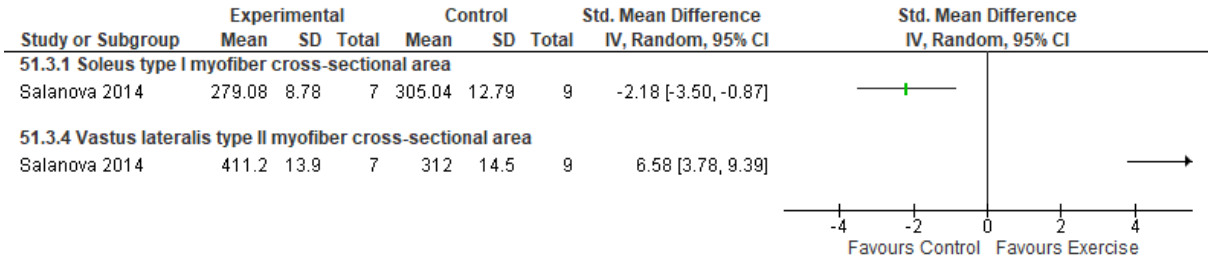

Figure 9.43 Forest plot of fibre CSA effect size differences for the resistive vibration exercise intervention

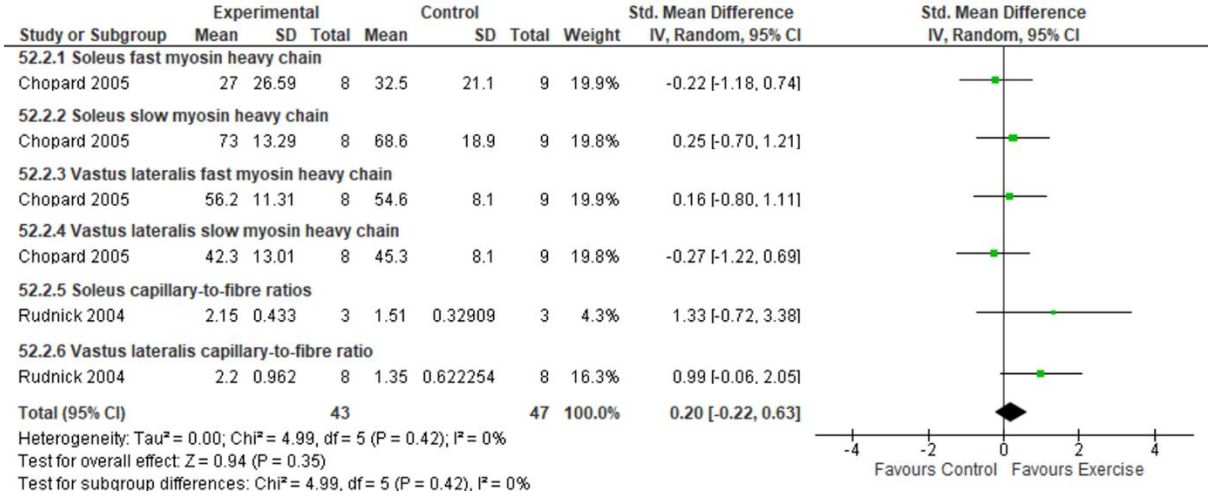

Figure 9.44 Forest plot of fibre composition effect size differences for the flywheel intervention

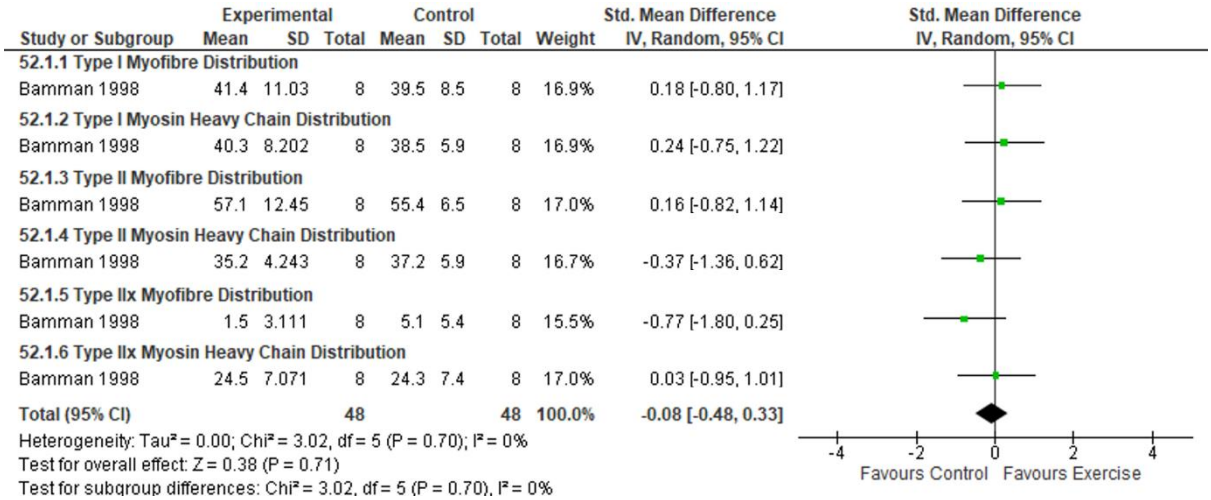

Figure 9.45 Forest plot of fibre composition effect size differences for the horizontal leg press intervention

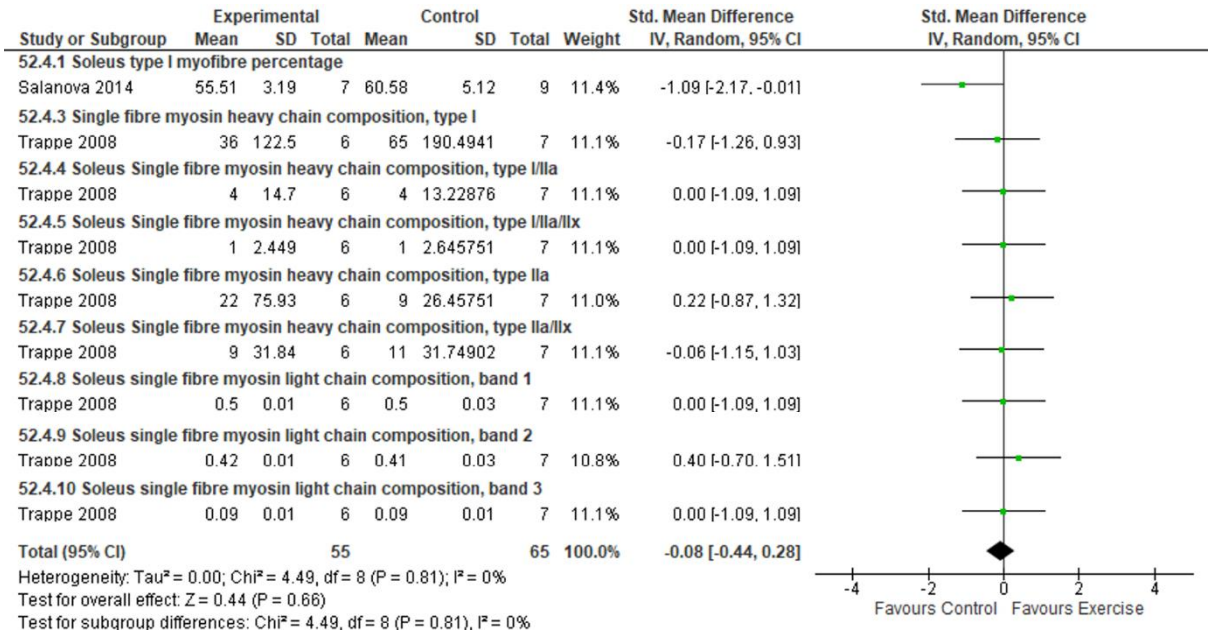

Figure 9.46 Forest plot of fibre composition effect size differences for the resistive vibration exercise intervention

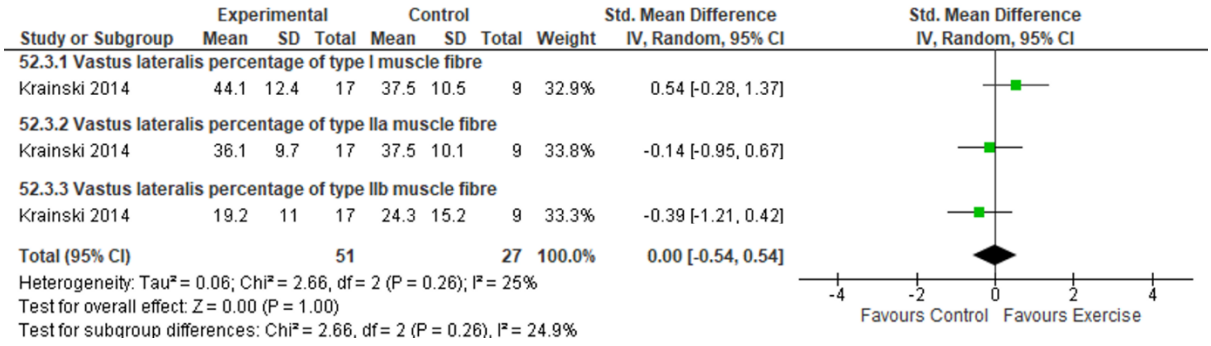

Figure 9.47 Forest plot of fibre composition effect size differences for the rowing ergometer + resistive exercise intervention

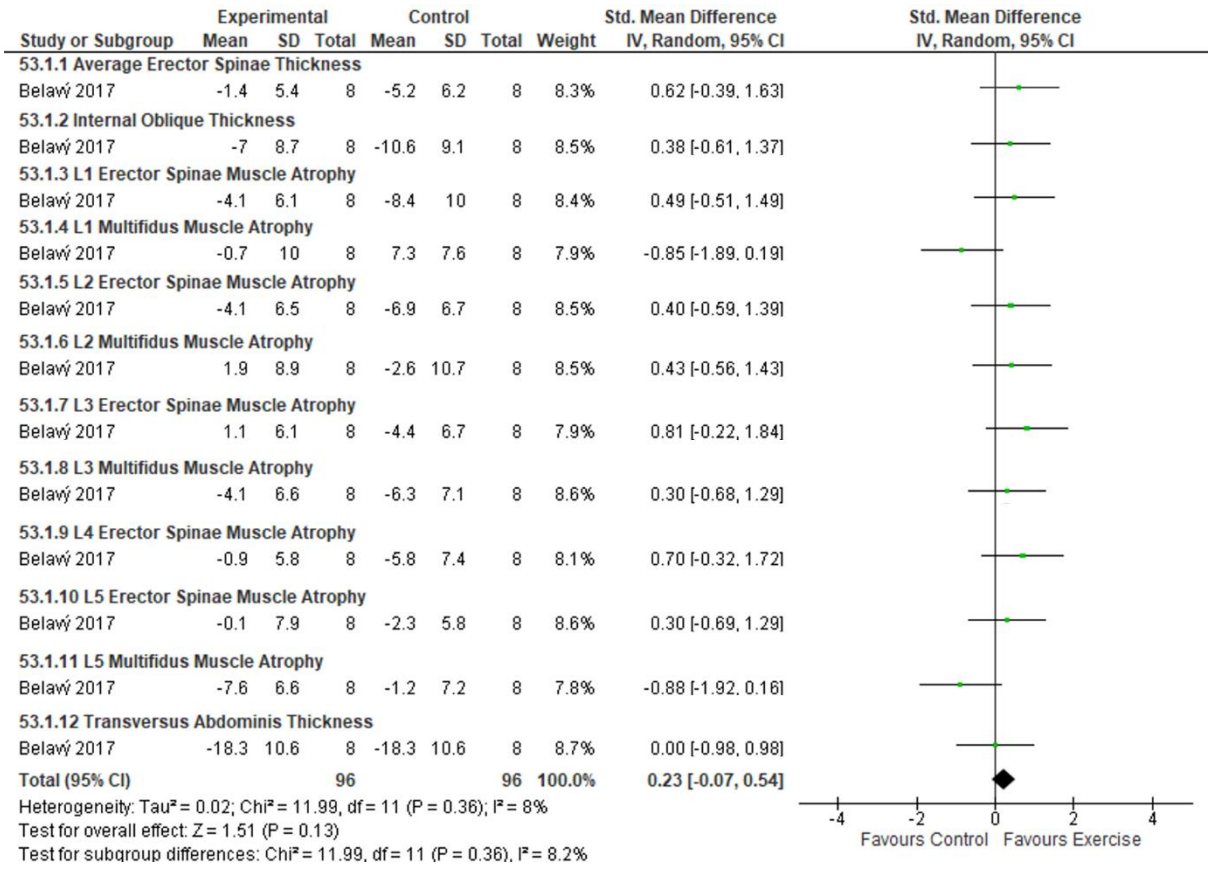

Figure 9.48 Forest plot of muscle thickness effect size differences for the resistive exercise intervention

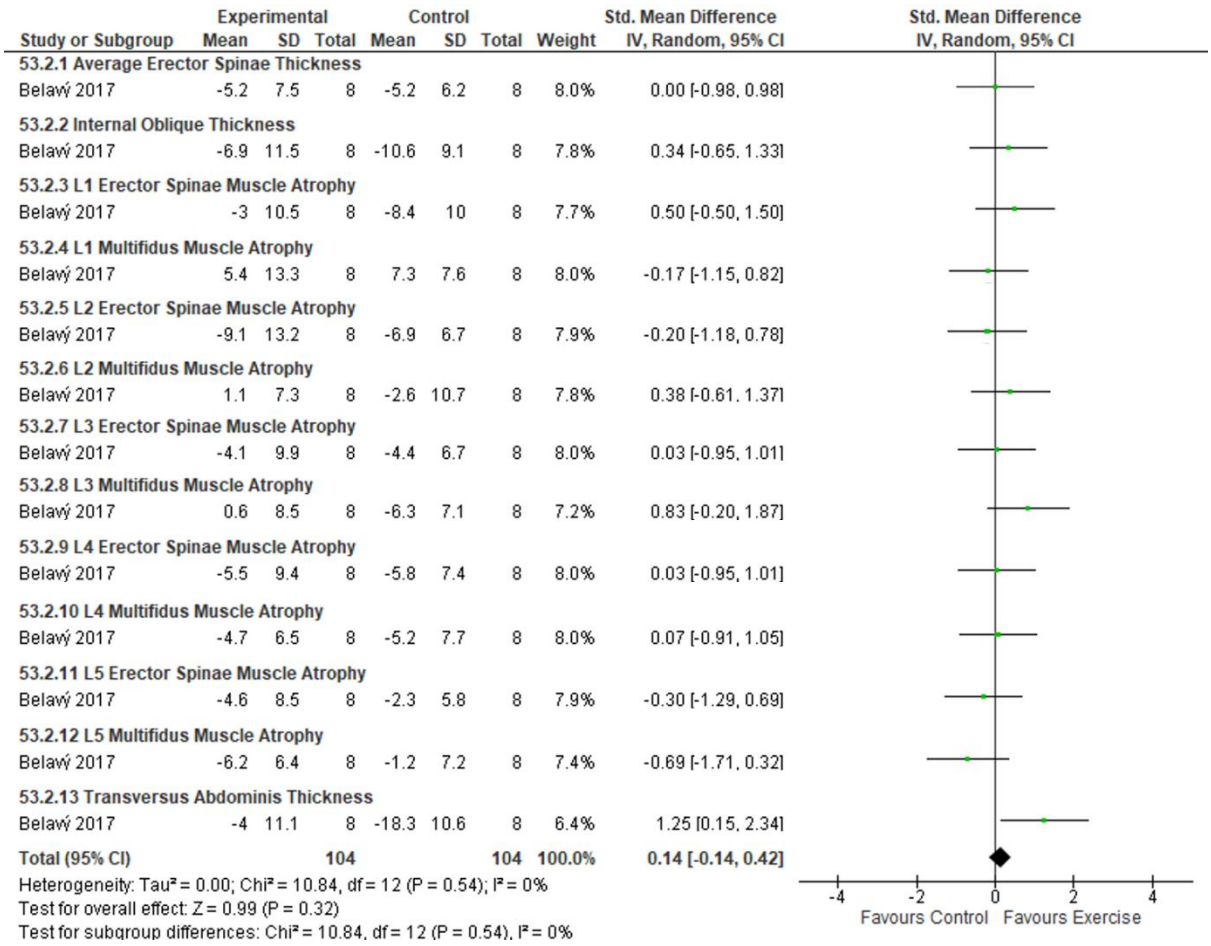

Figure 9.49 Forest plot of muscle thickness effect size differences for the resistive vibration exercise intervention

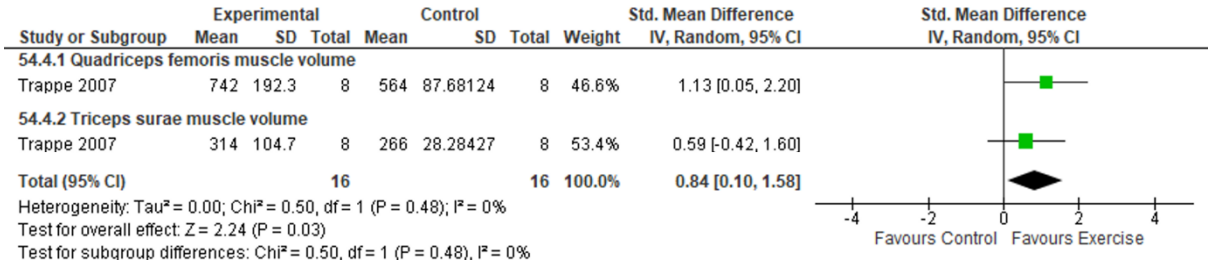

Figure 9.50 Forest plot of muscle volume effect size differences for the gravity-independent inertial ergometer intervention

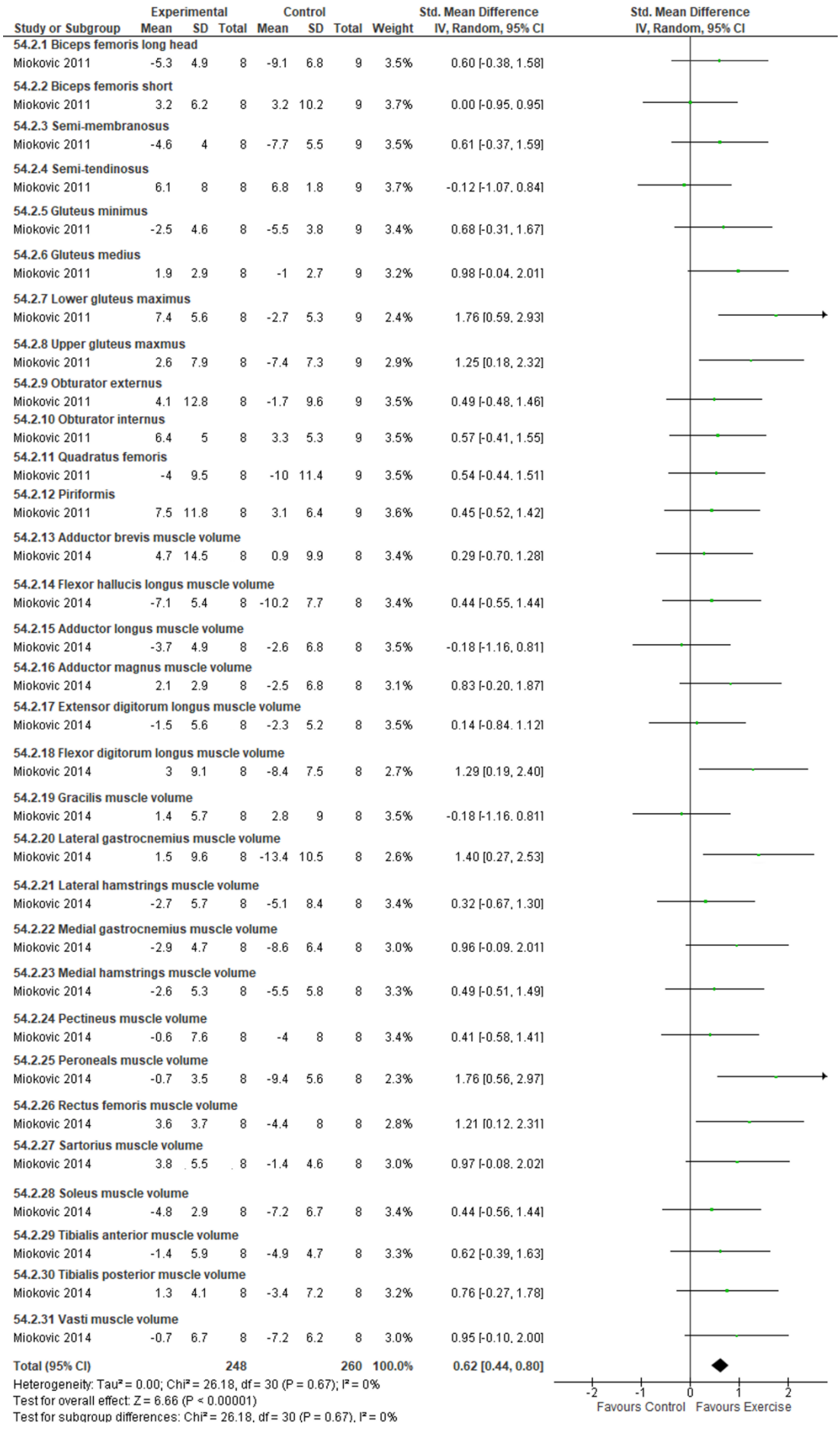
Experimental
Control
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
54.2.1 Biceps femoris long head
Miokovic 2011 -5.3 4.9 8 -9.1 6.8 9 3.5% 0.60 [-0.38, 1.58]
54.2.2 Biceps femoris short
Miokovic 2011 3.2 6.2 8 3.2 10.2 9 3.7% 0.00 [-0.95, 0.95]
54.2.3 Semi-membranosus
Miokovic 2011 -4.6 4 8 -7.7 5.5 9 3.5% 0.61 [-0.37, 1.59]
54.2.4 Semi-tendinosus
Miokovic 2011 6.1 8 8 6.8 1.8 9 3.7% -0.12 [-1.07, 0.84]
54.2.5 Gluteus minimus
Miokovic 2011 -2.5 4.6 8 -5.5 3.8 9 3.4% 0.68 [-0.31, 1.67]
54.2.6 Gluteus medius
Miokovic 2011 1.9 2.9 8 -1 2.7 9 3.2% 0.98 [-0.04, 2.01]
54.2.7 Lower gluteus maximus
Miokovic 2011 7.4 5.6 8 -2.7 5.3 9 2.4% 1.76 [0.59, 2.93]
54.2.8 Upper gluteus maxmus
Miokovic 2011 2.6 7.9 8 -7.4 7.3 9 2.9% 1.25 [0.18, 2.32]
54.2.9 Obturator externus
Miokovic 2011 4.1 12.8 8 -1.7 9.6 9 3.5% 0.49 [-0.48, 1.46]
54.2.10 Obturator internus
Miokovic 2011 6.4 5 8 3.3 5.3 9 3.5% 0.57 [-0.41, 1.55]
54.2.11 Quadratus femoris
Miokovic 2011 -4 9.5 8 -10 11.4 9 3.5% 0.54 [-0.44, 1.51]
54.2.12 Piriformis
Miokovic 2011 7.5 11.8 8 3.1 6.4 9 3.6% 0.45 [-0.52, 1.42]
54.2.13 Adductor brevis muscle volume
Miokovic 2014 4.7 14.5 8 0.9 9.9 8 3.4% 0.29 [-0.70, 1.28]
54.2.14 Flexor hallucis longus muscle volume
Miokovic 2014 -7.1 5.4 8 -10.2 7.7 8 3.4% 0.44 [-0.55, 1.44]
54.2.15 Adductor longus muscle volume
Miokovic 2014 -3.7 4.9 8 -2.6 6.8 8 3.5% -0.18 [-1.16, 0.81]
54.2.16 Adductor magnus muscle volume
Miokovic 2014 2.1 2.9 8 -2.5 6.8 8 3.1% 0.83 [-0.20, 1.87]
54.2.17 Extensor digitorum longus muscle volume
Miokovic 2014 -1.5 5.6 8 -2.3 5.2 8 3.5% 0.14 [-0.84, 1.12]
54.2.18 Flexor digitorum longus muscle volume
Miokovic 2014 3 9.1 8 -8.4 7.5 8 2.7% 1.29 [0.19, 2.40]
54.2.19 Gracilis muscle volume
Miokovic 2014 1.4 5.7 8 2.8 9 8 3.5% -0.18 [-1.16, 0.81]
54.2.20 Lateral gastrocnemius muscle volume
Miokovic 2014 1.5 9.6 8 -13.4 10.5 8 2.6% 1.40 [0.27, 2.53]
54.2.21 Lateral hamstrings muscle volume
Miokovic 2014 -2.7 5.7 8 -5.1 8.4 8 3.4% 0.32 [-0.67, 1.30]
54.2.22 Medial gastrocnemius muscle volume
Miokovic 2014 -2.9 4.7 8 -8.6 6.4 8 3.0% 0.96 [-0.09, 2.01]
54.2.23 Medial hamstrings muscle volume
Miokovic 2014 -2.6 5.3 8 -5.5 5.8 8 3.3% 0.49 [-0.51, 1.49]
54.2.24 Pectineus muscle volume
Miokovic 2014 -0.6 7.6 8 -4 8 8 3.4% 0.41 [-0.58, 1.41]
54.2.25 Peroneals muscle volume
Miokovic 2014 -0.7 3.5 8 -9.4 5.6 8 2.3% 1.76 [0.56, 2.97]
54.2.26 Rectus femoris muscle volume
Miokovic 2014 3.6 3.7 8 -4.4 8 8 2.8% 1.21 [0.12, 2.31]
54.2.27 Sartorius muscle volume
Miokovic 2014 3.8 5.5 8 -1.4 4.6 8 3.0% 0.97 [-0.08, 2.02]
54.2.28 Soleus muscle volume
Miokovic 2014 -4.8 2.9 8 -7.2 6.7 8 3.4% 0.44 [-0.56, 1.44]
54.2.29 Tibialis anterior muscle volume
Miokovic 2014 -1.4 5.9 8 -4.9 4.7 8 3.3% 0.62 [-0.39, 1.63]
54.2.30 Tibialis posterior muscle volume
Miokovic 2014 1.3 4.1 8 -3.4 7.2 8 3.2% 0.76 [-0.27, 1.78]
54.2.31 Vasti muscle volume
Miokovic 2014 -0.7 6.7 8 -7.2 6.2 8 3.0% 0.95 [-0.10, 2.00]
Total (95% CI) 248 260 100.0% 0.62 [0.44, 0.80]
Heterogeneity: Tau² = 0.00; Chi² = 26.18, df = 30 (P = 0.67); I² = 0%
Test for overall effect: Z = 6.66 (P < 0.00001)
Test for subgroup differences: Chi² = 26.18, df = 30 (P = 0.67), I² = 0%
-2 -1 0 1 2
Favours Control Favours Exercise

Figure 9.51 Forest plot of muscle volume effect size differences for the resistive exercise intervention

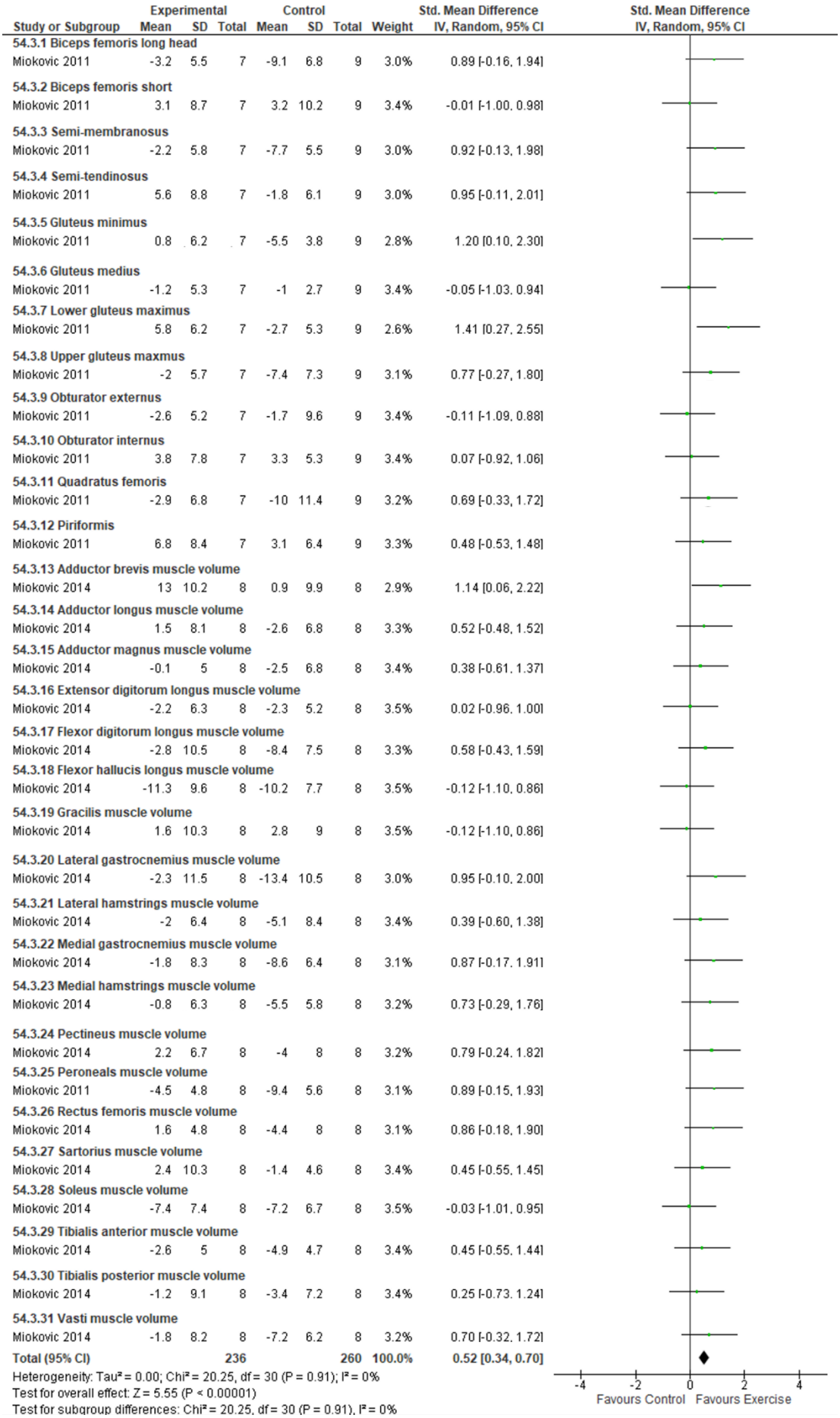
Experimental
Control
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
54.3.1 Biceps femoris long head
Miokovic 2011 -3.2 5.5 7 -9.1 6.8 9 3.0% 0.89 [-0.16, 1.94]
54.3.2 Biceps femoris short
Miokovic 2011 3.1 8.7 7 3.2 10.2 9 3.4% -0.01 [-1.00, 0.98]
54.3.3 Semi-membranosus
Miokovic 2011 -2.2 5.8 7 -7.7 5.5 9 3.0% 0.92 [-0.13, 1.98]
54.3.4 Semi-tendinosus
Miokovic 2011 5.6 8.8 7 -1.8 6.1 9 3.0% 0.95 [-0.11, 2.01]
54.3.5 Gluteus minimus
Miokovic 2011 0.8 6.2 7 -5.5 3.8 9 2.8% 1.20 [0.10, 2.30]
54.3.6 Gluteus medius
Miokovic 2011 -1.2 5.3 7 -1 2.7 9 3.4% -0.05 [-1.03, 0.94]
54.3.7 Lower gluteus maximus
Miokovic 2011 5.8 6.2 7 -2.7 5.3 9 2.6% 1.41 [0.27, 2.55]
54.3.8 Upper gluteus maxmus
Miokovic 2011 -2 5.7 7 -7.4 7.3 9 3.1% 0.77 [-0.27, 1.80]
54.3.9 Obturator externus
Miokovic 2011 -2.6 5.2 7 -1.7 9.6 9 3.4% -0.11 [-1.09, 0.88]
54.3.10 Obturator internus
Miokovic 2011 3.8 7.8 7 3.3 5.3 9 3.4% 0.07 [-0.92, 1.06]
54.3.11 Quadratus femoris
Miokovic 2011 -2.9 6.8 7 -10 11.4 9 3.2% 0.69 [-0.33, 1.72]
54.3.12 Piriformis
Miokovic 2011 6.8 8.4 7 3.1 6.4 9 3.3% 0.48 [-0.53, 1.48]
54.3.13 Adductor brevis muscle volume
Miokovic 2014 13 10.2 8 0.9 9.9 8 2.9% 1.14 [0.06, 2.22]
54.3.14 Adductor longus muscle volume
Miokovic 2014 1.5 8.1 8 -2.6 6.8 8 3.3% 0.52 [-0.48, 1.52]
54.3.15 Adductor magnus muscle volume
Miokovic 2014 -0.1 5 8 -2.5 6.8 8 3.4% 0.38 [-0.61, 1.37]
54.3.16 Extensor digitorum longus muscle volume
Miokovic 2014 -2.2 6.3 8 -2.3 5.2 8 3.5% 0.02 [-0.96, 1.00]
54.3.17 Flexor digitorum longus muscle volume
Miokovic 2014 -2.8 10.5 8 -8.4 7.5 8 3.3% 0.58 [-0.43, 1.59]
54.3.18 Flexor hallucis longus muscle volume
Miokovic 2014 -11.3 9.6 8 -10.2 7.7 8 3.5% -0.12 [-1.10, 0.86]
54.3.19 Gracilis muscle volume
Miokovic 2014 1.6 10.3 8 2.8 9 8 3.5% -0.12 [-1.10, 0.86]
54.3.20 Lateral gastrocnemius muscle volume
Miokovic 2014 -2.3 11.5 8 -13.4 10.5 8 3.0% 0.95 [-0.10, 2.00]
54.3.21 Lateral hamstrings muscle volume
Miokovic 2014 -2 6.4 8 -5.1 8.4 8 3.4% 0.39 [-0.60, 1.38]
54.3.22 Medial gastrocnemius muscle volume
Miokovic 2014 -1.8 8.3 8 -8.6 6.4 8 3.1% 0.87 [-0.17, 1.91]
54.3.23 Medial hamstrings muscle volume
Miokovic 2014 -0.8 6.3 8 -5.5 5.8 8 3.2% 0.73 [-0.29, 1.76]
54.3.24 Pectineus muscle volume
Miokovic 2014 2.2 6.7 8 -4 8 8 3.2% 0.79 [-0.24, 1.82]
54.3.25 Peroneals muscle volume
Miokovic 2011 -4.5 4.8 8 -9.4 5.6 8 3.1% 0.89 [-0.15, 1.93]
54.3.26 Rectus femoris muscle volume
Miokovic 2014 1.6 4.8 8 -4.4 8 8 3.1% 0.86 [-0.18, 1.90]
54.3.27 Sartorius muscle volume
Miokovic 2014 2.4 10.3 8 -1.4 4.6 8 3.4% 0.45 [-0.55, 1.45]
54.3.28 Soleus muscle volume
Miokovic 2014 -7.4 7.4 8 -7.2 6.7 8 3.5% -0.03 [-1.01, 0.95]
54.3.29 Tibialis anterior muscle volume
Miokovic 2014 -2.6 5 8 -4.9 4.7 8 3.4% 0.45 [-0.55, 1.44]
54.3.30 Tibialis posterior muscle volume
Miokovic 2014 -1.2 9.1 8 -3.4 7.2 8 3.4% 0.25 [-0.73, 1.24]
54.3.31 Vasti muscle volume
Miokovic 2014 -1.8 8.2 8 -7.2 6.2 8 3.2% 0.70 [-0.32, 1.72]
Total (95% CI) 236 260 100.0% 0.52 [0.34, 0.70]
Heterogeneity: Tau² = 0.00; Chi² = 20.25, df = 30 (P = 0.91); I² = 0%
Test for overall effect: Z = 5.55 (P < 0.00001)
Test for subgroup differences: Chi² = 20.25, df = 30 (P = 0.91), I² = 0%
-4
-2
0
2
4
Favours Control
Favours Exercise

Figure 9.52 Forest plot of muscle volume effect size differences for the resistive vibration exercise intervention

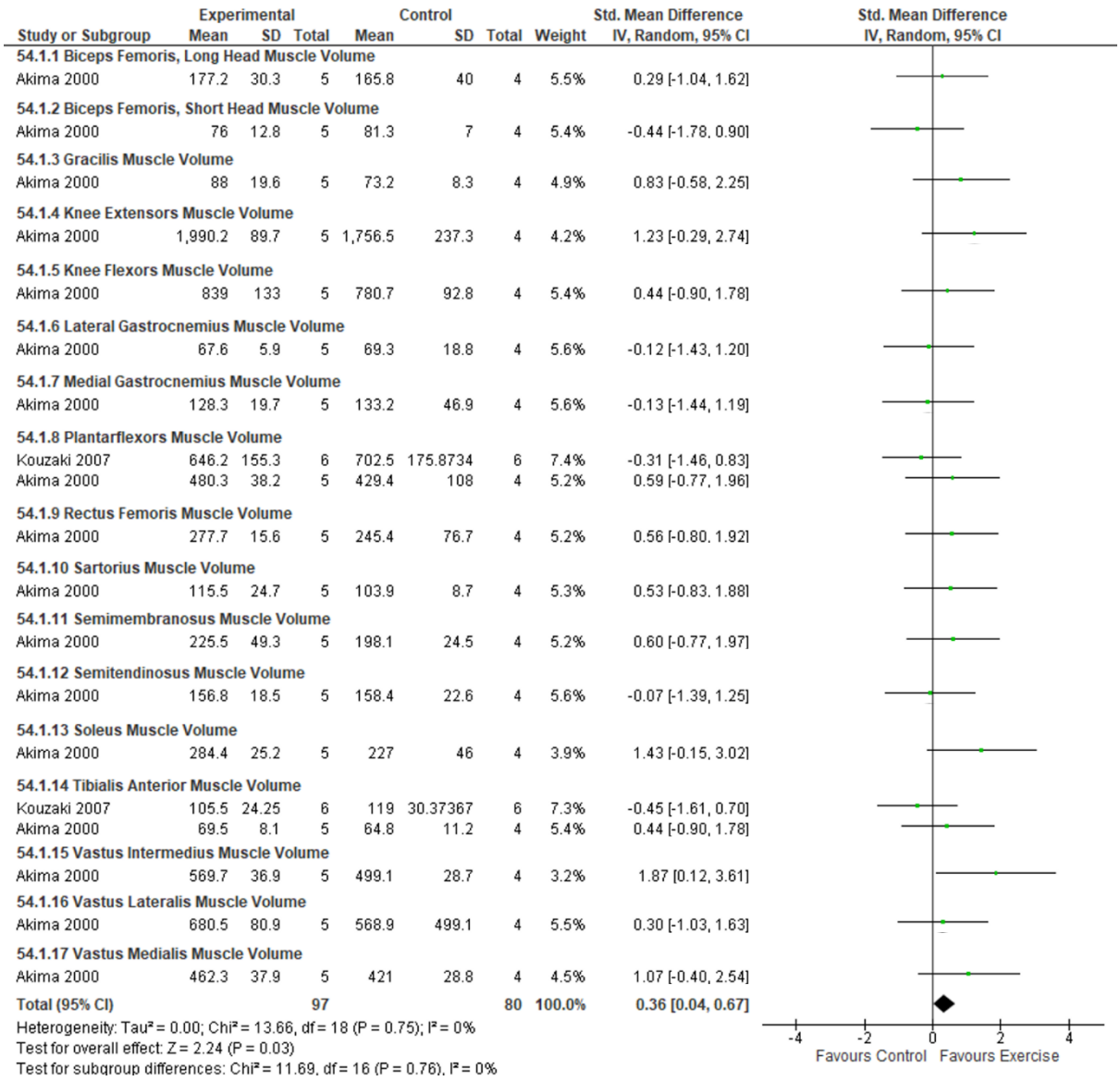

Figure 9.53 Forest plot of muscle volume effect size differences for the horizontal leg press intervention

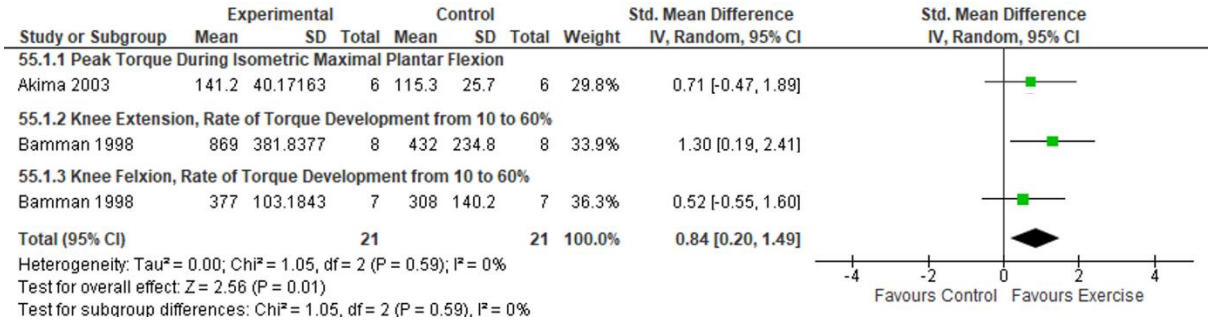

Figure 9.54 Forest plot of muscle torque effect size differences for the horizontal leg press intervention

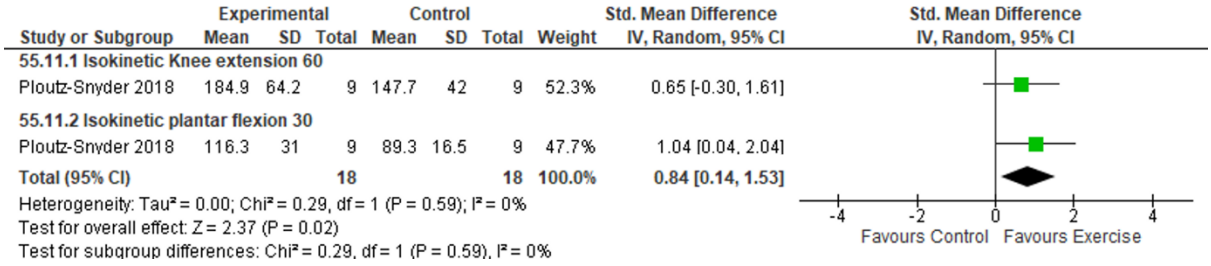

Figure 9.55 Forest plot of muscle torque effect size differences for the zero-gravity treadmill + cycle ergometer intervention

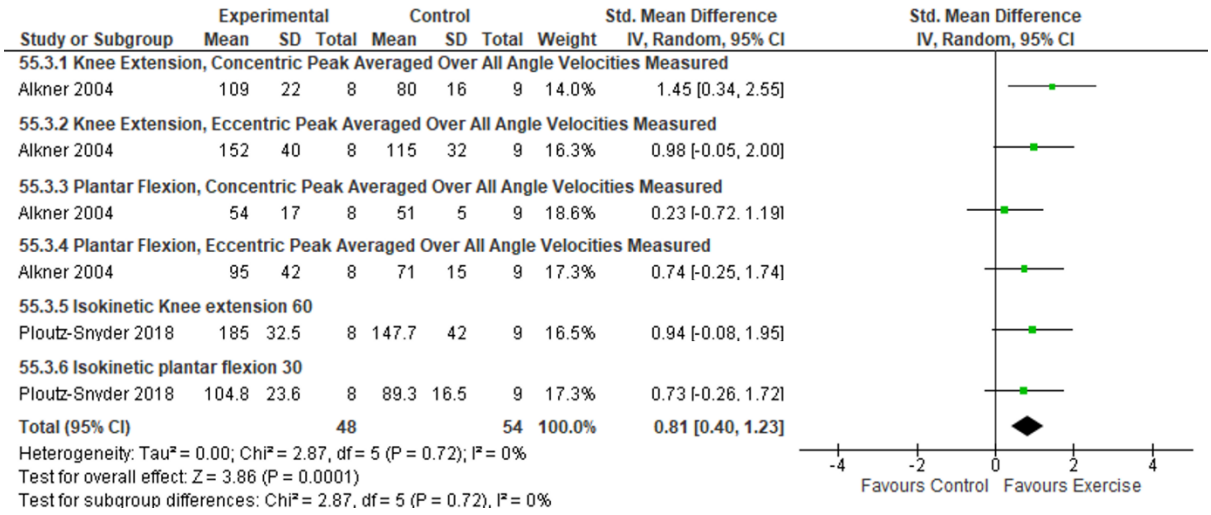

Figure 9.56 Forest plot of muscle torque effect size differences for the flywheel intervention

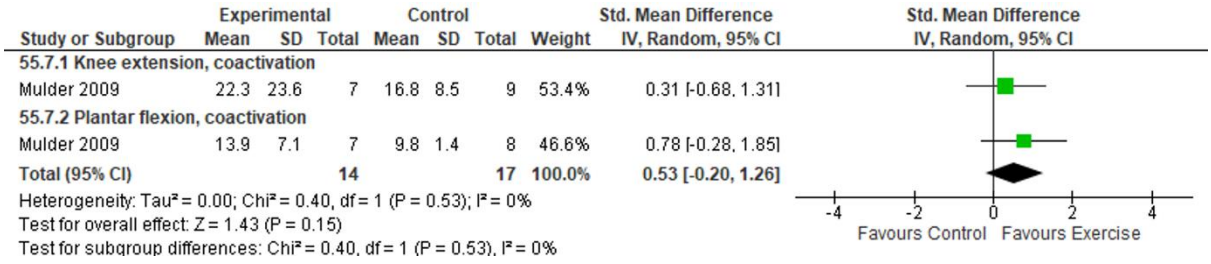

Figure 9.57 Forest plot of muscle torque effect size differences for the resistive vibration exercise intervention

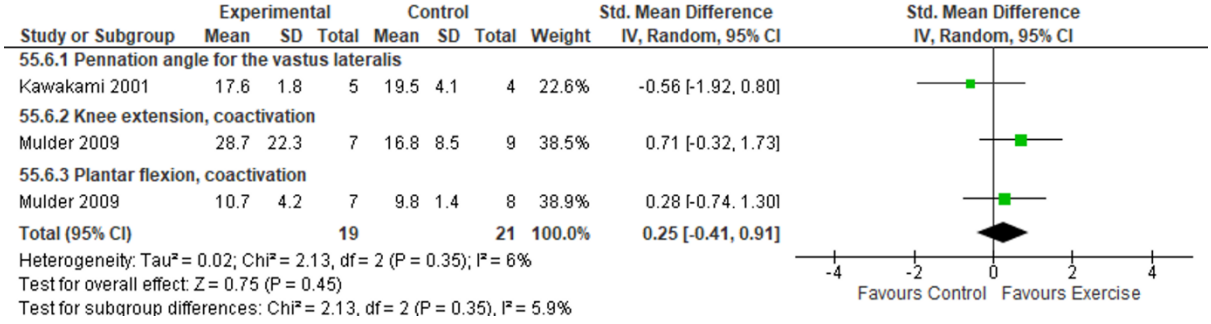

Figure 9.58 Forest plot of muscle torque effect size differences for the resistive exercise intervention

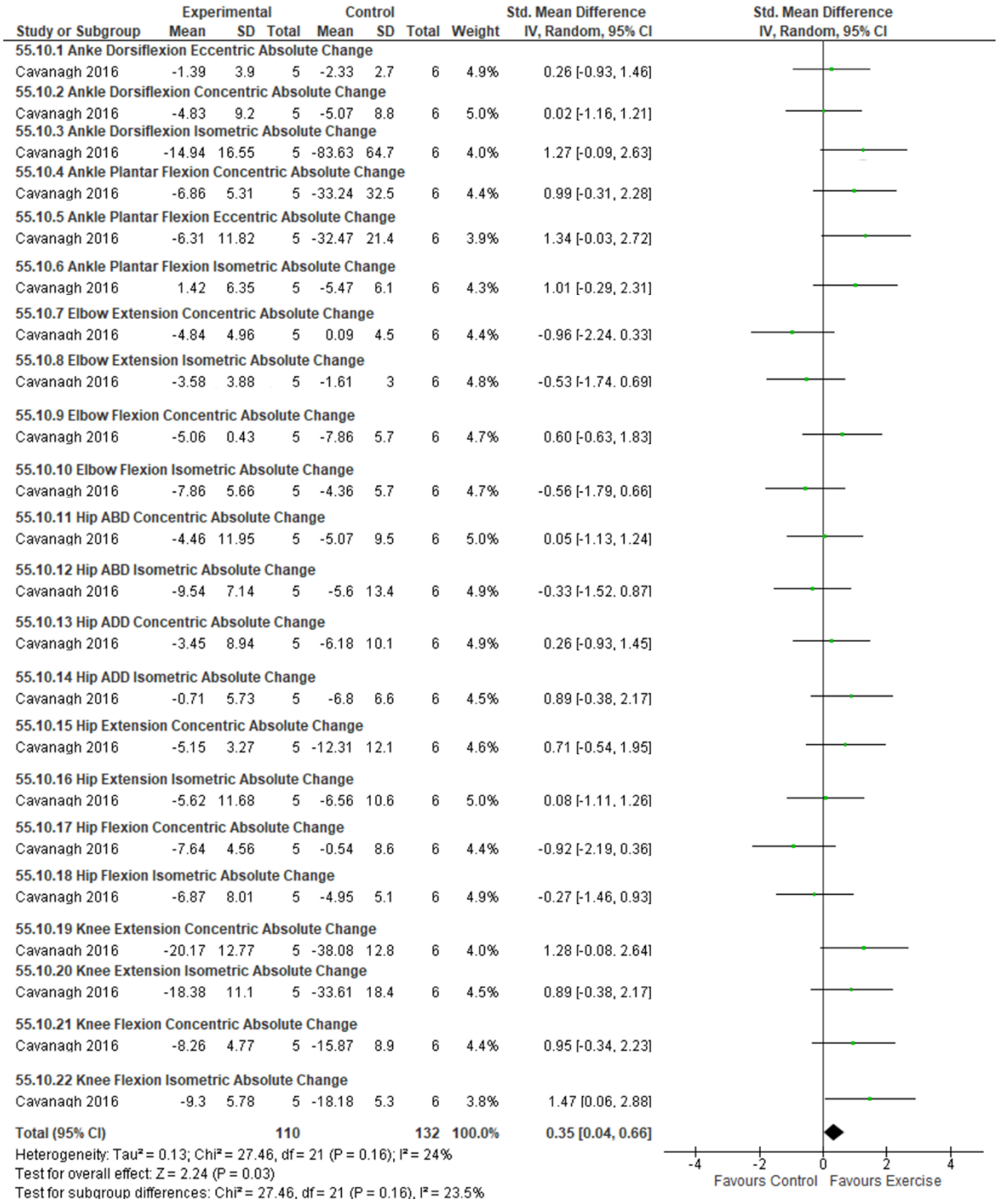

Figure 9.59 Forest plot of muscle torque effect size differences for the zero-gravity treadmill intervention

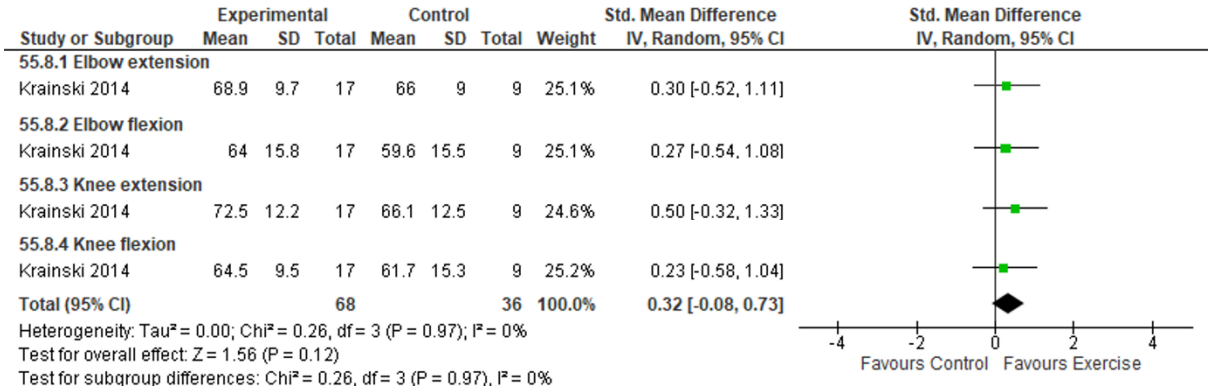

Figure 9.60 Forest plot of muscle torque effect size differences for the rowing ergometer + resistive exercise intervention

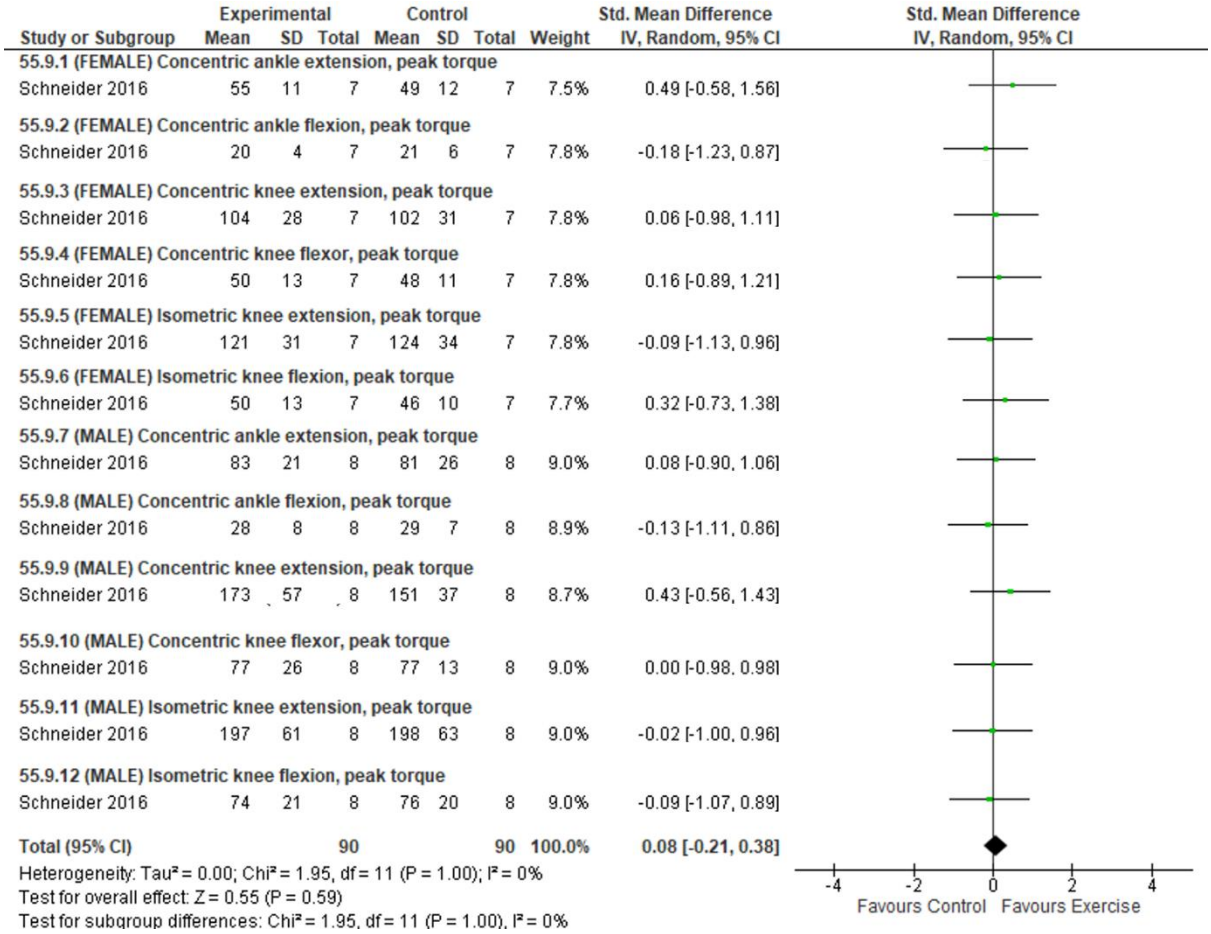

Figure 9.61 Forest plot of muscle torque effect size differences for the treadmill LBNP intervention

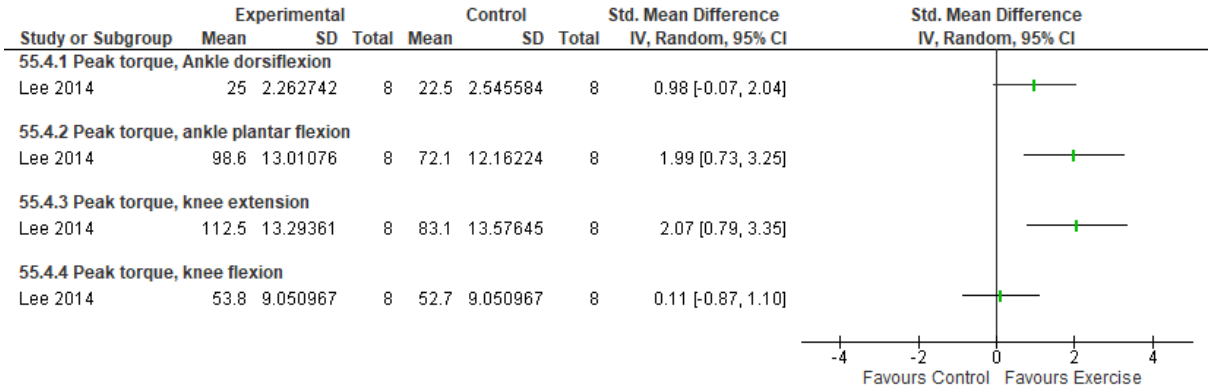

Figure 9.62 Forest plot of muscle torque effect size differences for the flywheel + treadmill LBNP intervention

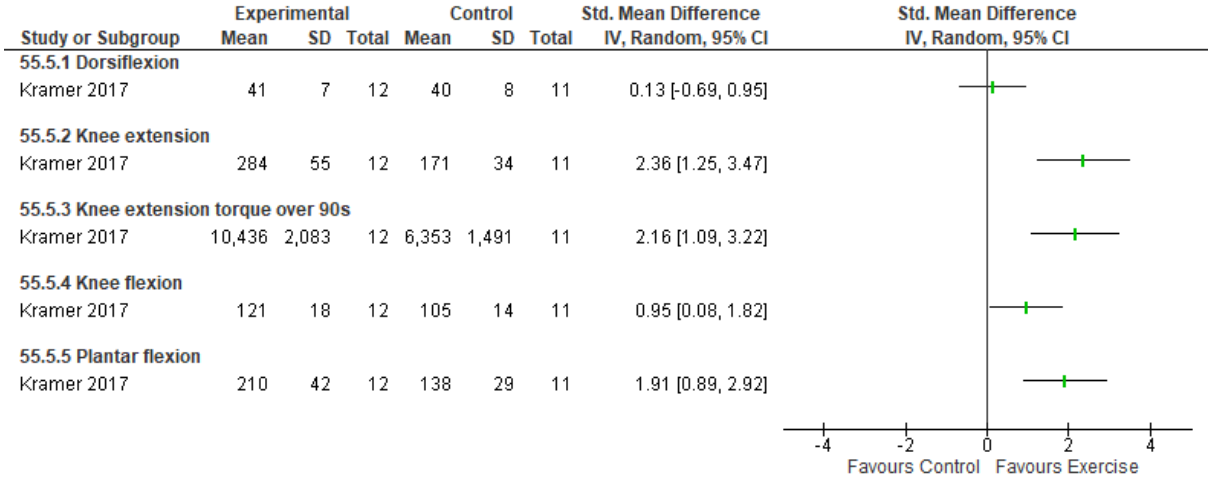

Figure 9.63 Forest plot of muscle torque effect size differences for the horizontal sledge jump system intervention

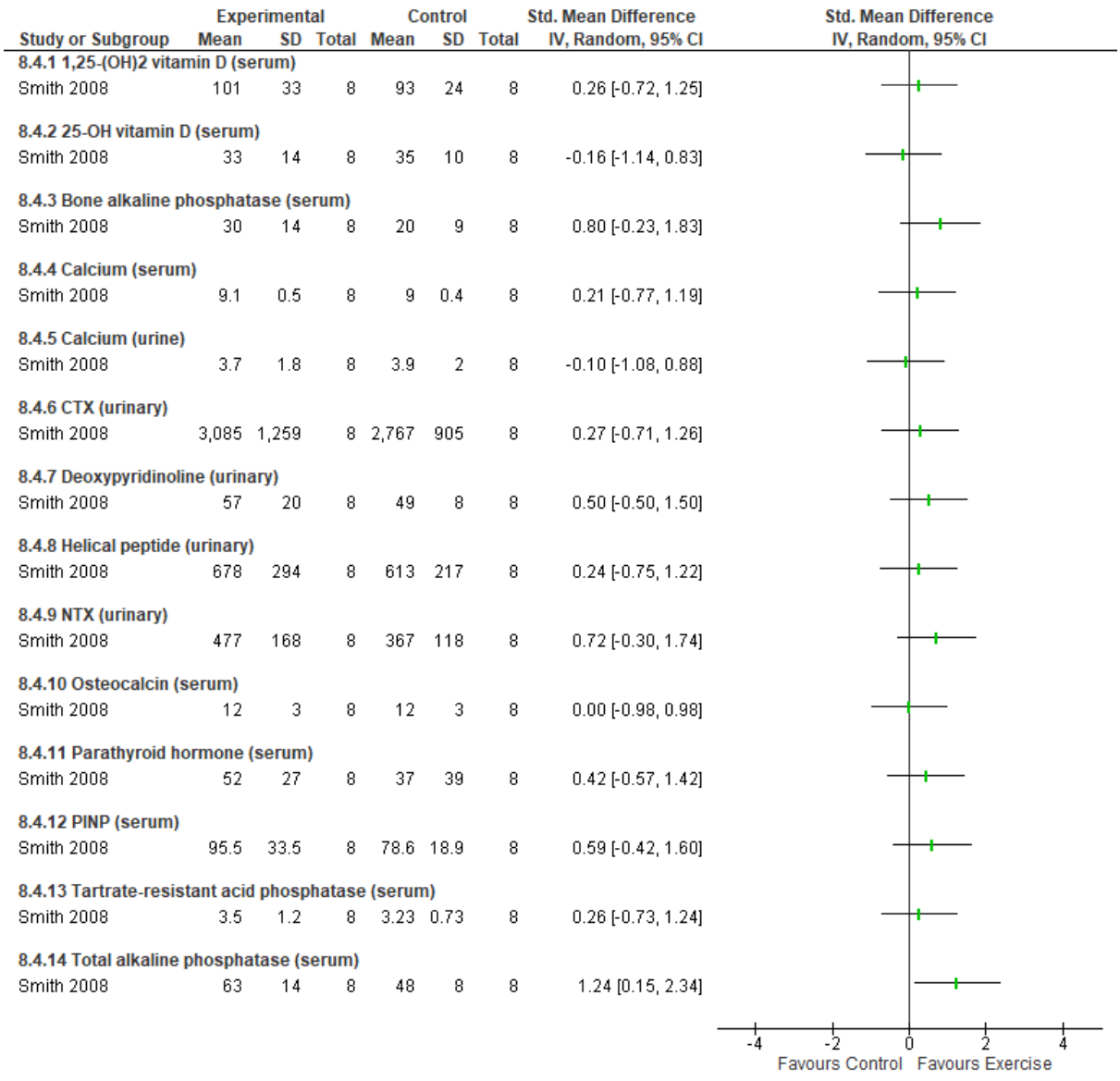

Figure 9.64 Forest plot of skeletal biomarker effect size differences for the flywheel + treadmill LBNP intervention

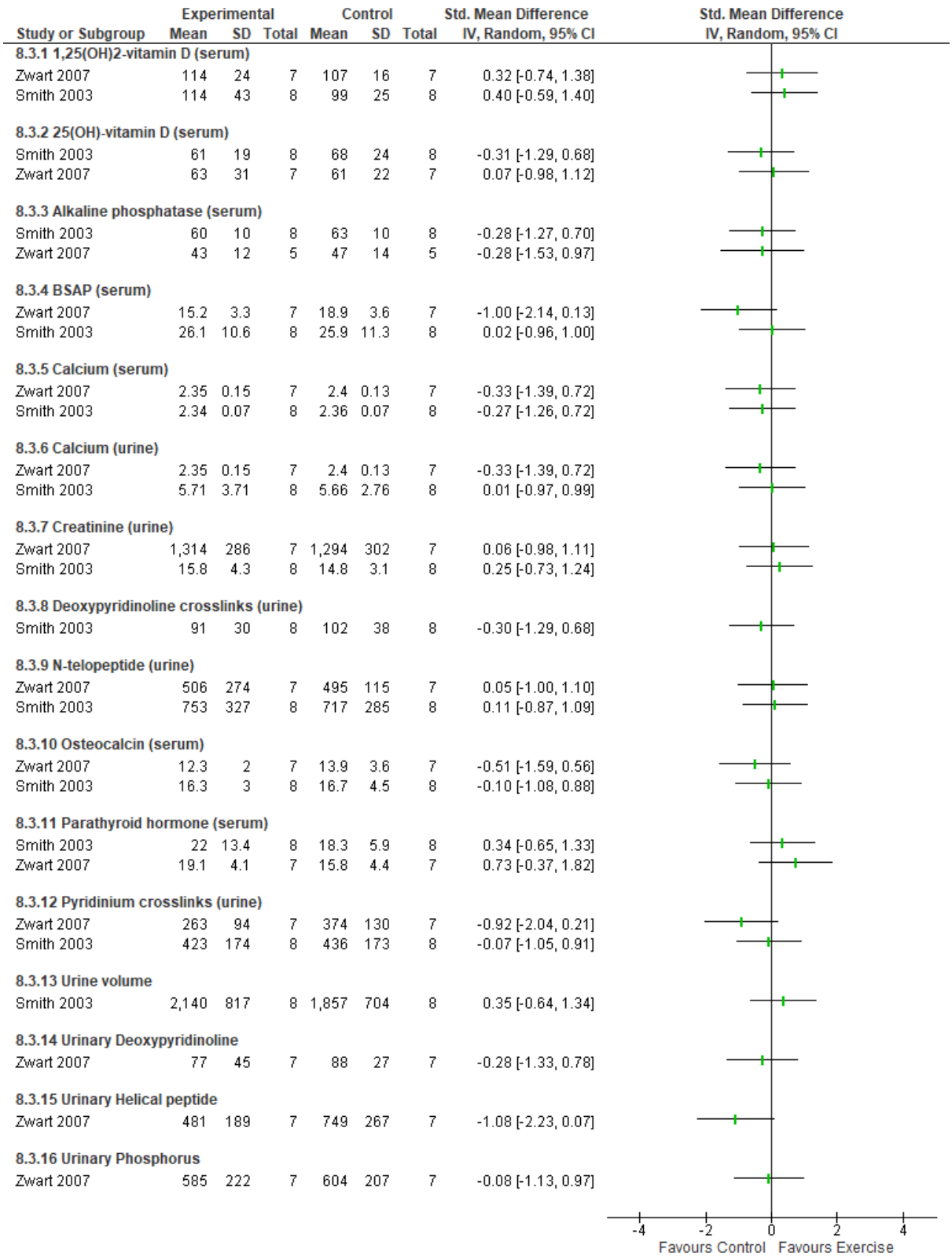

Figure 9.65 Forest plot of skeletal biomarker effect size differences for the treadmill LBNP intervention

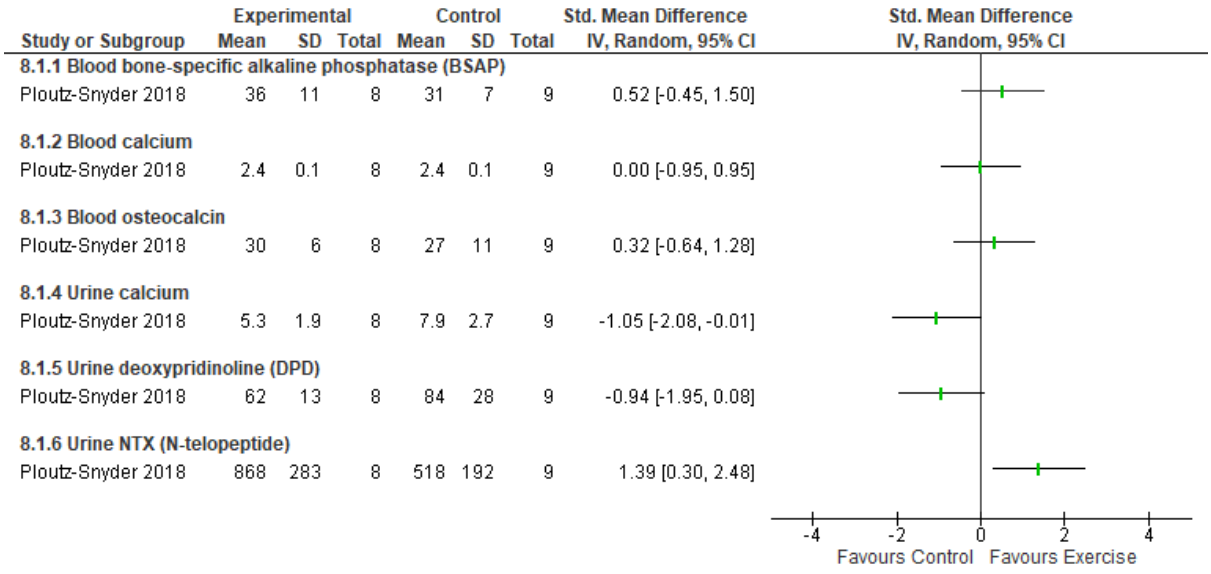

Figure 9.66 Forest plot of skeletal biomarker effect size differences for the flywheel intervention

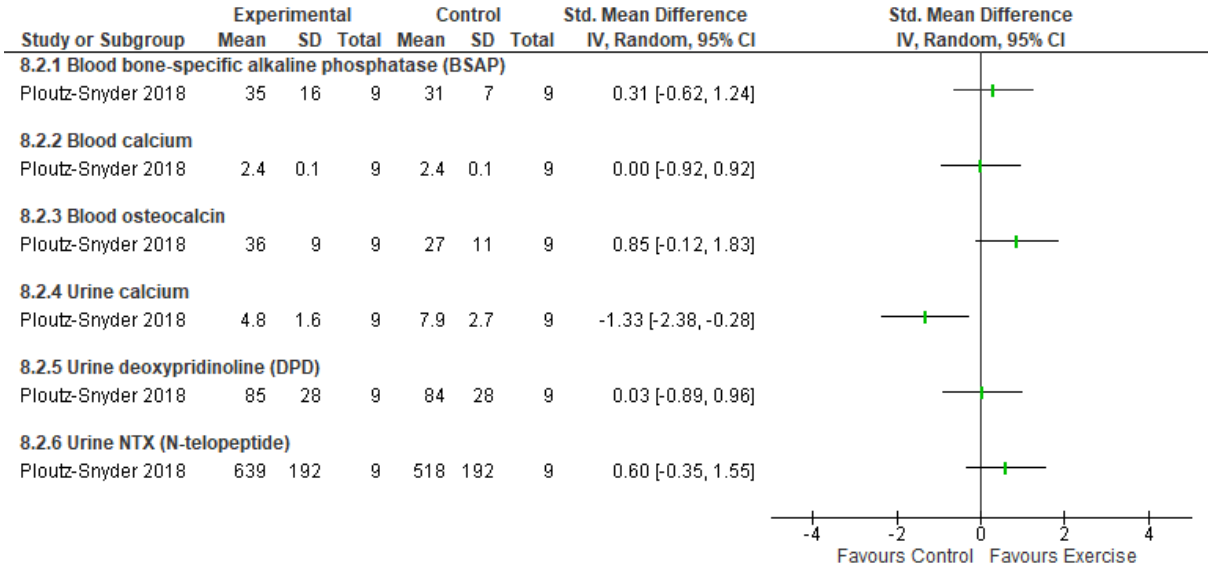

Figure 9.67 Forest plot of skeletal biomarker effect size differences for the zero-gravity treadmill + cycle ergometer intervention

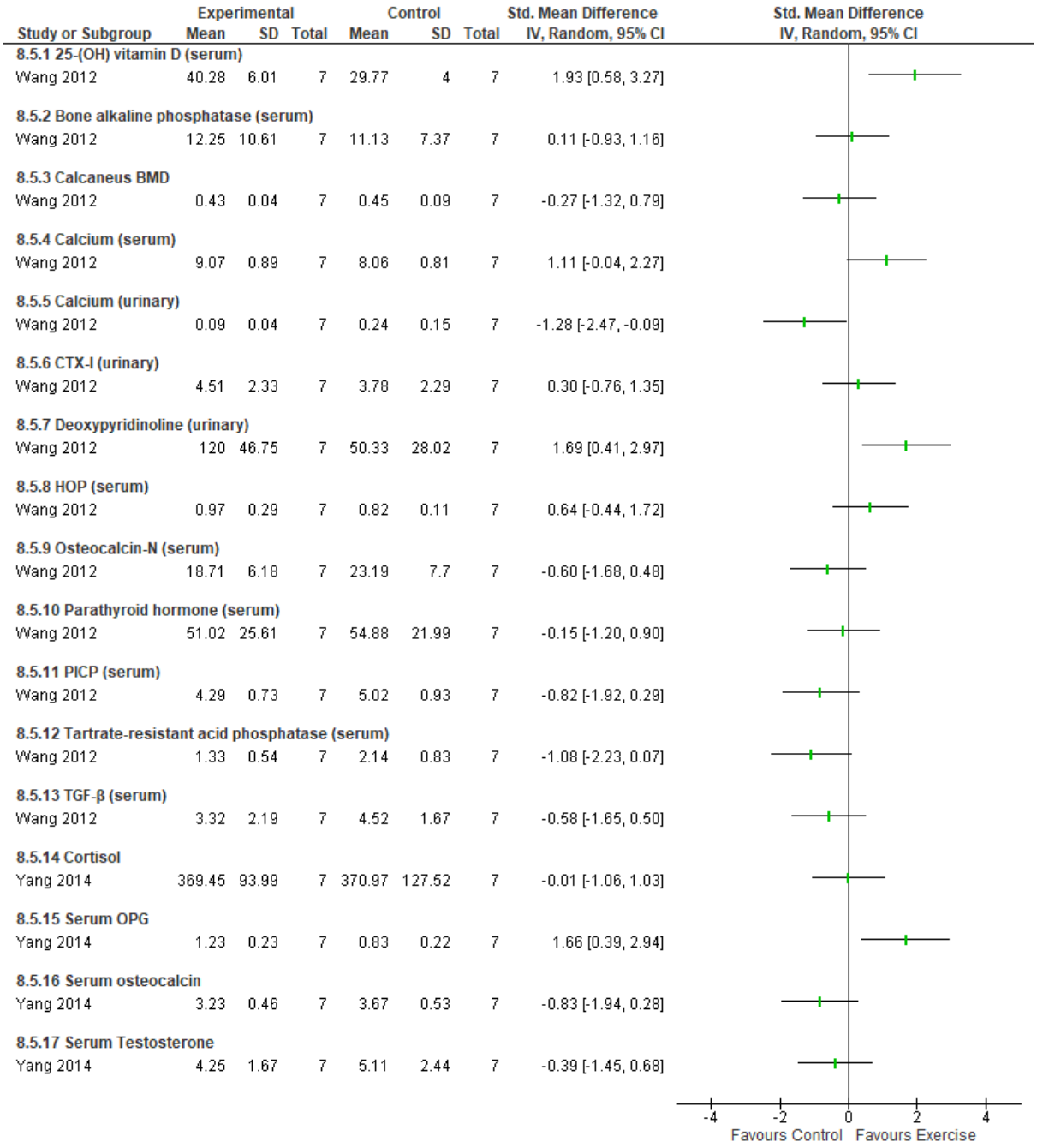

Figure 9.68 Forest plot of skeletal biomarker effect size differences for the resistive vibration exercise intervention

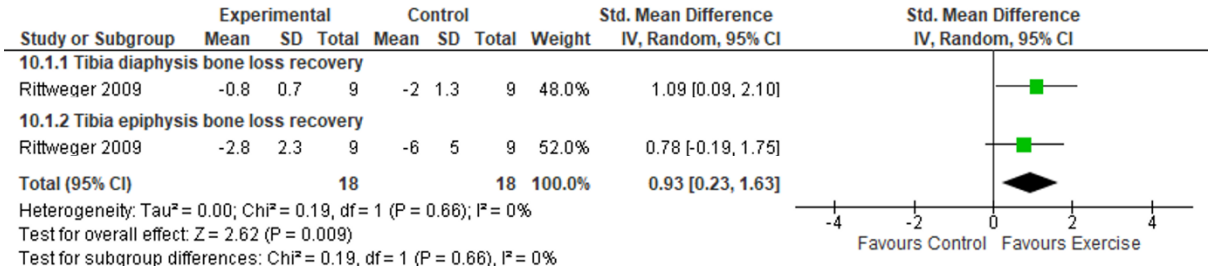

Figure 9.69 Forest plot of bone loss recovery effect size differences for the flywheel intervention

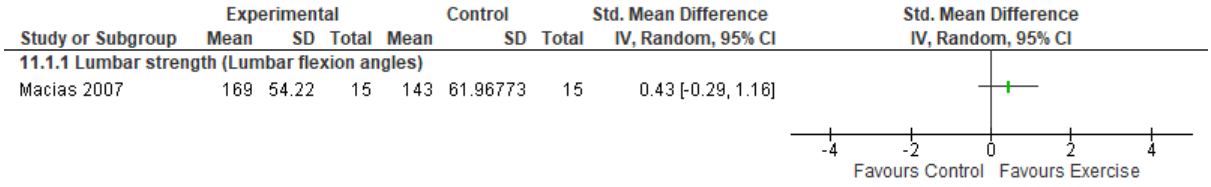

Figure 9.70 Forest plot of bone strength effect size differences for the treadmill LBNP intervention

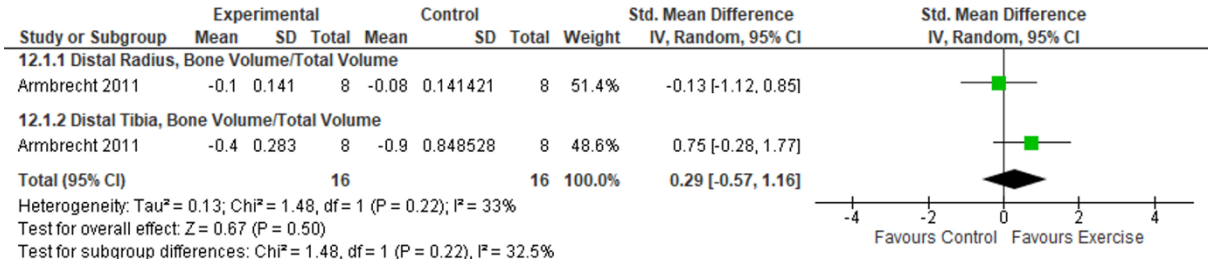

Figure 9.71 Forest plot of bone volume effect size differences for the flywheel + treadmill LBNP intervention

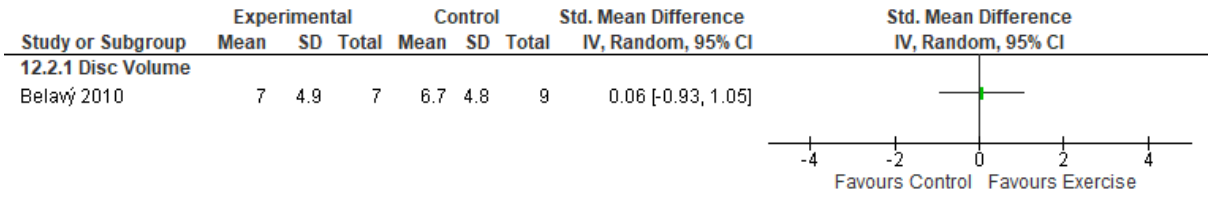

Figure 9.72 Forest plot of bone volume effect size differences for the resistive exercise intervention

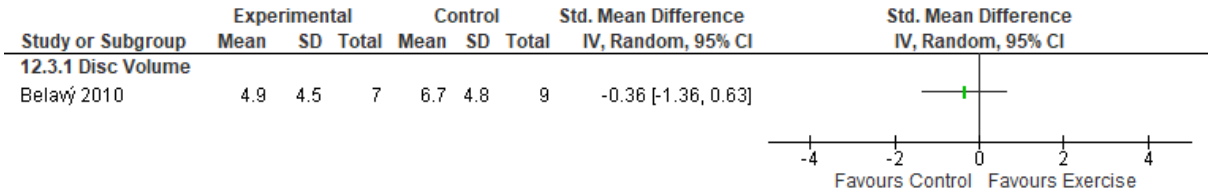

Figure 9.73 Forest plot of bone volume effect size differences for the resistive vibration exercise intervention

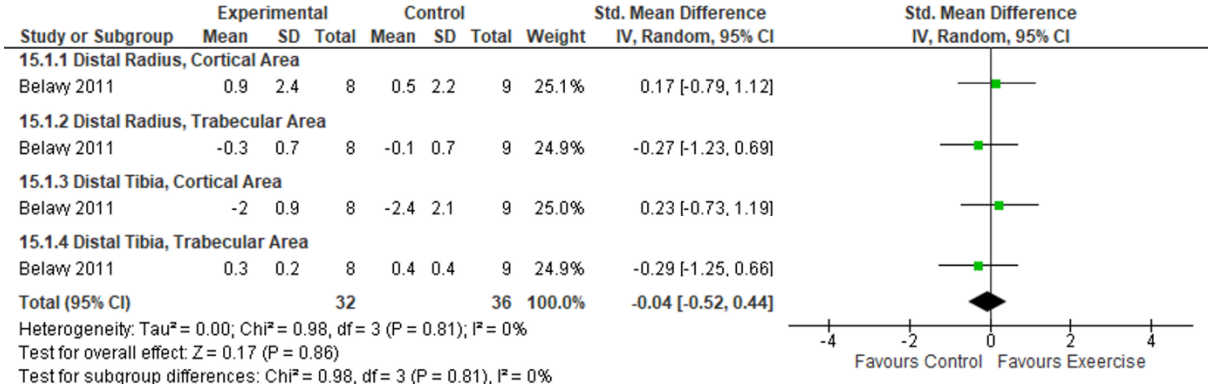

Figure 9.74 Forest plot of skeletal CSA effect size differences for the resistive exercise intervention

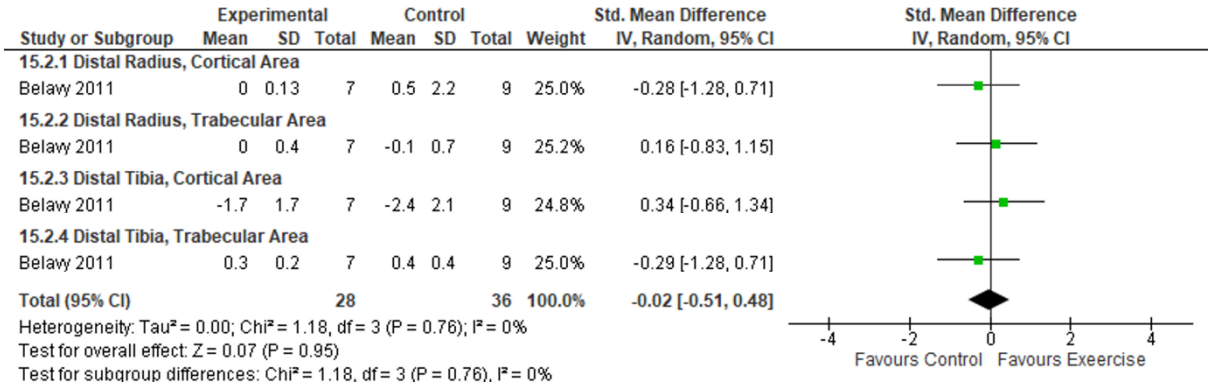

Figure 9.75 Forest plot of skeletal CSA effect size differences for the resistive vibration exercise intervention

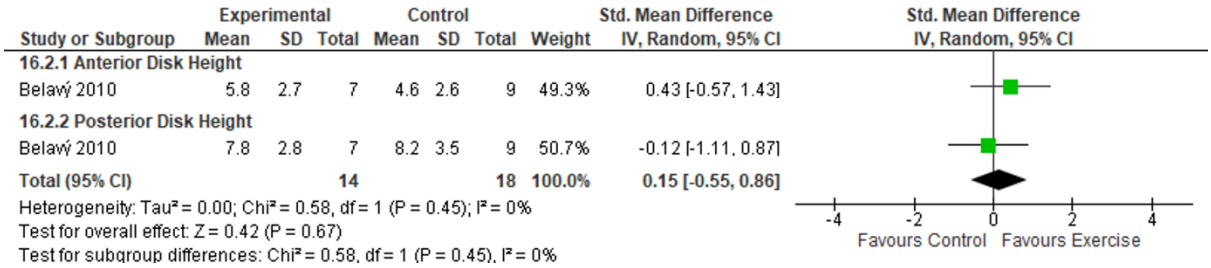

Figure 9.76 Forest plot of IVD height effect size differences for the resistive vibration exercise intervention

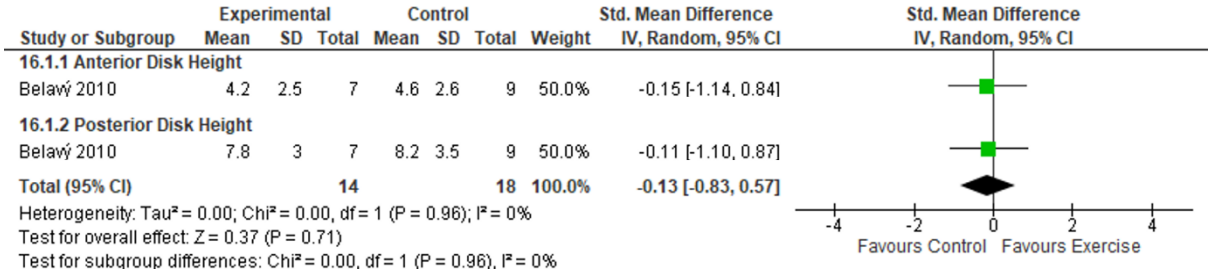

Figure 9.77 Forest plot of IVD height effect size differences for the resistive exercise intervention

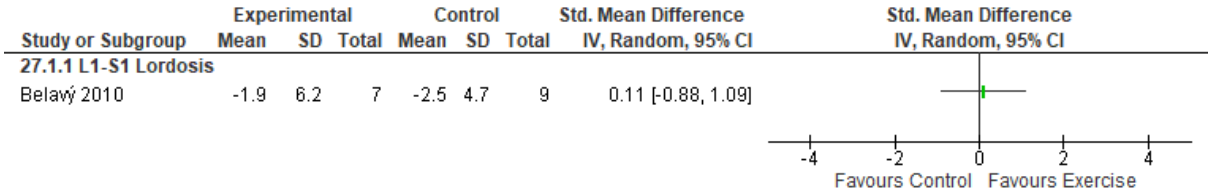

Figure 9.78 Forest plot of lumbar lordosis effect size differences for the resistive exercise intervention

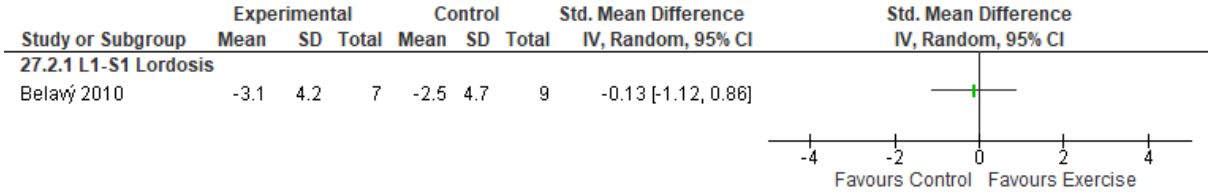

Figure 9.79 Forest plot of lumbar lordosis effect size differences for the resistive vibration exercise intervention

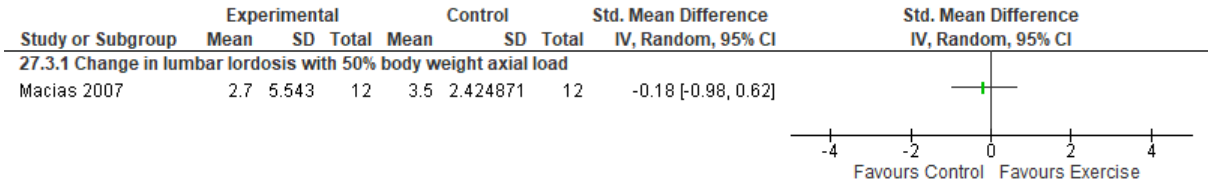

Figure 9.80 Forest plot of lumbar lordosis effect size differences for the treadmill LBNP intervention

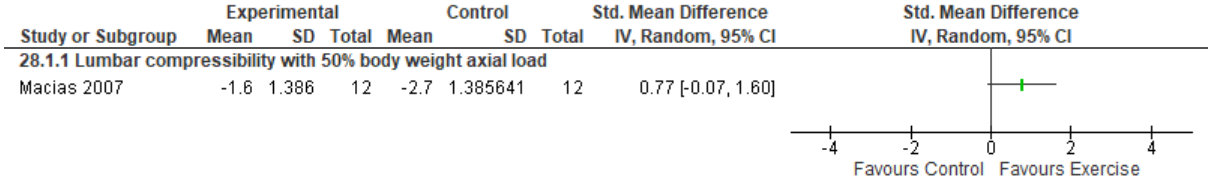

Figure 9.81 Forest plot of lumbar compressibility with 50% body weight axial load effect size differences for the treadmill LBNP intervention

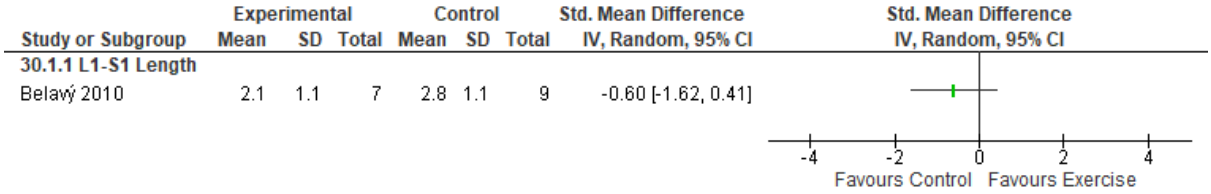

Figure 9.82 Forest plot of spinal length effect size differences for the resistive exercise intervention

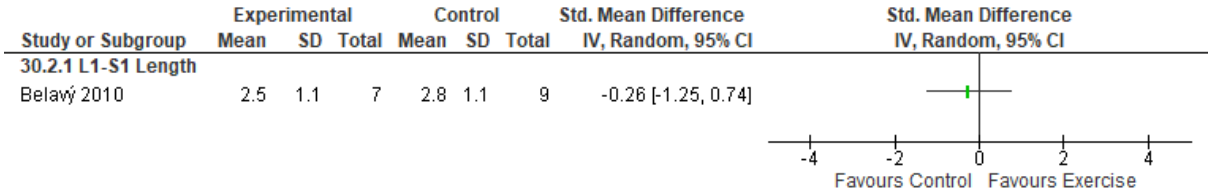

Figure 9.83 Forest plot of spinal length effect size differences for the resistive vibration exercise intervention

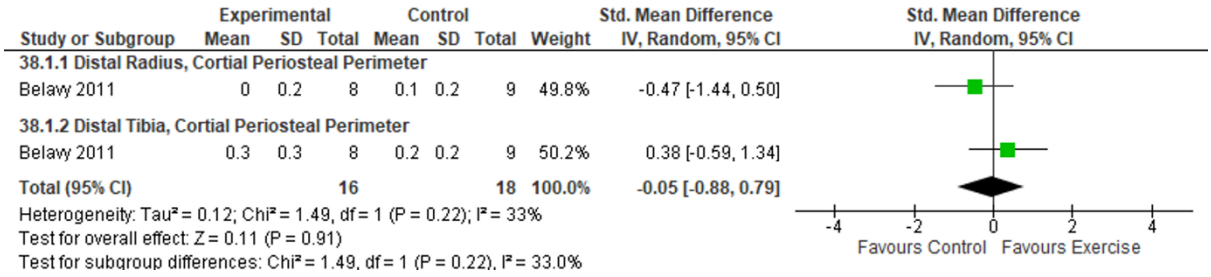

Figure 9.84 Forest plot of periosteal perimeter effect size differences for the resistive exercise intervention

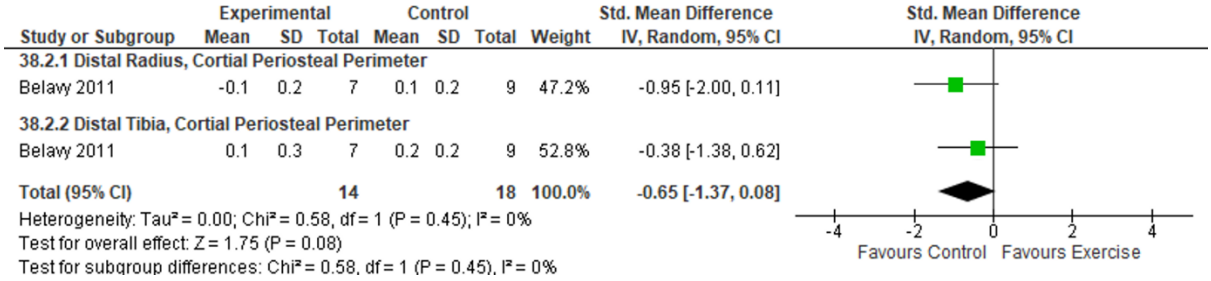

Figure 9.85 Forest plot of periosteal perimeter effect size differences for the resistive vibration exercise intervention

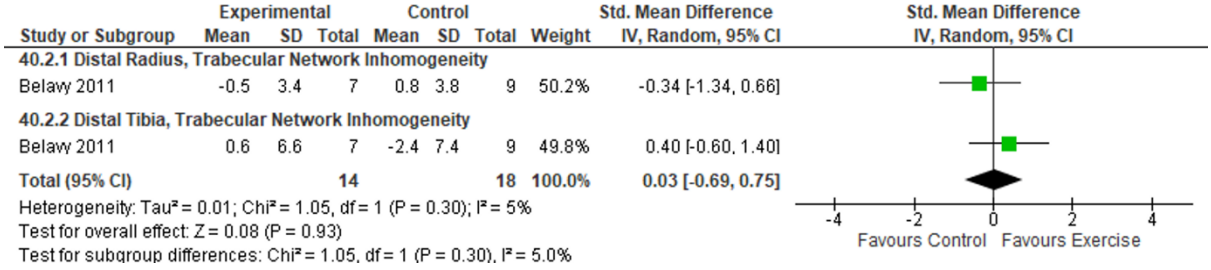

Figure 9.86 Forest plot of trabecular network inhomogeneity effect size differences for the resistive vibration exercise intervention

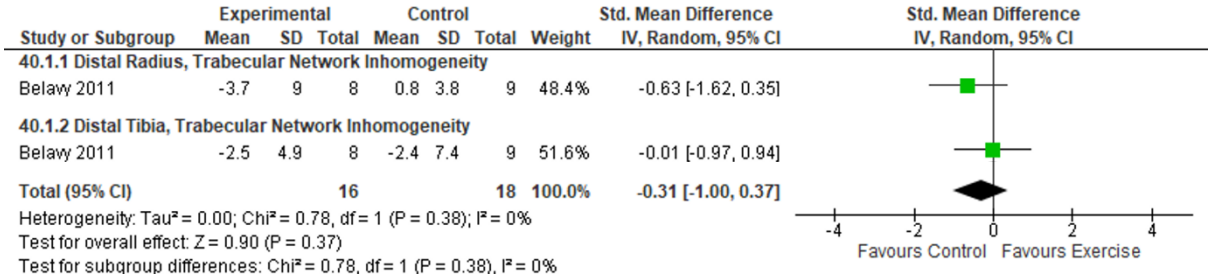

Figure 9.87 Forest plot of trabecular network inhomogeneity effect size differences for the resistive exercise intervention

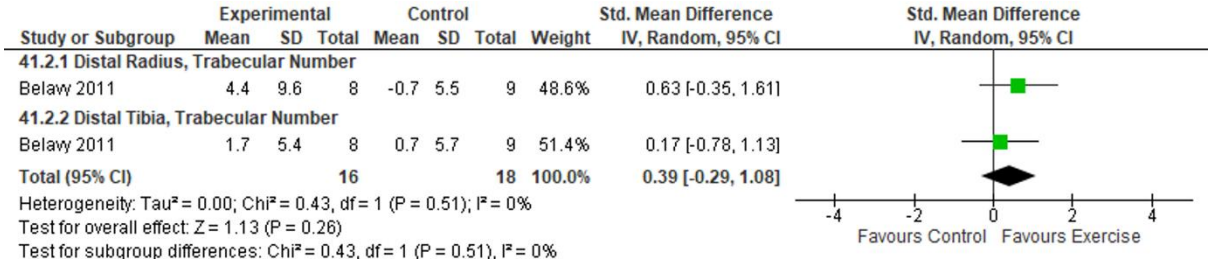

Figure 9.88 Forest plot of trabecular number effect size differences for the resistive exercise intervention

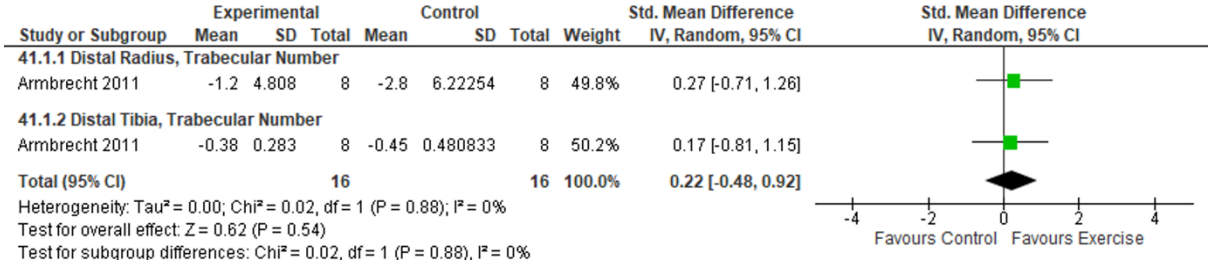

Figure 9.89 Forest plot of trabecular number effect size differences for the flywheel + treadmill LBNP intervention

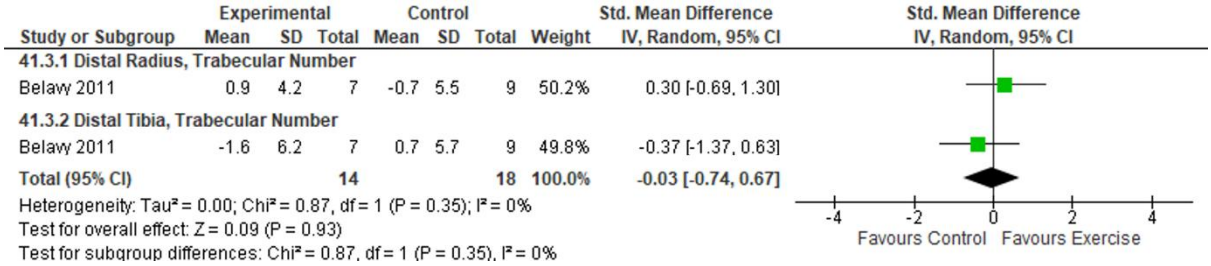

Figure 9.90 Forest plot of trabecular number effect size differences for the resistive vibration exercise intervention

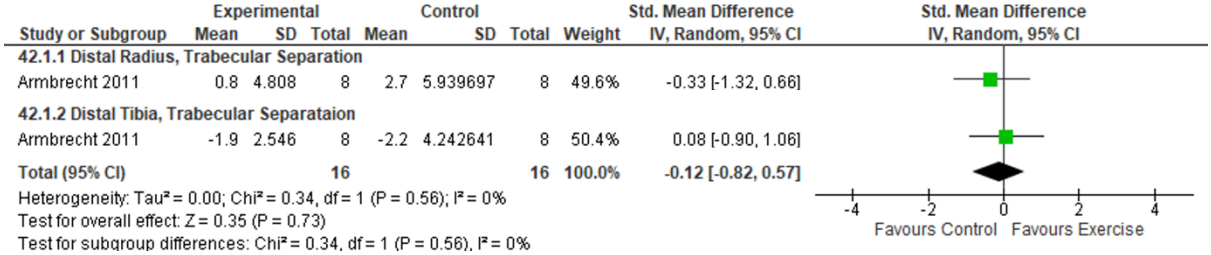

Figure 9.91 Forest plot of trabecular separation effect size differences for the flywheel + treadmill LBNP intervention

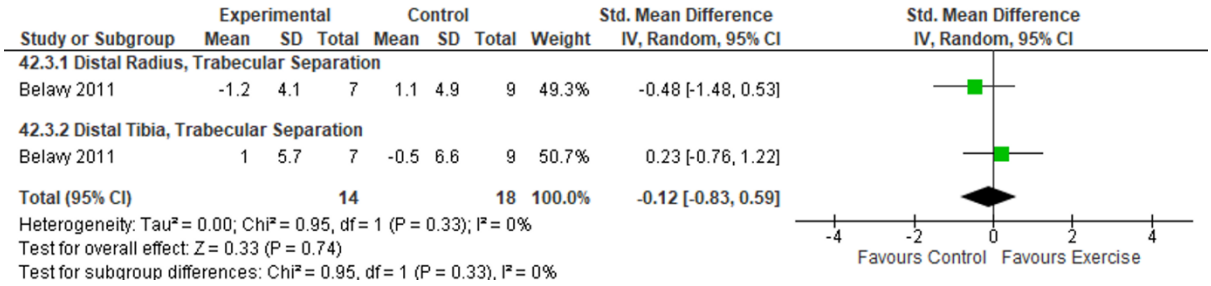

Figure 9.92 Forest plot of trabecular separation effect size differences for the resistive vibration exercise intervention

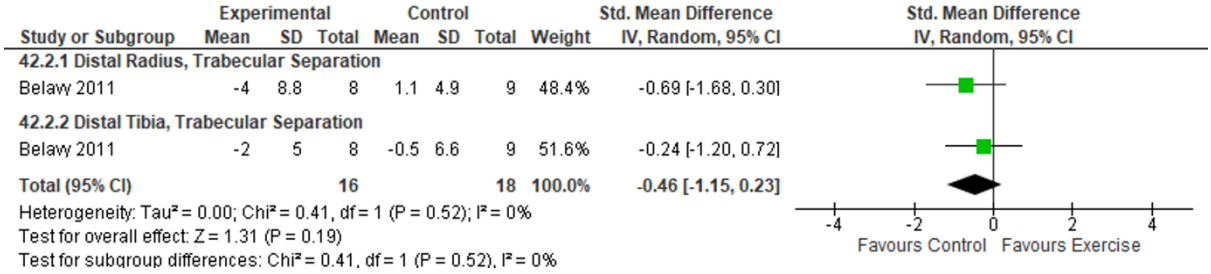

Figure 9.93 Forest plot of trabecular separation effect size differences for the resistive exercise intervention

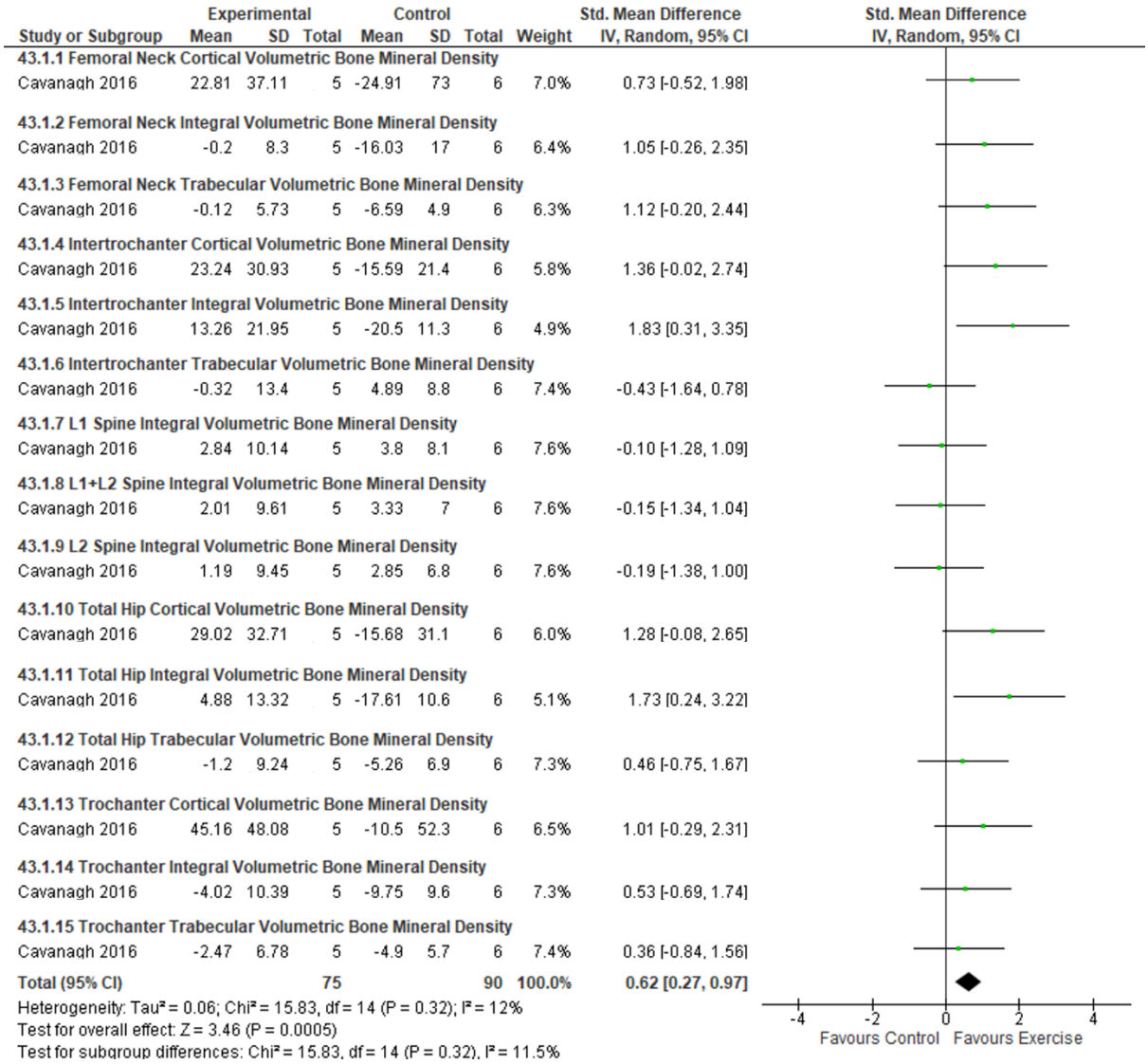

Figure 9.94 Forest plot of volumetric bone mineral density effect size differences for the zero-gravity treadmill intervention

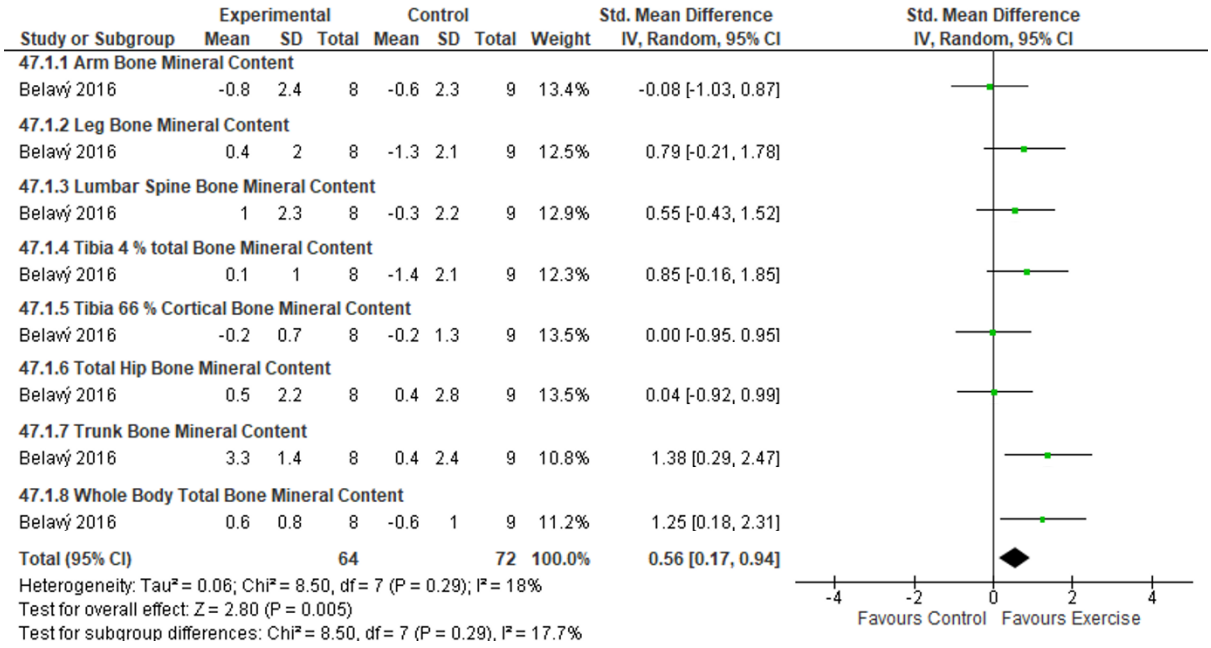

Figure 9.95 Forest plot of bone mineral content effect size differences for the resistive exercise intervention

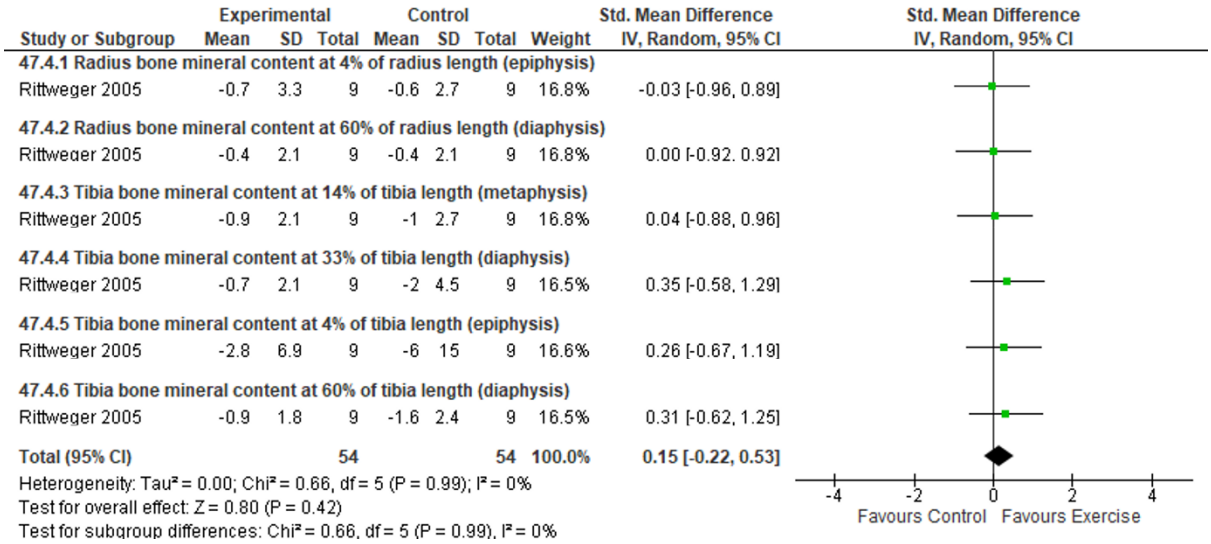

Figure 9.96 Forest plot of bone mineral content effect size differences for the flywheel intervention

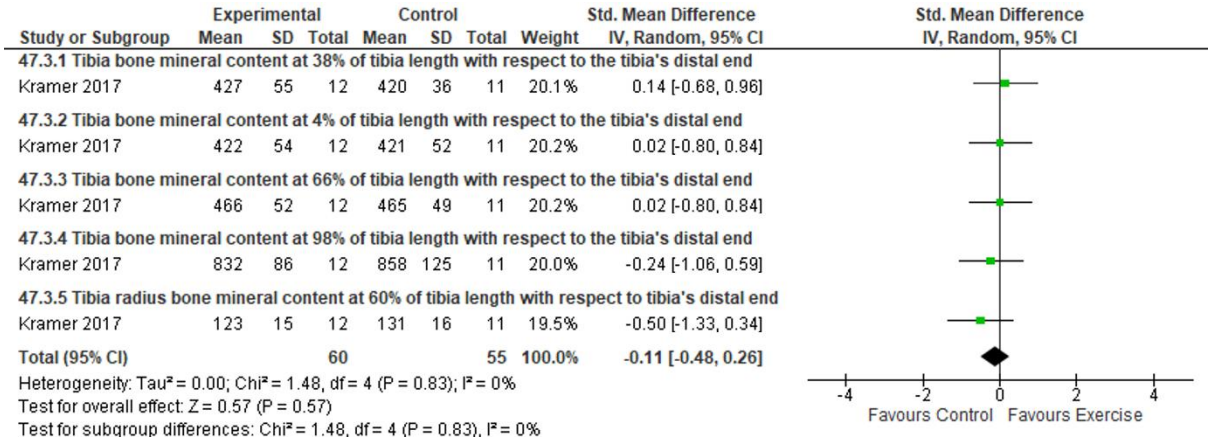

Figure 9.97 Forest plot of bone mineral content effect size differences for the horizontal sledge jump system intervention

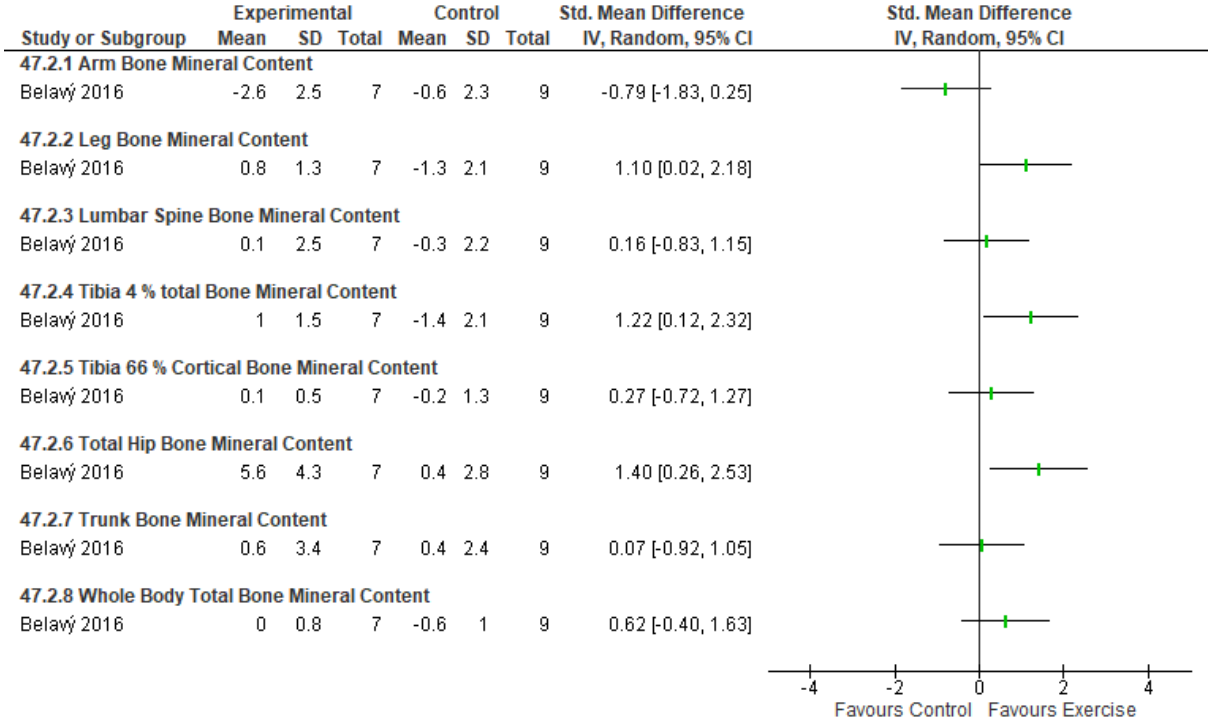

Figure 9.98 Forest plot of bone mineral content effect size differences for the resistive vibration exercise intervention

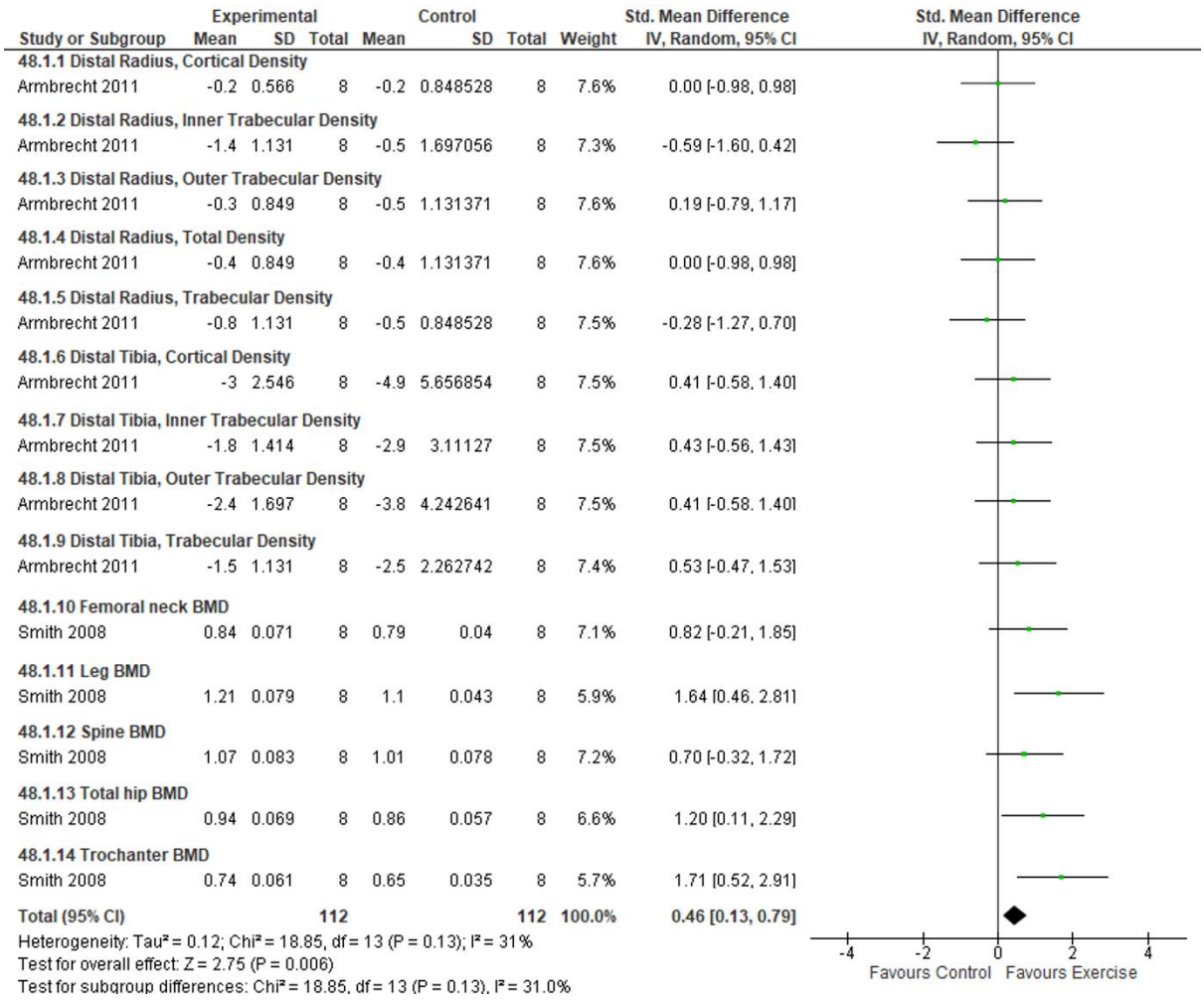

Figure 9.99 Forest plot of bone mineral density effect size differences for the flywheel + treadmill LBNP intervention

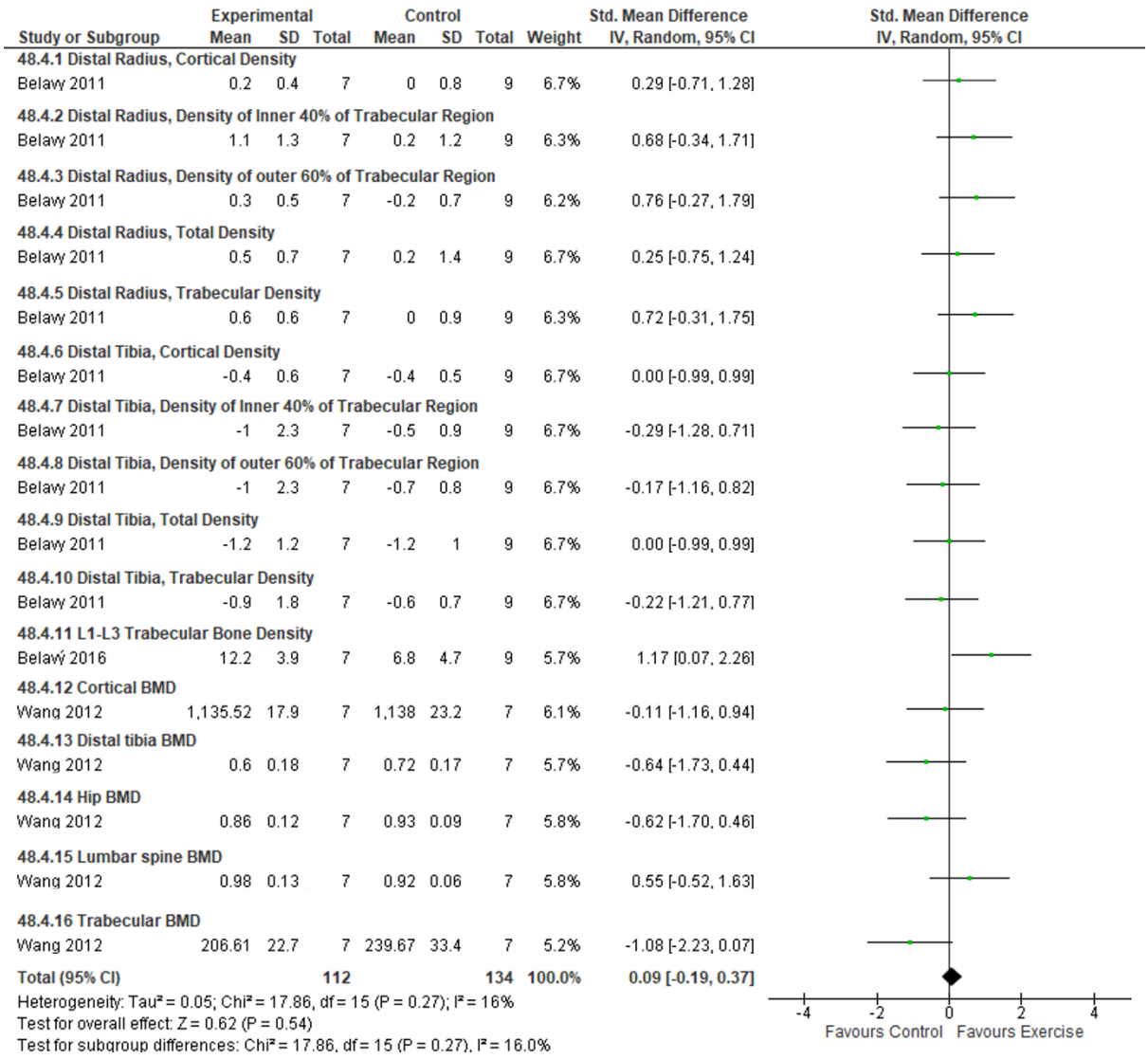

Figure 9.100 Forest plot of bone mineral density effect size differences for the resistive vibration exercise intervention

Figure 9.101 Forest plot of bone mineral density effect size differences for the horizontal sledge jump system intervention

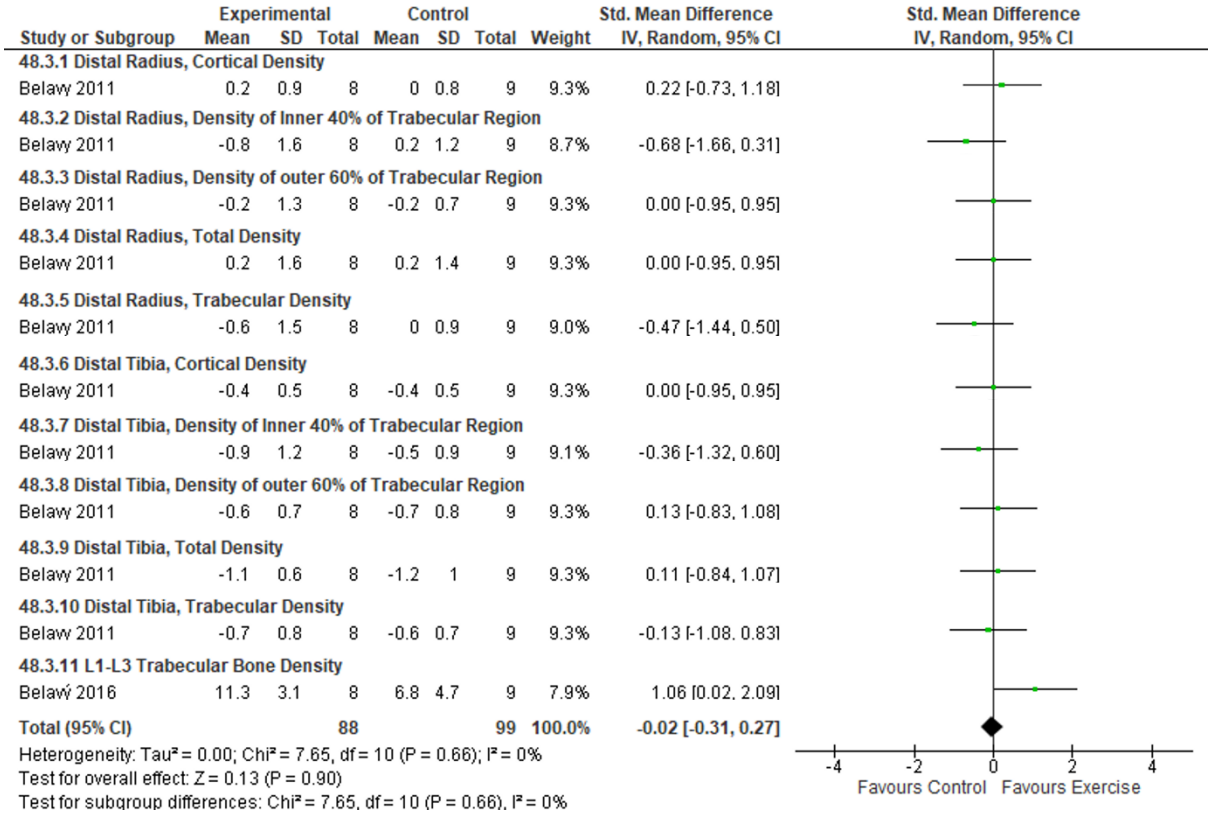

Figure 9.102 Forest plot of bone mineral density effect size differences for the resistive exercise intervention

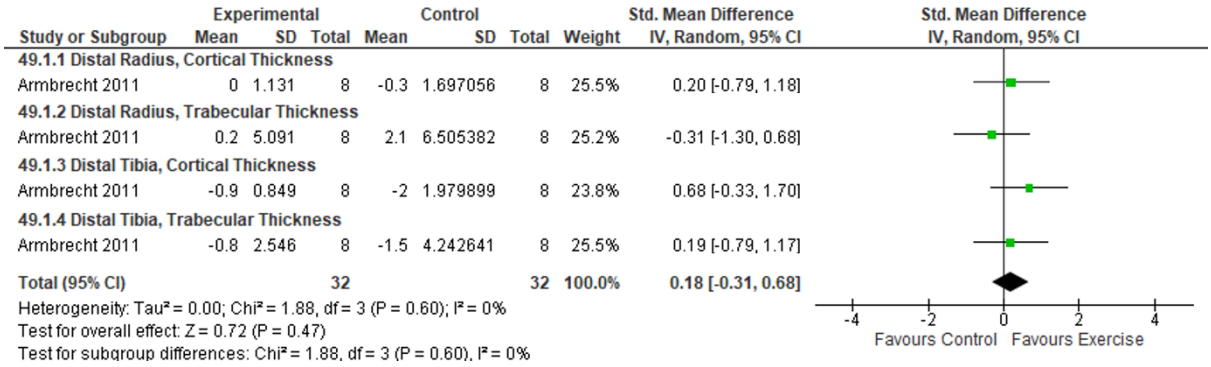

Figure 9.103 Forest plot of bone thickness effect size differences for the flywheel + treadmill LBNP intervention

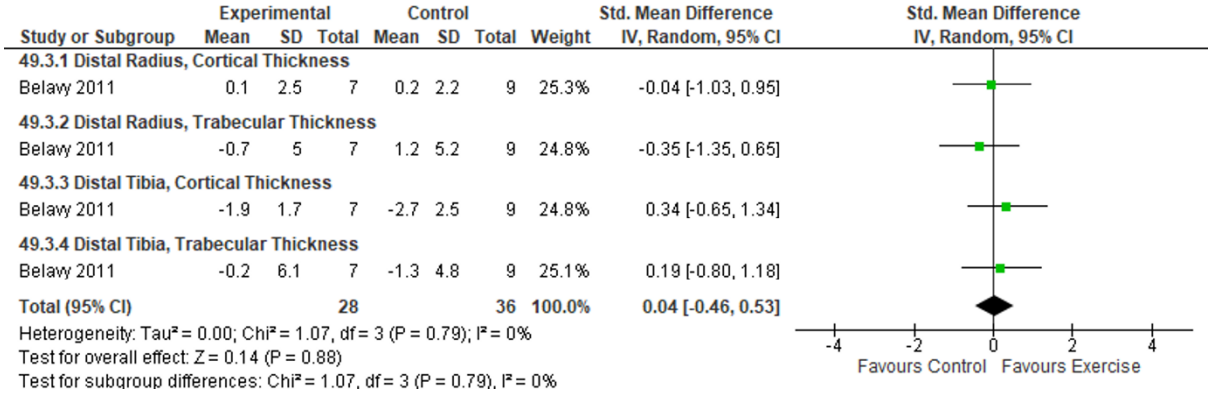

Figure 9.104 Forest plot of bone thickness effect size differences for the resistive vibration exercise intervention

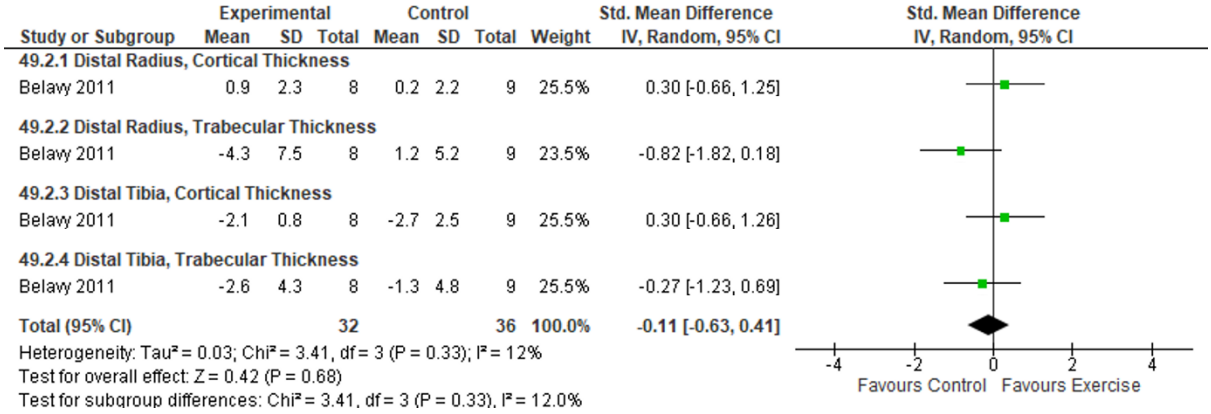

Figure 9.105 Forest plot of bone thickness effect size differences for the resistive exercise intervention

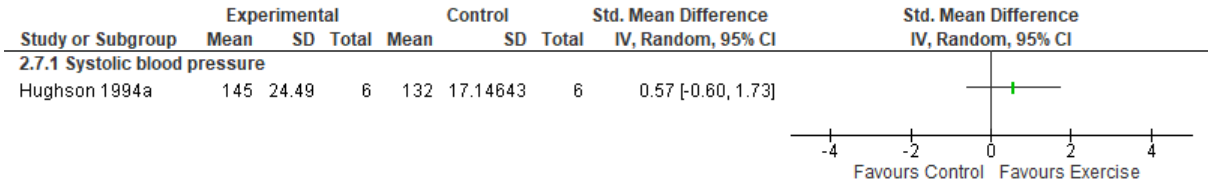

Figure 9.106 Forest plot of arterial/blood pressure effect size differences for the resistive exercise + LBNP intervention

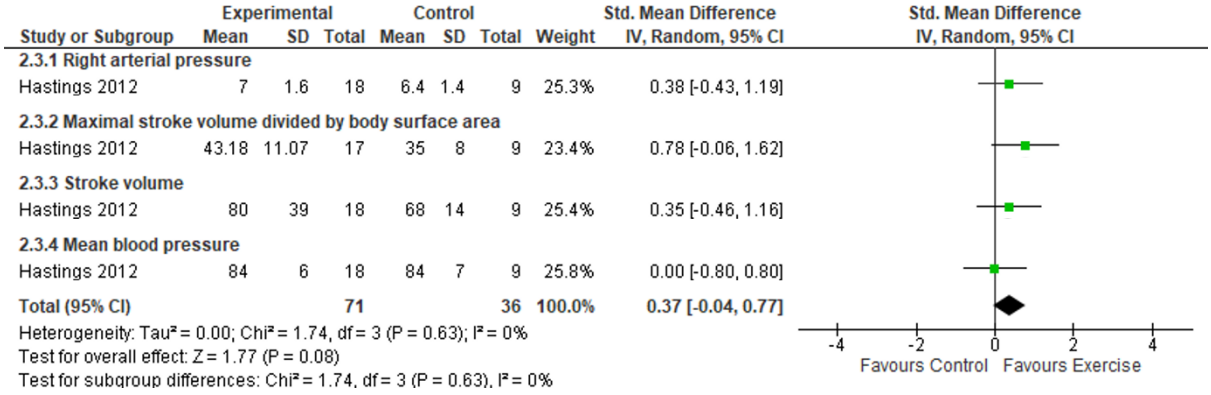

Figure 9.107 Forest plot of arterial/blood pressure effect size differences for the rowing ergometer + resistive exercise intervention

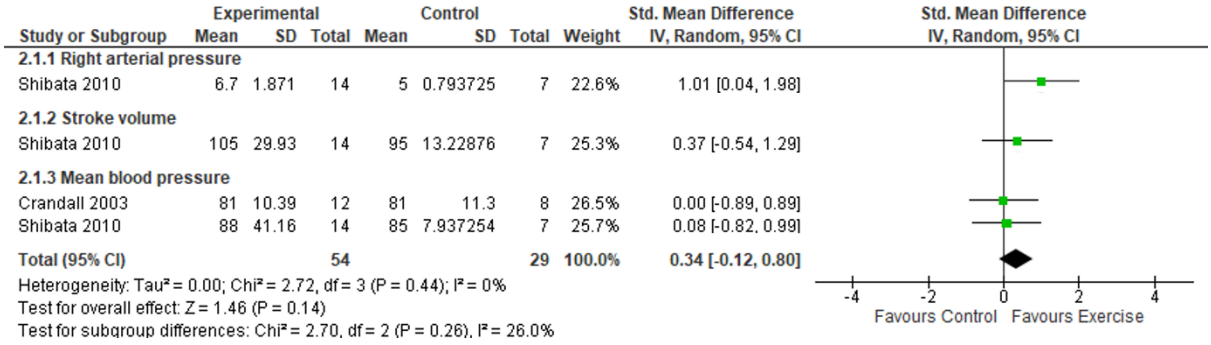

Figure 9.108 Forest plot of arterial/blood pressure effect size differences for the cycle ergometer intervention

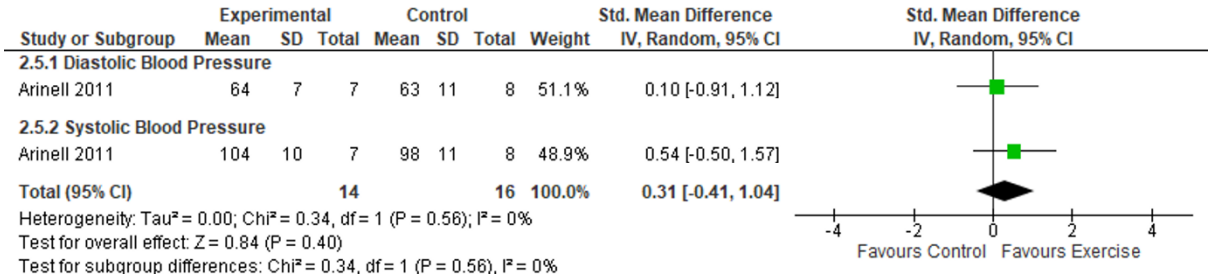

Figure 9.109 Forest plot of arterial/blood pressure effect size differences for the flywheel + treadmill intervention

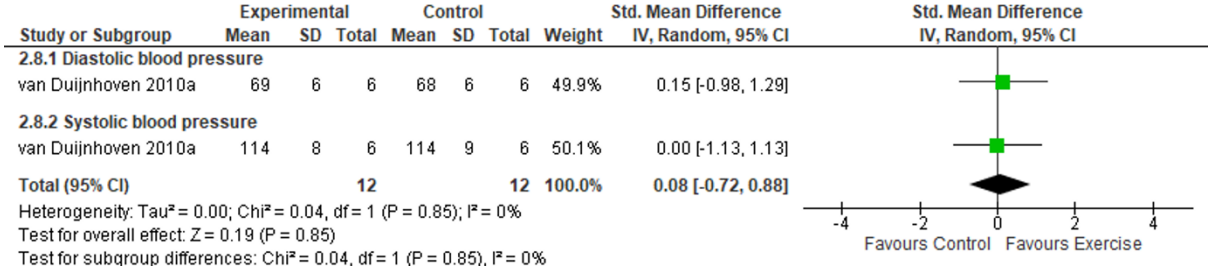

Figure 9.110 Forest plot of arterial/blood pressure effect size differences for the resistive vibration exercise intervention

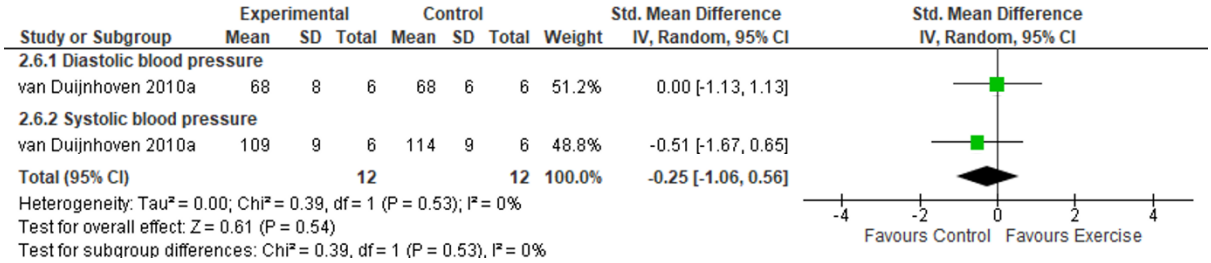

Figure 9.111 Forest plot of arterial/blood pressure effect size differences for the resistive exercise intervention

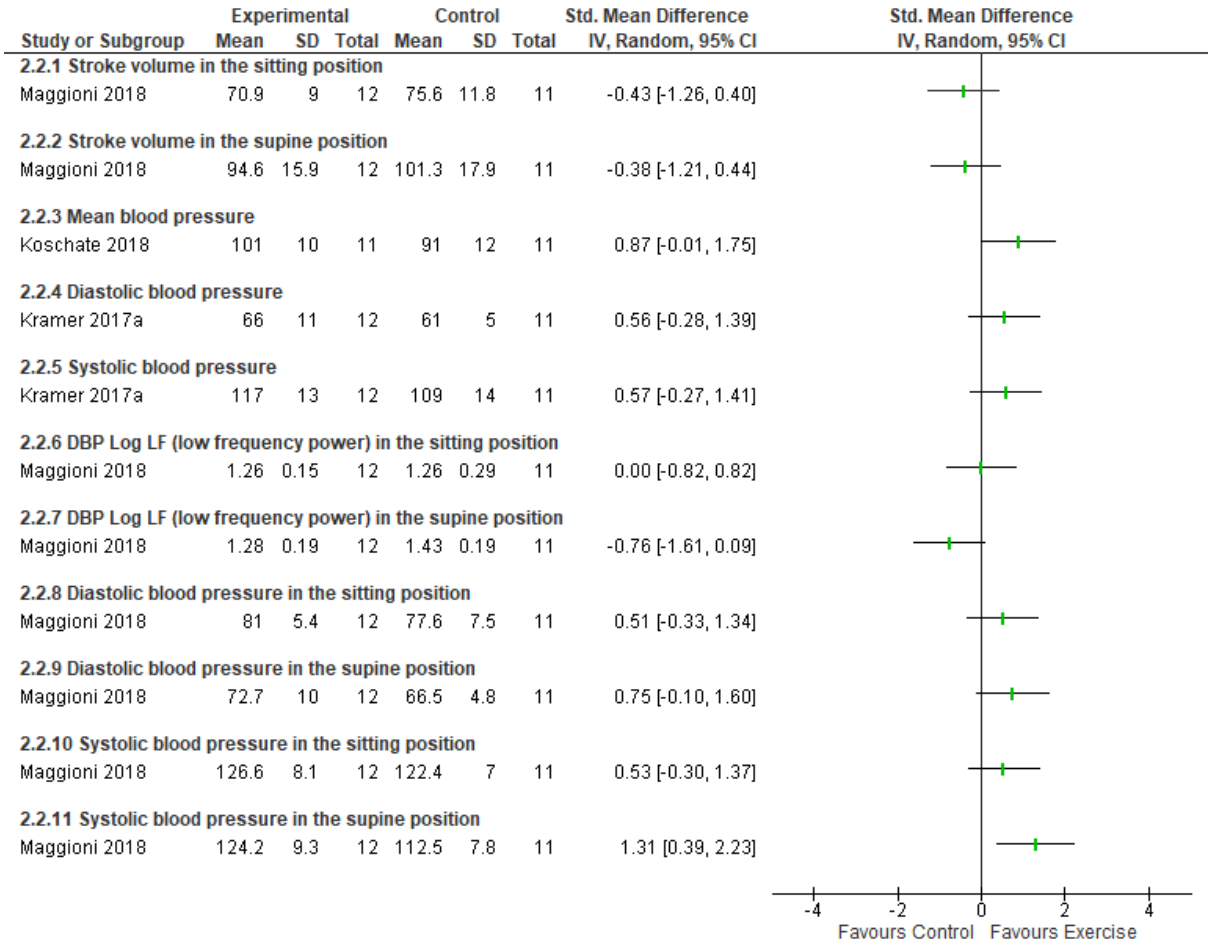

Figure 9.112 Forest plot of arterial/blood pressure effect size differences for the horizontal sledge jump system intervention

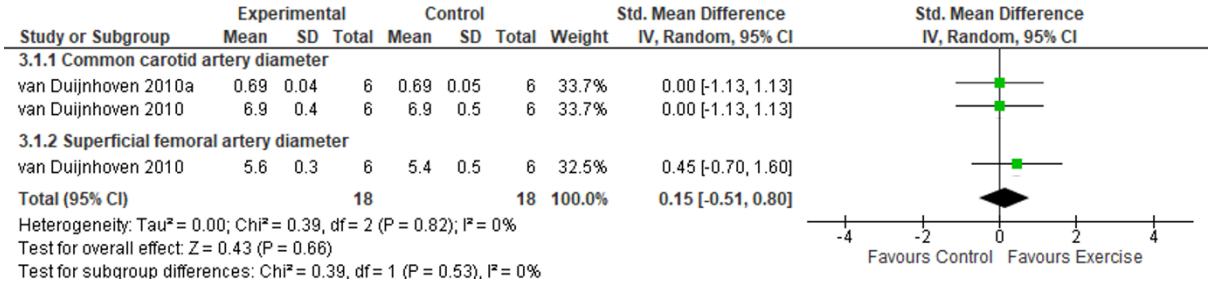

Figure 9.113 Forest plot of artery diamter effect size differences for the resistive vibration exercise intervention

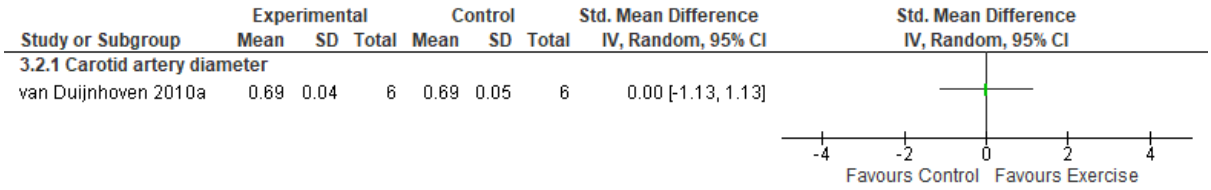

Figure 9.114 Forest plot of artery diamter effect size differences for the resistive exercise intervention

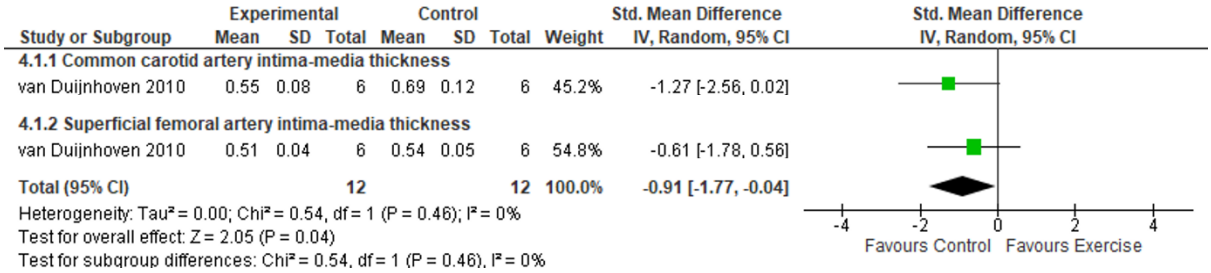

Figure 9.115 Forest plot of artery thickness effect size differences for the resistive vibration exercise intervention

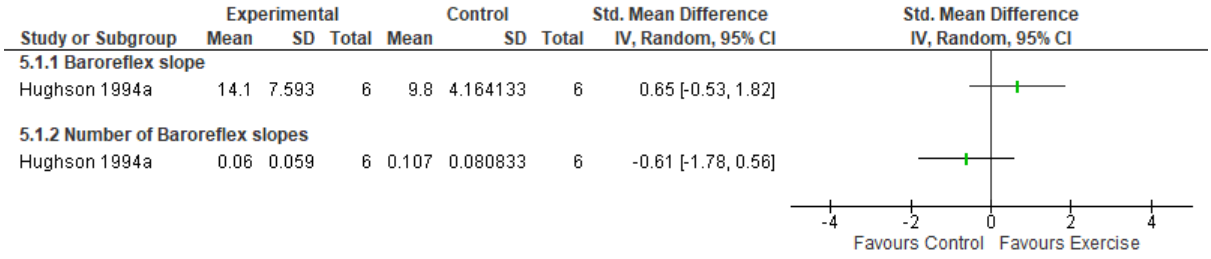

Figure 9.116 Forest plot of baroreflex effect size differences for the resistive exercise + LBNP intervention

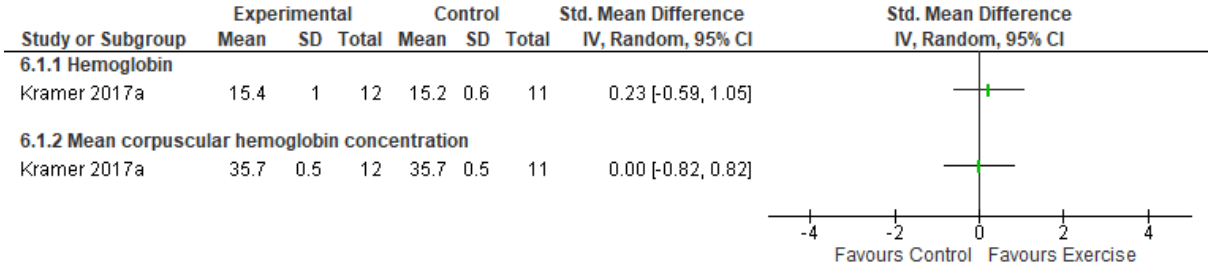

Figure 9.117 Forest plot of cardiovascular biomarker effect size differences for the horizontal sledge jump system intervention

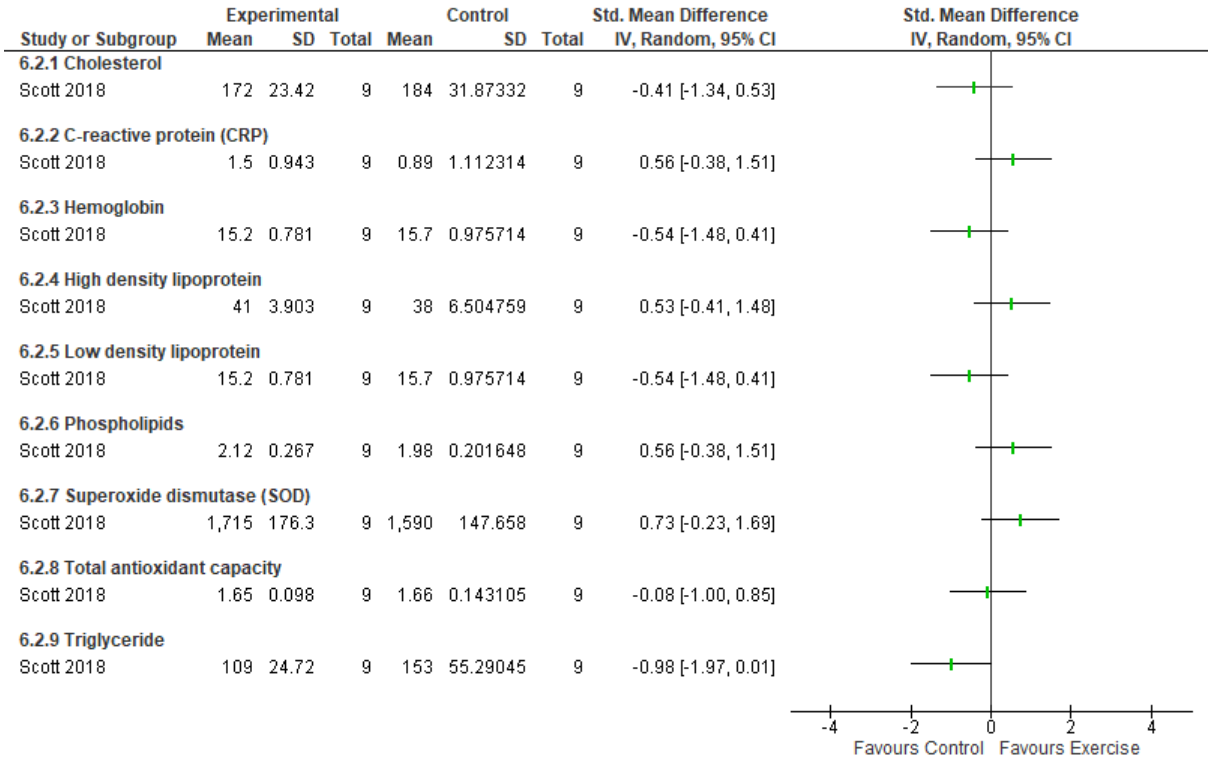

Figure 9.118 Forest plot of cardiovascular biomarker effect size differences for the zero-gravity treadmill + cycle ergometer intervention

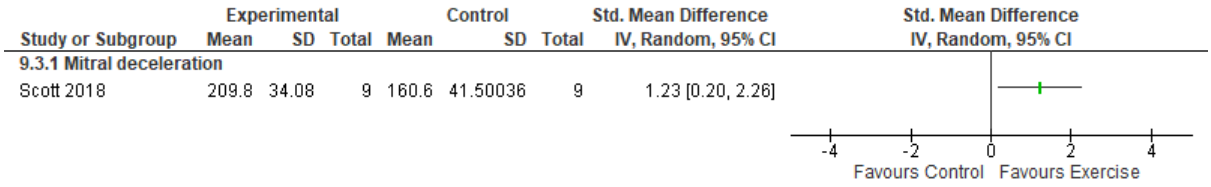

Figure 9.119 Forest plot of blood flow effect size differences for the zero-gravity treadmill + cycle ergometer intervention

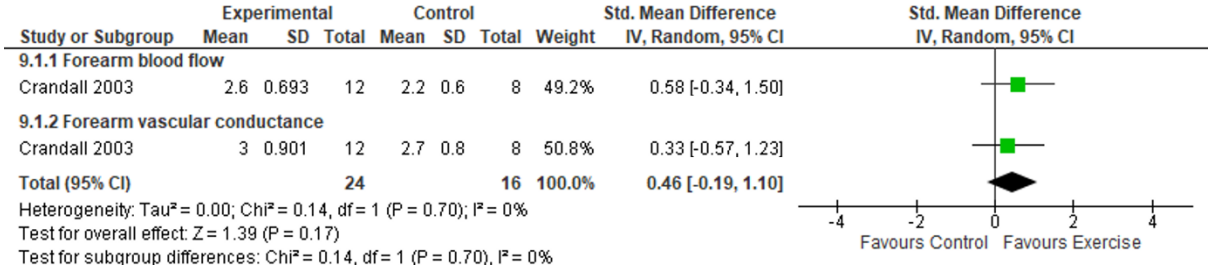

Figure 9.120 Forest plot of blood flow effect size differences for the cycle ergometer intervention

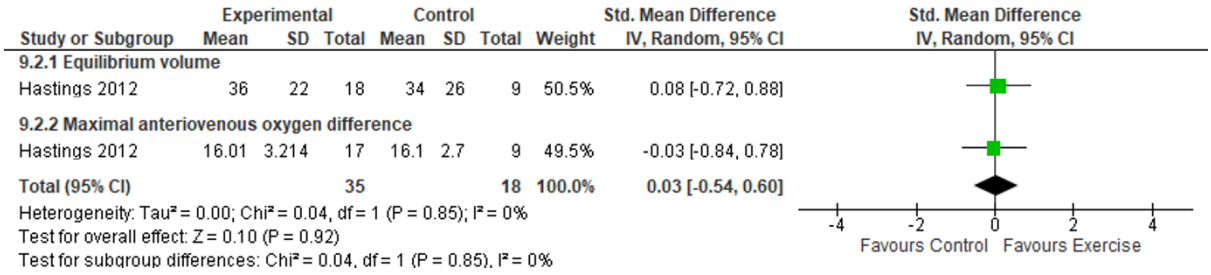

Figure 9.121 Forest plot of blood flow effect size differences for the rowing ergometer + resistive exercise intervention

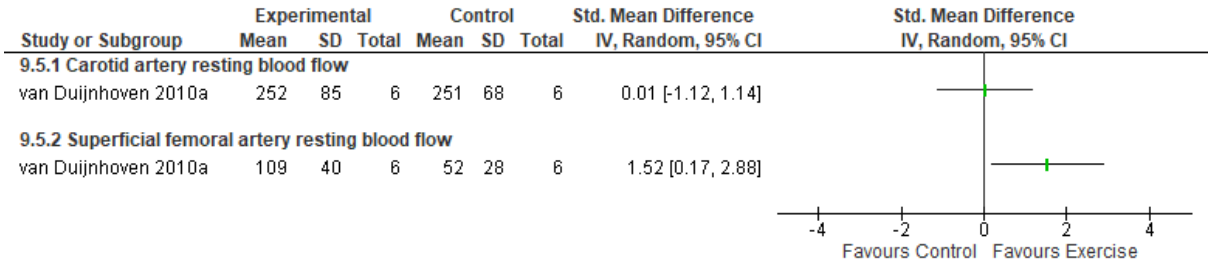

Figure 9.122 Forest plot of blood flow effect size differences for the resistive vibration exercise intervention

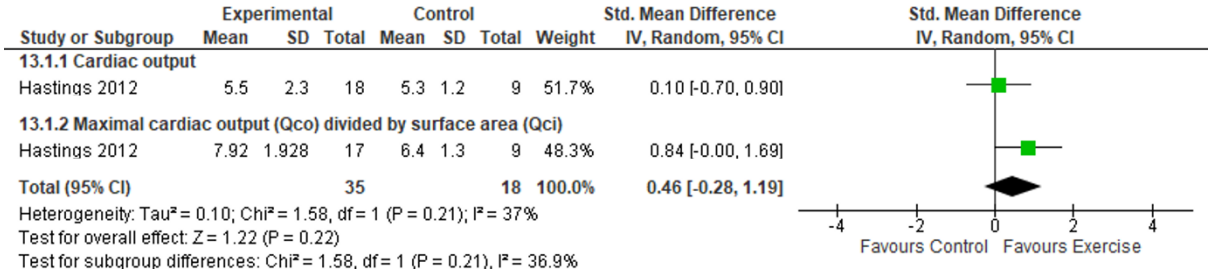

Figure 9.123 Forest plot of cardiac output effect size differences for the rowing ergometer + resistive exercise intervention

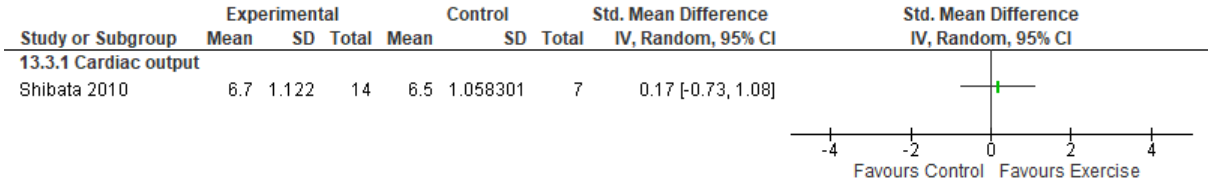

Figure 9.124 Forest plot of cardiac output effect size differences for the cycle ergometer intervention

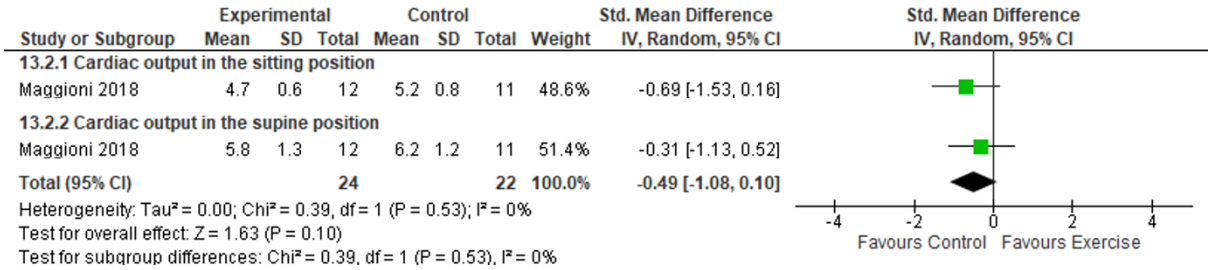

Figure 9.125 Forest plot of cardiac output effect size differences for the horizontal sledge jump system intervention

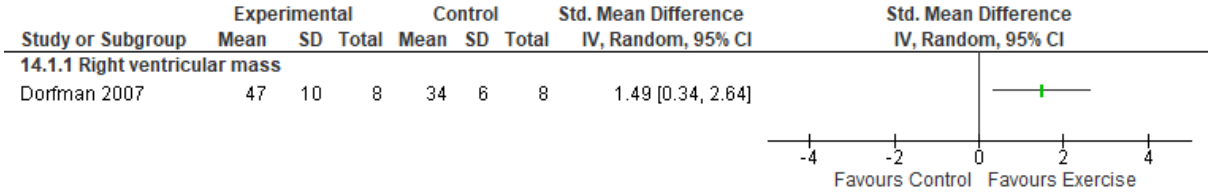

Figure 9.126 Forest plot of cardiac structural properties effect size differences for the treadmill LBNP intervention

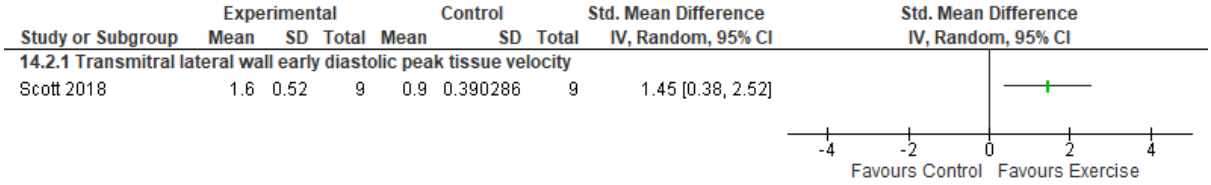

Figure 9.127 Forest plot of cardiac structural properties effect size differences for the zero-gravity treadmill + cycle ergometer intervention

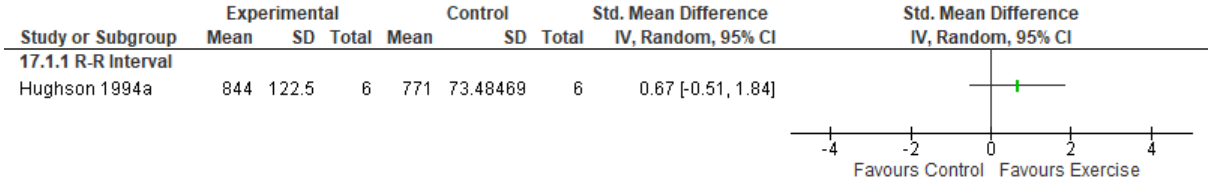

Figure 9.128 Forest plot of ECG activity effect size differences for the resistive exercise + LBNP intervention

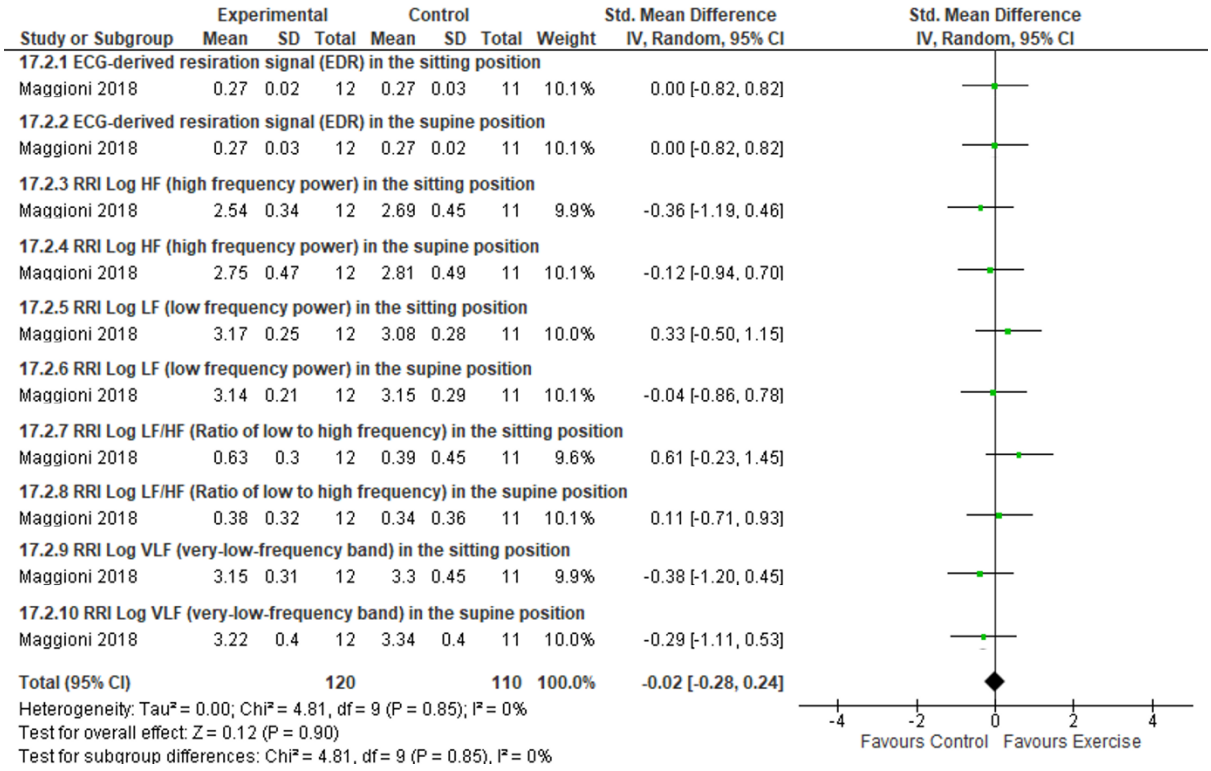

Figure 9.129 Forest plot of ECG activity effect size differences for the horizontal sledge jump system intervention

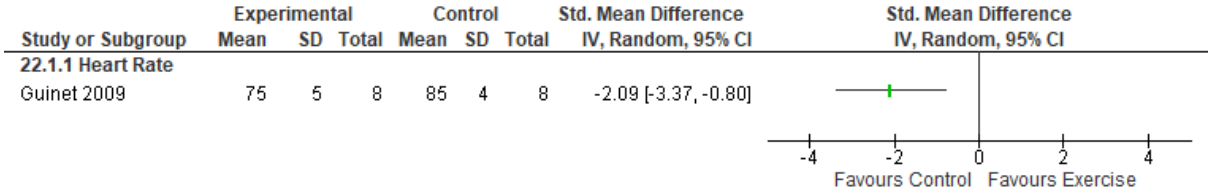

Figure 9.130 Forest plot of heart rate effect size differences for the treadmill LBNP intervention

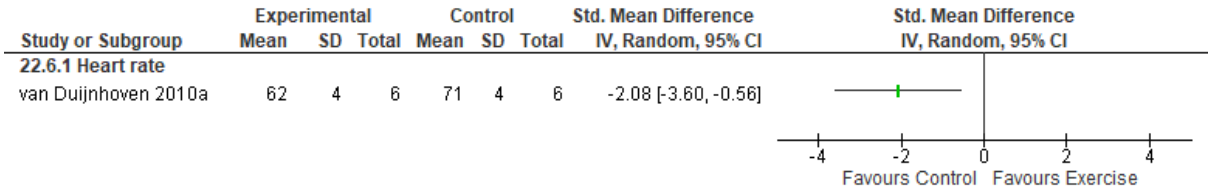

Figure 9.131 Forest plot of heart rate effect size differences for the resistive vibration exercise intervention

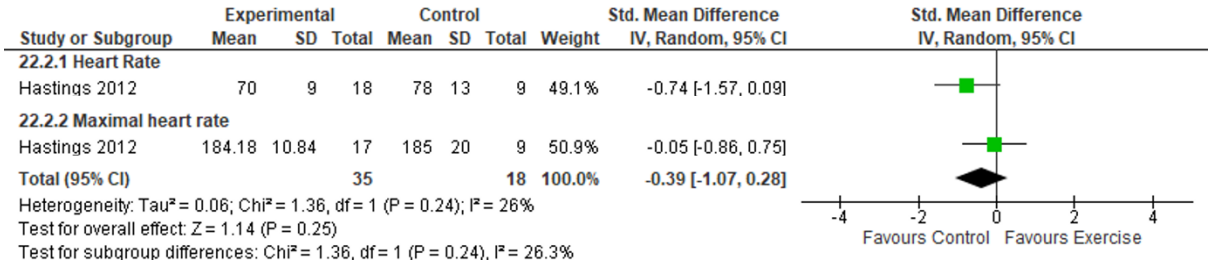

Figure 9.132 Forest plot of heart rate effect size differences for the rowing ergometer + resistive exercise intervention.

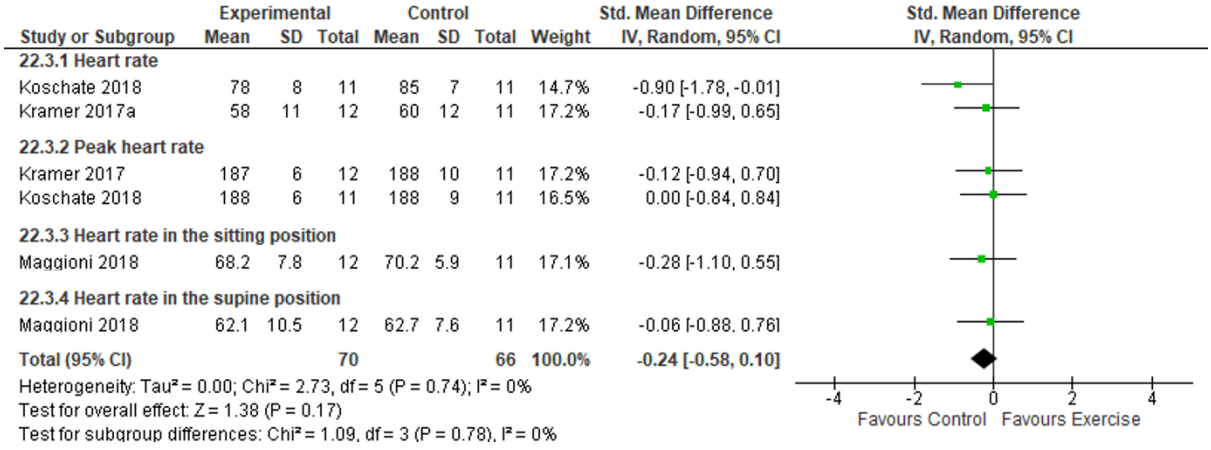

Figure 9.133 Forest plot of heart rate effect size differences for the horizontal sledge jump system intervention

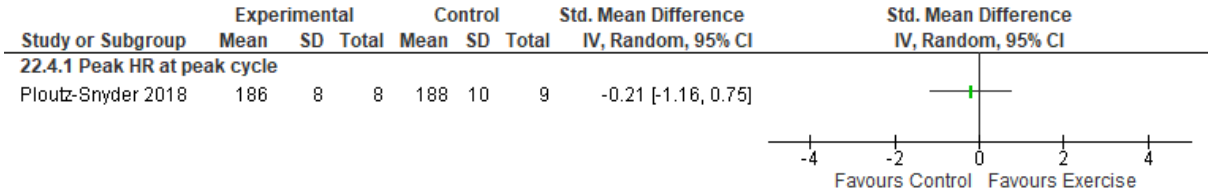

Figure 9.134 Forest plot of heart rate effect size differences for the flywheel intervention

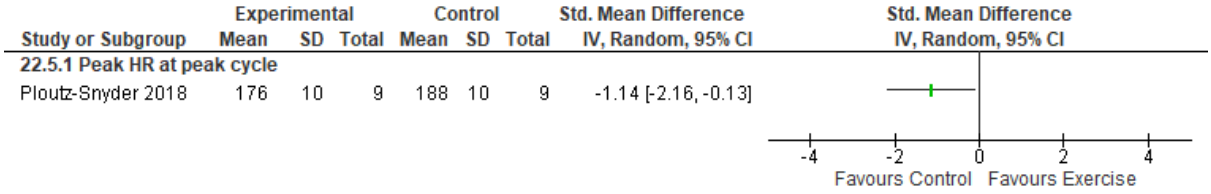

Figure 9.135 Forest plot of heart rate effect size differences for the resistive exercise intervention

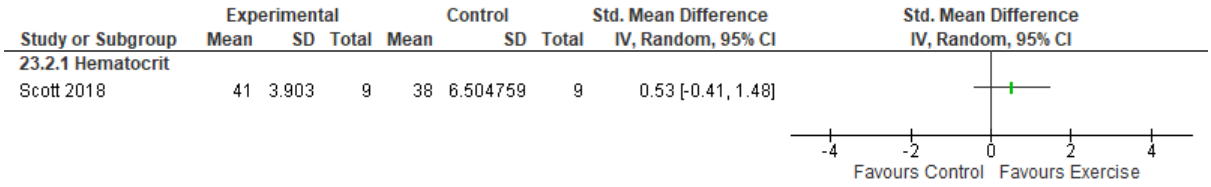

Figure 9.136 Forest plot of hematocrit effect size differences for the zero-gravity treadmill + cycle ergometer intervention

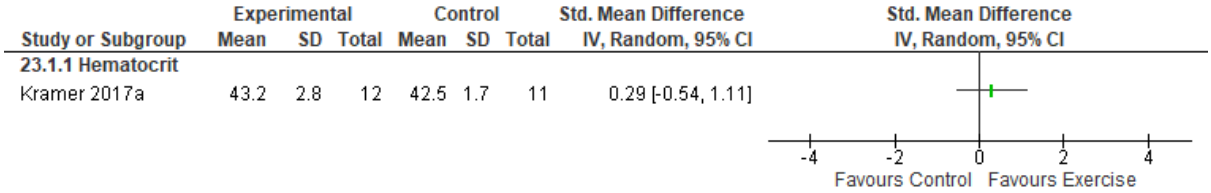

Figure 9.137 Forest plot of hematocrit effect size differences for the horizontal sledge jump system intervention

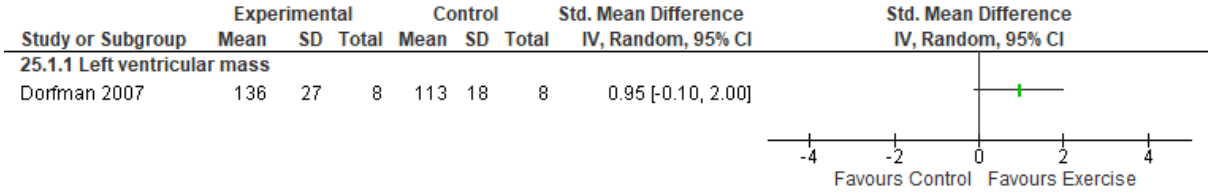

Figure 9.138 Forest plot of left ventricular architectural properties effect size differences for the treadmill LBNP intervention

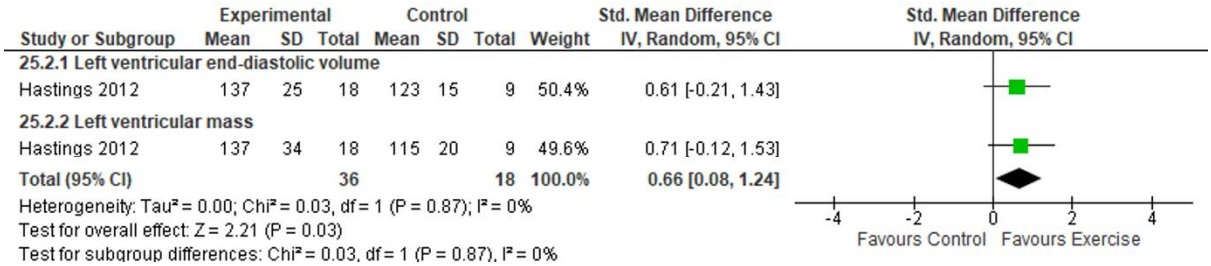

Figure 9.139 Forest plot of left ventricular architectural properties effect size differences for the rowing ergometer + resistive exercise intervention

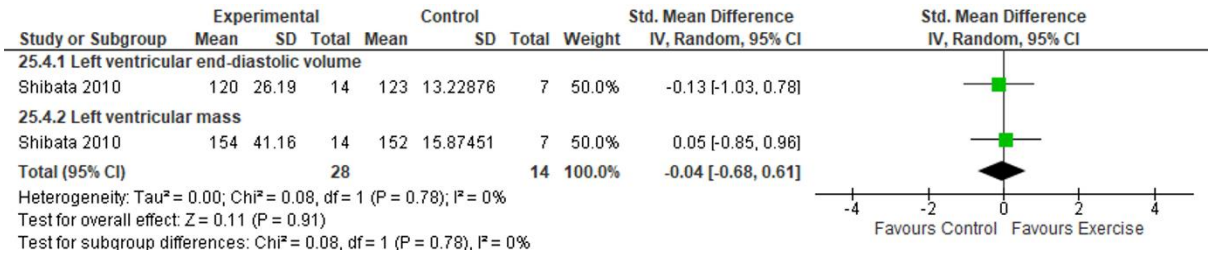

Figure 9.140 Forest plot of left ventricular architectural properties effect size differences for the cycle ergometer intervention

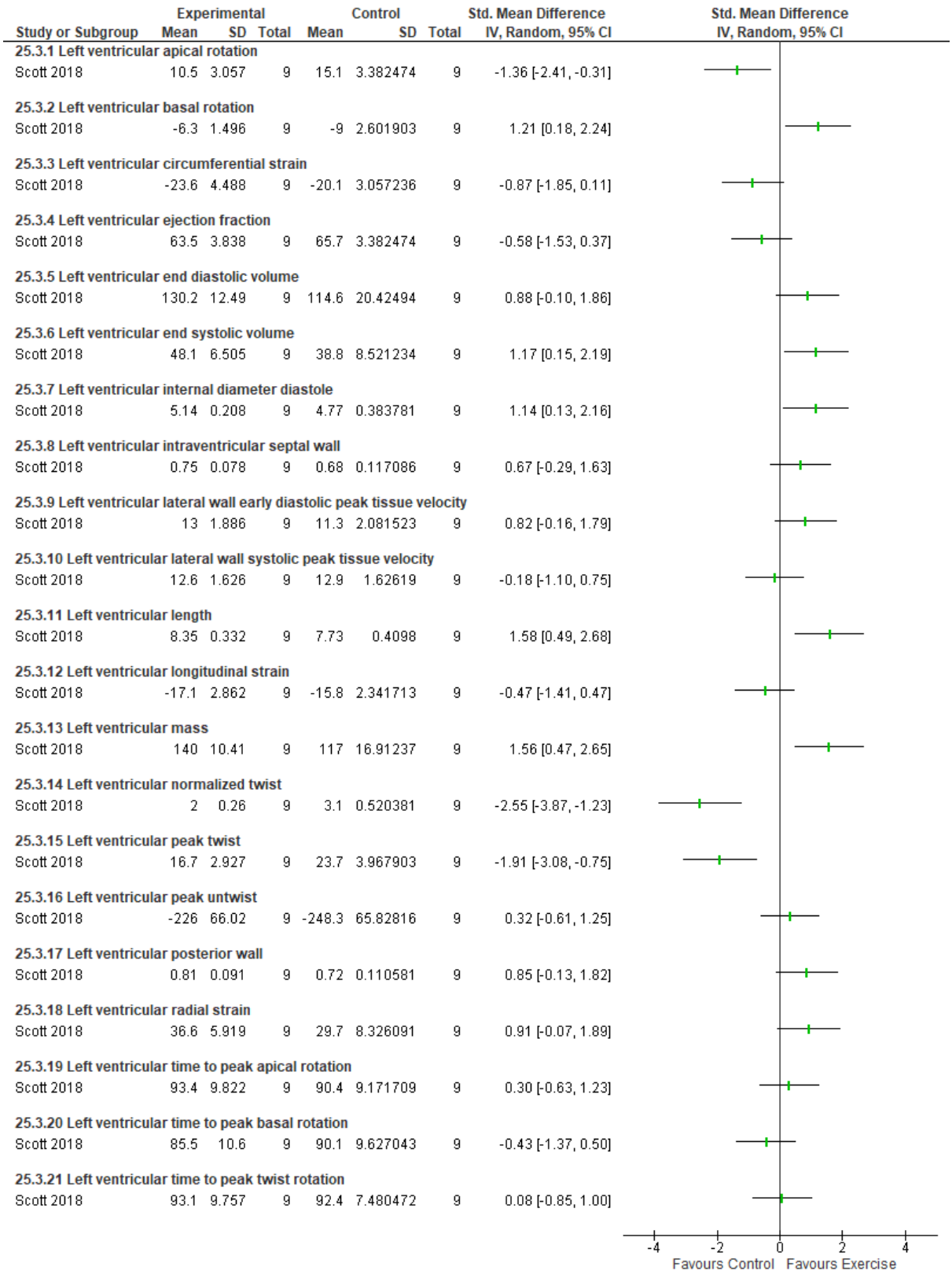

Figure 9.141 Forest plot of left ventricular architectural properties effect size differences for the zero-gravity treadmill + cycle ergometer intervention

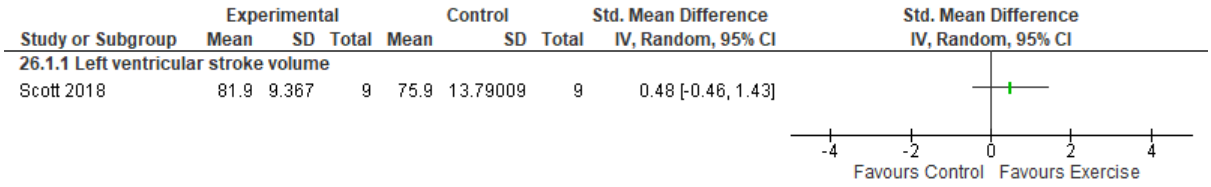

Figure 9.142 Forest plot of left ventricular functional properties effect size differences for the zero-gravity treadmill + cycle ergometer intervention

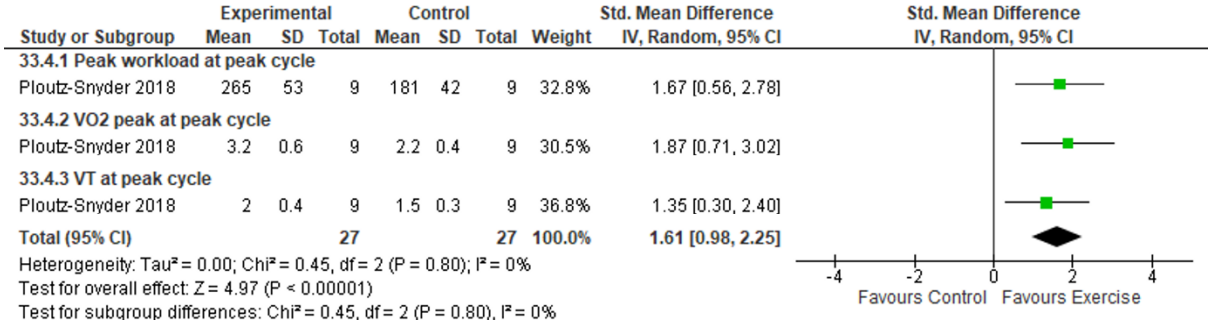

Figure 9.143 Forest plot of pulmonary functional properties effect size differences for the zero-gravity treadmill + cycle ergometer intervention

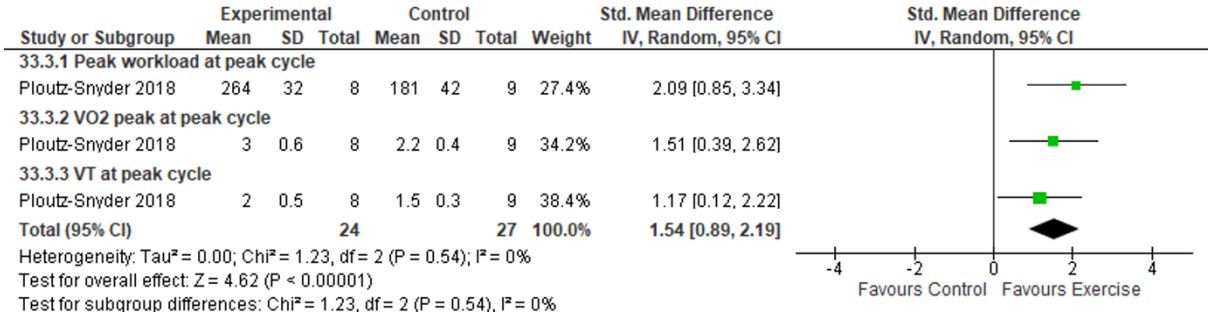

Figure 9.144 Forest plot of pulmonary functional properties effect size differences for the flywheel intervention

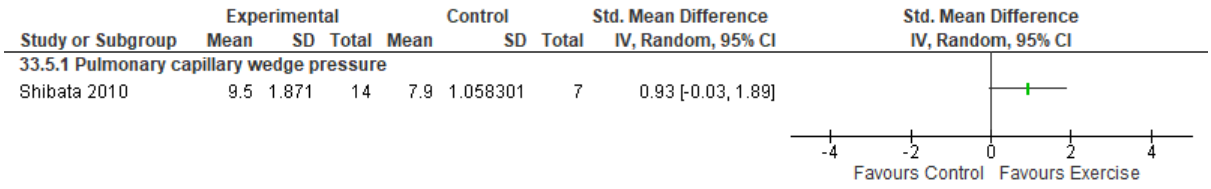

Figure 9.145 Forest plot of pulmonary functional properties effect size differences for the cycle ergometer intervention

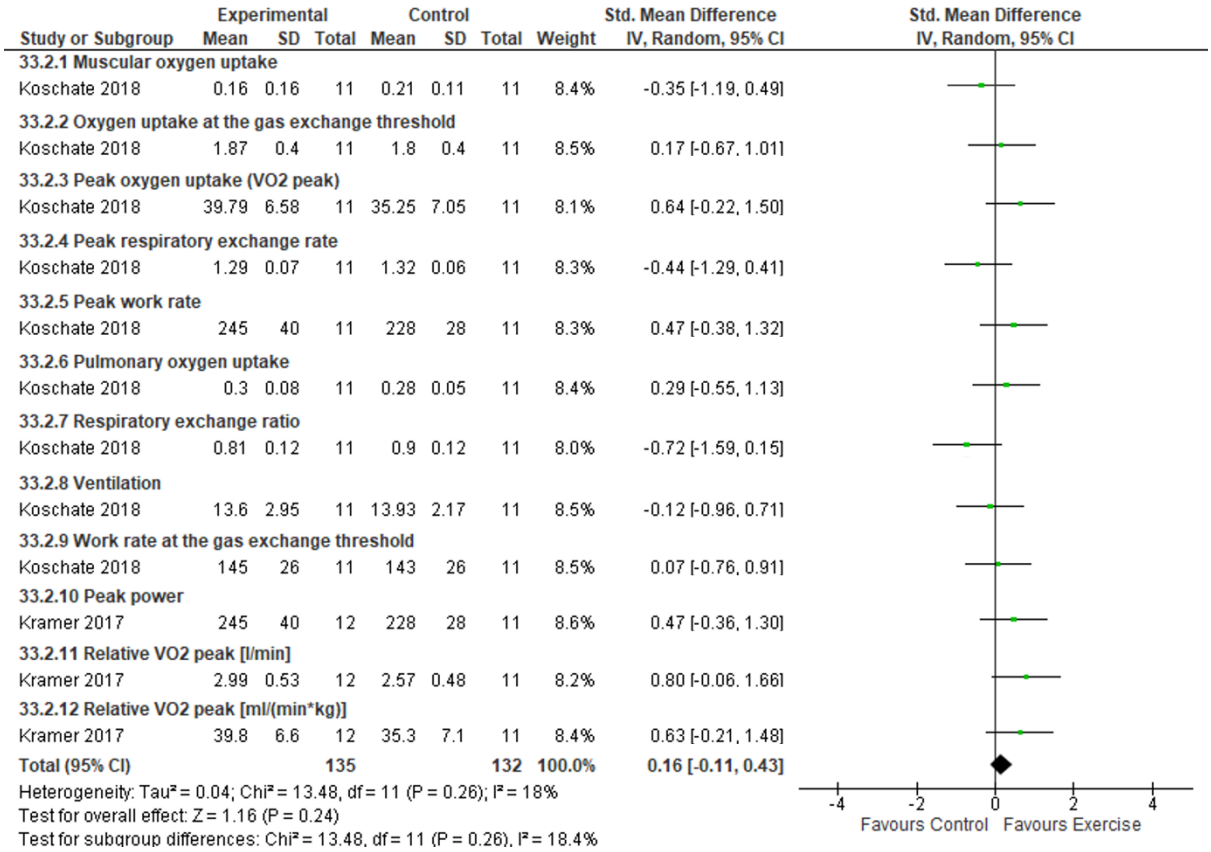

Figure 9.146 Forest plot of pulmonary functional properties effect size differences for the horizontal sledge jump system intervention

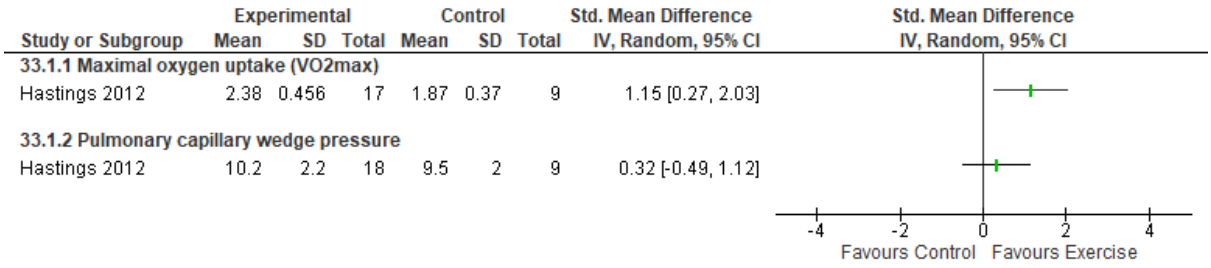

Figure 9.147 Forest plot of pulmonary functional properties effect size differences for the rowing ergometer + resistive exercise intervention

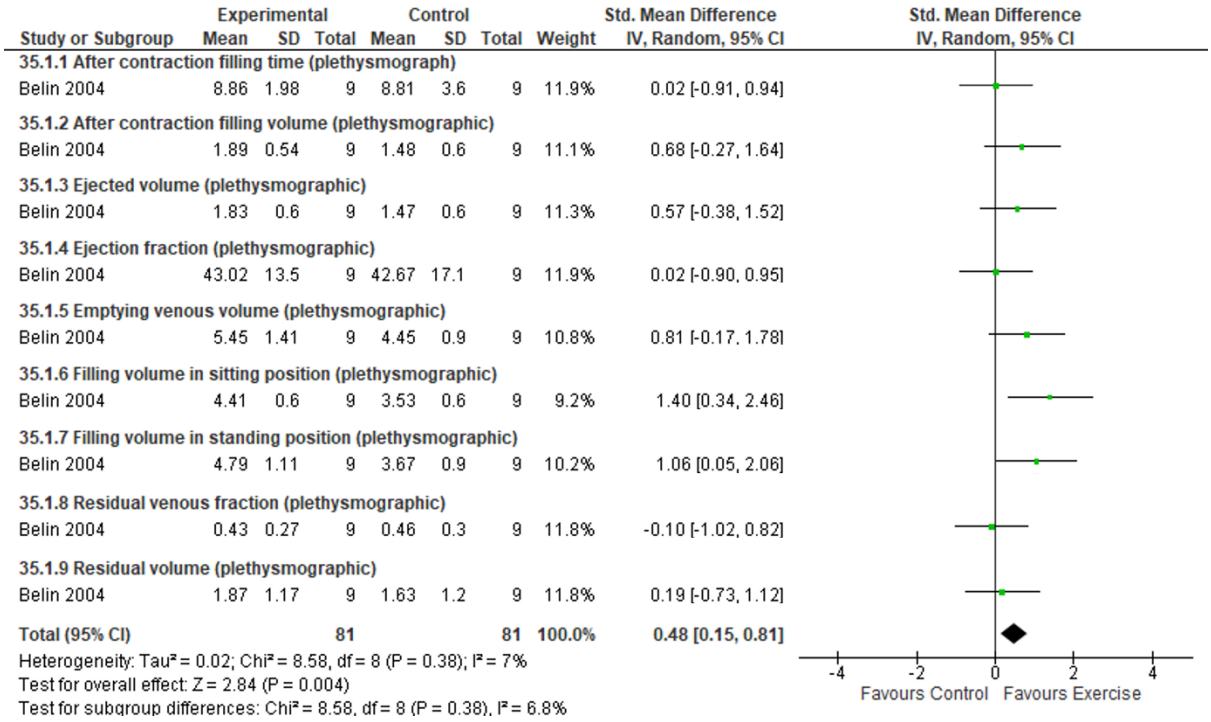

Figure 9.148 Forest plot of plethysmograph activity effect size differences for the flywheel intervention

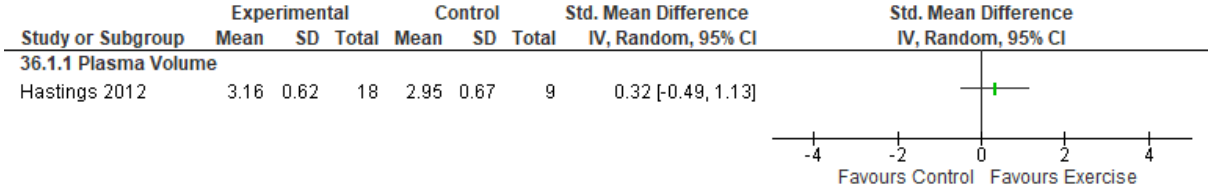

Figure 9.149 Forest plot of plasma volume effect size differences for the rowing ergometer + resistive exercise intervention

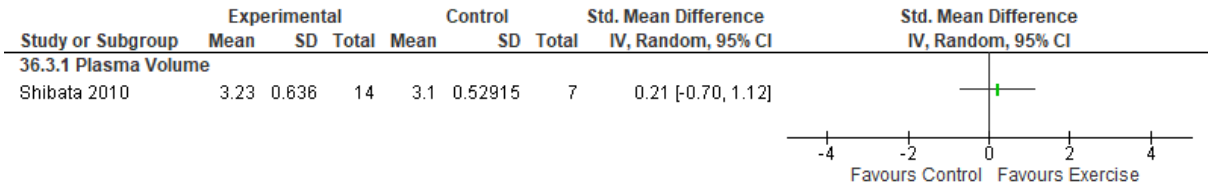

Figure 9.150 Forest plot of plasma volume effect size differences for the cycle ergometer intervention

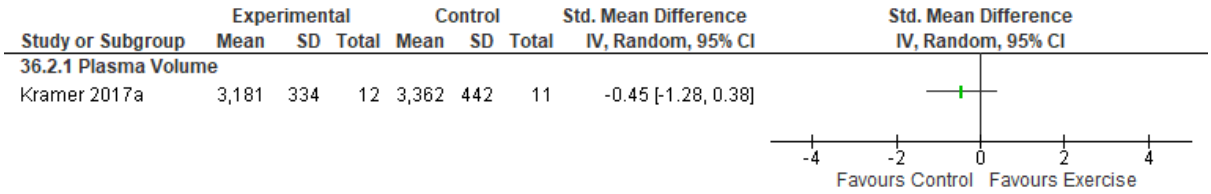

Figure 9.151 Forest plot of plasma volume effect size differences for the horizontal sledge jump system intervention

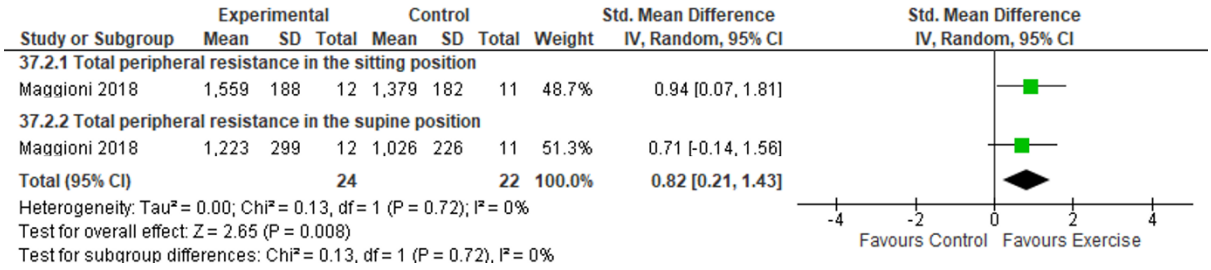

Figure 9.152 Forest plot of peripheral resistance effect size differences for the horizontal sledge jump system intervention

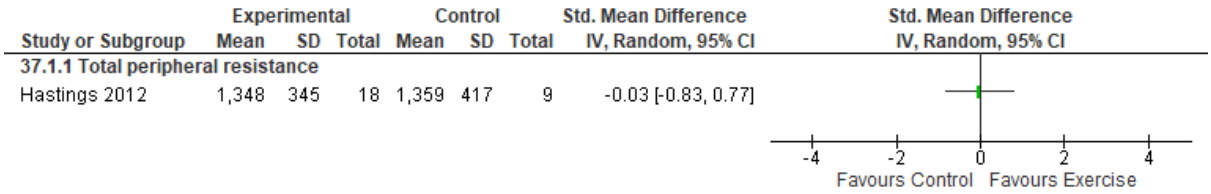

Figure 9.153 Forest plot of peripheral resistance effect size differences for the rowing ergometer + resistive exercise intervention

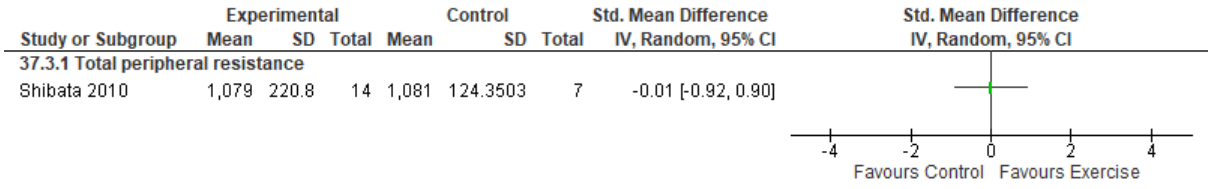

Figure 9.154 Forest plot of peripheral resistance effect size differences for the cycle ergometer intervention

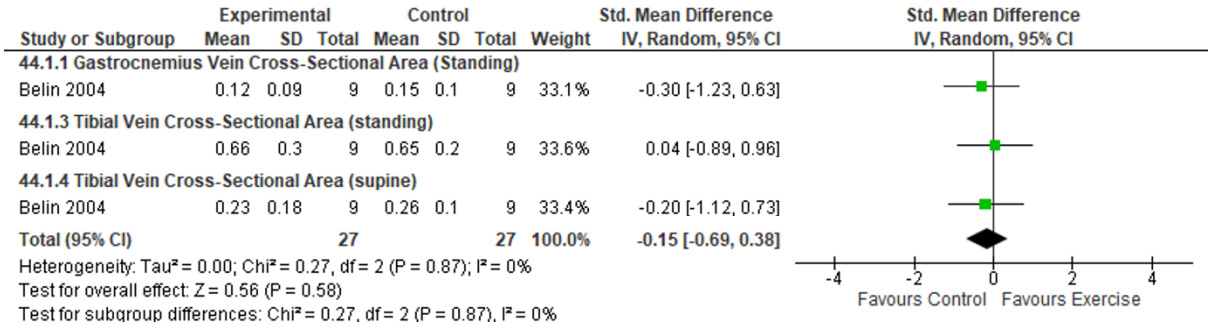

Figure 9.155 Forest plot of vein CSA effect size differences for the flywheel intervention

9.6. Appendix F

Transcripts from Chapter 5 astronaut survey.

Q1: What factors would you consider most important to you for the design of an exercise countermeasure device for use during spaceflight, and why?

P1: Ease of use, effectiveness, covers a broad range of exercises, practical Exercise in space needs to be an activity that crew will enjoy, contributing to both physical and mental wellbeing. To that end, the device needs to appeal to a broad range of possible activities (both in terms of offering a full body workout and different types of exercise e.g HIT vs endurance) and crewmember preferences. In addition, given the limited volume in a spacecraft, crew will want to exercise without being disturbed or disturbing other crew where possible.

P2: Ease of setup and use Replication of terrestrial loading, so as to avoid musculoskeletal deterioration during flight Avoidance of "hot spots" and overuse injuries as a result of restraint systems

P3: Ease of setup and takedown in terms of time and searching for parts. Varied routines to reduce boredom. Use of the spaceflight environment. For example, fly from one bulkhead to the other, push off, fly back. This makes the exercise time much more enjoyable and engaging.

Q2: Would you prefer to use multiple exercise devices during spaceflight or a single exercise device? Why is this the case?

P1: Multiple devices currently offer a variety of different exercises and the ability for multiple crewmembers to train at the same time. However, this is not high on my priority list. If a new, single, device could offer a similar variety of exercises then a single device would suffice.

P2: Multiple exercises for variety and to assure total body exercise

P3: Mutliple. Otherwise the exercise time can be tedious.

Q3: Would you feel bored using only a single exercise countermeasure device? If so, how do you think this this boredom impact you?

P1: No - not if it offered a good variety and range of possible exercises. Crew enjoyment during exercise often comes from listening to music/podcasts, watching TV etc. I enjoyed running and biking using a tablet app 'Run Social', which enabled me to immerse myself in an almost virtual environment (Swiss/Scottish mountains etc). I think entertainment during exercise is an extremely important element to consider for integration or at least compatibility with future countermeasure devices.

P2: Yes, most definitely. Could avoid boredom through VR/AR augmentation and/or Peloton-type motivation with virtual instructors.

P3: Yes. It would make me less likely to do the exercise and also less likely to do it well.

Q4: Would you feel less likely to engage fully with an exercise prescription during spaceflight if there was only a single exercise device? Why is this the case?

P1: No. If it is well designed it will offer something for everyone and enough range of possible exercises to allow sufficient variety for a week-long exercise programme.

P2: Boredom, likely ineffectiveness of a single prescription/single device.

P3: One device is fine, especially if it means that device can remain assembled in place, so it is easy to use. However, the routine should vary.

Q5: Thinking about your health and wellbeing, would you feel confident using only a flywheel exercise countermeasure device for a mission of 30 days or less beyond low Earth orbit? Why is this the case?

P1: Yes. For a mission of such short duration then a flywheel, although perhaps not able to fulfil the points raised above, would suffice.

P2: Short duration, for which 30 days is at the upper limit, would probably be OK with a simple flywheel device. There are clever adaptations with a flywheel that could make exercise less boring, however (and more effective for total body resistance training).

P3: For 30 days or less, a simple flywheel is fine. It's not about the device, it is about the routine.

Q6: Is there anything else that you would like to add?

P1: N/A

P2: Different modes of resistance and endurance training can easily be envisioned with a flywheel - so don't treat it as a single exercise device. Think about other adapters for different exercise modalities.

P3: Exercise devices in flight have historically mimicked exercise devices on earth. There is a better way. [*Name and mission redacted for anonymity*] introduced to the crew some active exercises that were fun and engaging. For example, we pushed off a bulkhead with our feet, flew fast to the opposite bulkhead and pushed off that to return. At first, this is hard to do-- you don't fly straight. After just a

few minutes, you improve a lot. After a while, everyone got really good and we were tumbling between the bulkheads and going very fast so that we got strength training, impact training to the long bones, coordination exercises, spacial orientation exercises, all at the same time, while having a lot of fun. We would go in pairs and eventually we could get four people going simultaneously, rushing past each other. We really learned to fly! We also played games for exercise. We played tag and king of the mountain. We played a form of Quidditch in an emptied supply module where we used a red rubber ball as the snitch and went after it, pushing and pulling each other all over the place. In the current ISS, you could do that in the airlock. I encourage you to find exercises that utilize the unique environment of spaceflight rather than just reproducing earth-based exercise devices.

Yes, I think there are plenty of exercises that could be done utilizing weightlessness within 5 cubic meters. For example, two crewmembers could simultaneously dribble each other off the walls like basketballs (that would be a hoot and a half!). However, I don't think much exercise is needed for the short duration that most crews will spend in those capsules. Yes, we did get a call from the ground during our high impact exercises that we were registering on the station accelerometers and to go look at the solar arrays which were indeed flapping. However, there are lots of ways around that issue, for example, install a springboard at the bulkhead that isolates the impact from the vehicle.

Power needed for biofeedback is minimal-- use a coin battery for example. Or use a fitbit or a cell phone with batteries. Or use a USB3 port on a laptop. If there is really no power, then use a hand generator (squeeze to turn a wheel that generates power) with a super capacitor and consider the power generation as part of the exercise routine (It's quantifiable and you need hand strength for EVA!).

10. Additional published and under-review works based upon this thesis