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

Laws, J.M.*[1], Caplan, N.[1], Bruce, C.[1], McGrogan, C.[1], Lindsay, K.[1], Wild, B.[2], Debuse, D.[1], Wotring, V.[3], Winnard, A.[1]

DOI: https://doi.org/10.1016/j.actaastro.2020.02.038

[1]Faculty of Health and Life Sciences, Northumbria University, Newcastle-upon-Tyne, United Kingdom

[2]Faculty of Science, Technology, Engineering and Mathematics, Open University, Milton Keynes, United Kingdom

[3]Associate professor, International Space University, Illkirch-Graffenstaden, France.

Corresponding author:

Mr Jonathan Laws

Faculty of Health and Life Sciences

Northumbria University

Northumberland Building

Newcastle-upon-Tyne

NE1 8ST

Tel: 01912437030

Email: jonathan.m.laws@northumbria.ac.uk

Declarations of interests

Declarations of interest: None.

Abstract:

Background: The constraints of the Orion Multi-Purpose Crew Vehicle present challenges to the use of current exercise countermeasures necessary to prevent severe deconditioning of physiological systems during microgravity exposure beyond Low Earth Orbit. The purpose of this qualitative systematic review was to determine the technical constraints of the Orion Multi-Purpose Crew Vehicle which may hinder astronauts' capabilities to effectively exercise during long distance spaceflight.

Methods: Databases were searched from the start of their records to December 2018. Included documents were quality assessed with the AMSRG quality scoring tool and Thematic Analysis was used to analyse the included documents to assess technical constraints of the Orion Multi-Purpose Crew Vehicle.

Results: 19 studies were included in the final review. All identified constraints, other than data transmission limitations, were found to ultimately be a result of the volume and upload mass constraints of the Orion Multi-Purpose Crew Vehicle. There was a lack of detailed studies and lack of consistency in specifying spacecraft in the literature that limit the conclusions of this review

Conclusion: Space agencies are advised to ensure that information on relevant spacecraft constraints is readily available to researchers. 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.

Keywords:

Orion Multi-Purpose Crew Vehicle
Exercice contraints
Spaceflight
Astronaut

1. Introduction

The future of human spaceflight will take us beyond Low Earth Orbit (LEO): back to the moon; to asteroids; and, within 30 years by current estimates, to the planet Mars (Kanas, 2013; Williams, Kuipers, Mukai, & Thirsk, 2009). The Orion Multi-Purpose Crew Vehicle (MPCV) is the newest generation of exploration class spacecraft that has been planned for use during many of these missions beyond LEO (Thompson et al., 2014). Microgravity exposure during spaceflight beyond LEO presents challenges to the health, safety and performance of astronauts (Harding, Taylor, Takemoto, & Vargis, 2017). 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 & Stambaugh, 2015).

Exposure to microgravity during spaceflight results in deconditioning of human physiological systems due to the gravitational unloading of the body (Hargens, Bhattacharya, & Schneider, 2013). Physiological deconditioning may affect crew performance during spaceflight, impacting their capability to perform prolonged or strenuous tasks (Moore, Lee, Stenger, & Platts, 2010). These negative physiological outcomes may become amplified as a result of longer duration spaceflight beyond LEO (Kanas & Manzey, 2008), such as during transit periods to the Moon, Mars, and beyond (Williams et al., 2009).

The most frequently used countermeasure for physiological deconditioning is physical exercise (LeBlanc, Spector, Evans, & Sibonga, 2007). In order to reduce physiological deconditioning, it is necessary for astronauts to exercise for up to 2.5 hours per day, 6 days per week (seven days per week for ESA astronauts (Petersen et al., 2016)), including 60 minutes preparation time (Richter, Braunstein, Winnard, Nasser, & Weber, 2017). Current countermeasures are not individually capable of fully protecting the musculoskeletal and cardiovascular systems during long duration spaceflight (Hargens et al., 2013). For example, some astronauts experience more than a 20% reduction in muscle strength during spaceflight (Ploutz-Snyder, Ryder, English, Haddad, & Baldwin, 2015) and astronauts experience monthly bone loss of 1-2% on average (Rittweger, 2019) due to the inadequate effectiveness of current exercise countermeasures (Hargens et al., 2013). While other physiological systems are impacted by microgravity exposure, for example the vestibular system (Hallgren et al., 2015; Van Ombergen et al., 2017), it is unknown if these effects are attenuated by exercise countermeasures (Mulavara et al., 2018) and therefore are outside the scope of this review.

The Orion MPCV is the newest generation of capsular exploration class spacecraft that has been designed for missions beyond LEO (Thompson et al., 2014) of up to 21 days (Burns et al., 2013). A number of 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.

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 physiological deconditioning (Thompson et al., 2014). Currently there is no publically 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, up to 30 minutes of exercise per person, per 90 minutes (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 in this area 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 International Space Station (ISS) (Thompson et al., 2015), the multi-mission space exploration vehicle, and the lunar lander (Metcalf, Peterson, Carrasquillo, & Bagdigian, 2012).

The constraints of the MPCV and future spacecraft for long distance spaceflight present challenges to the use of current exercise countermeasures necessary to prevent deconditioning of the musculoskeletal and cardiovascular systems beyond LEO (Perusek et al., 2015). The evidence base of this field must be reviewed to determine the technical limitations of the MPCV and future exploration mission spacecraft, so that future research may be informed on the most effective exercise countermeasures against musculoskeletal and cardiovascular deconditioning with respect to the operational constraints of those vehicles on missions beyond LEO. 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 and physiological constraints of the MPCV and similar exploration 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 spacecraft.

The aim of this systematic review was to identify the technical constraints of the Orion MPCV or transferable spacecraft that will have an impact on the capability of astronauts to exercise effectively during spaceflight.

2. Material and Methods

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), the 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 to ensure that each search would capture the most relevant results possible. The full search strategy can be seen in Table 1.

Table 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. 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.

Table 2 Inclusion Criteria

Participants/**P**opulations	**I**ntervention/**I**nterest	**C**ontrol/**C**omparison	**O**utcome Measures	**S**tudy 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.

2.3. Study Selection and Data Extraction

The initial screening of documents, using abstracts and titles, was carried out by the lead author (JL) and a co-author (CM) using the Rayyan systematic review online application (Ouzzani, Hammady, Fedorowicz, & Elmagarmid, 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 and agreed upon with a third co-author (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 co-author (BW) to increase reliability. An additional academic colleague (CB) advised and assisted with the extraction of data from NVivo. Any disagreements were discussed until a consensus was reached.

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 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 & Winnard, 2019). 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 to 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 authors (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 third co-author (AW) was consulted.

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 & Clarke, 2006; Braun, Clarke, Hayfield, & Terry, 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 & Harden, 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).

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 (Figure 1). The final number of documents included in the review was 19 (see PRISMA diagram below).

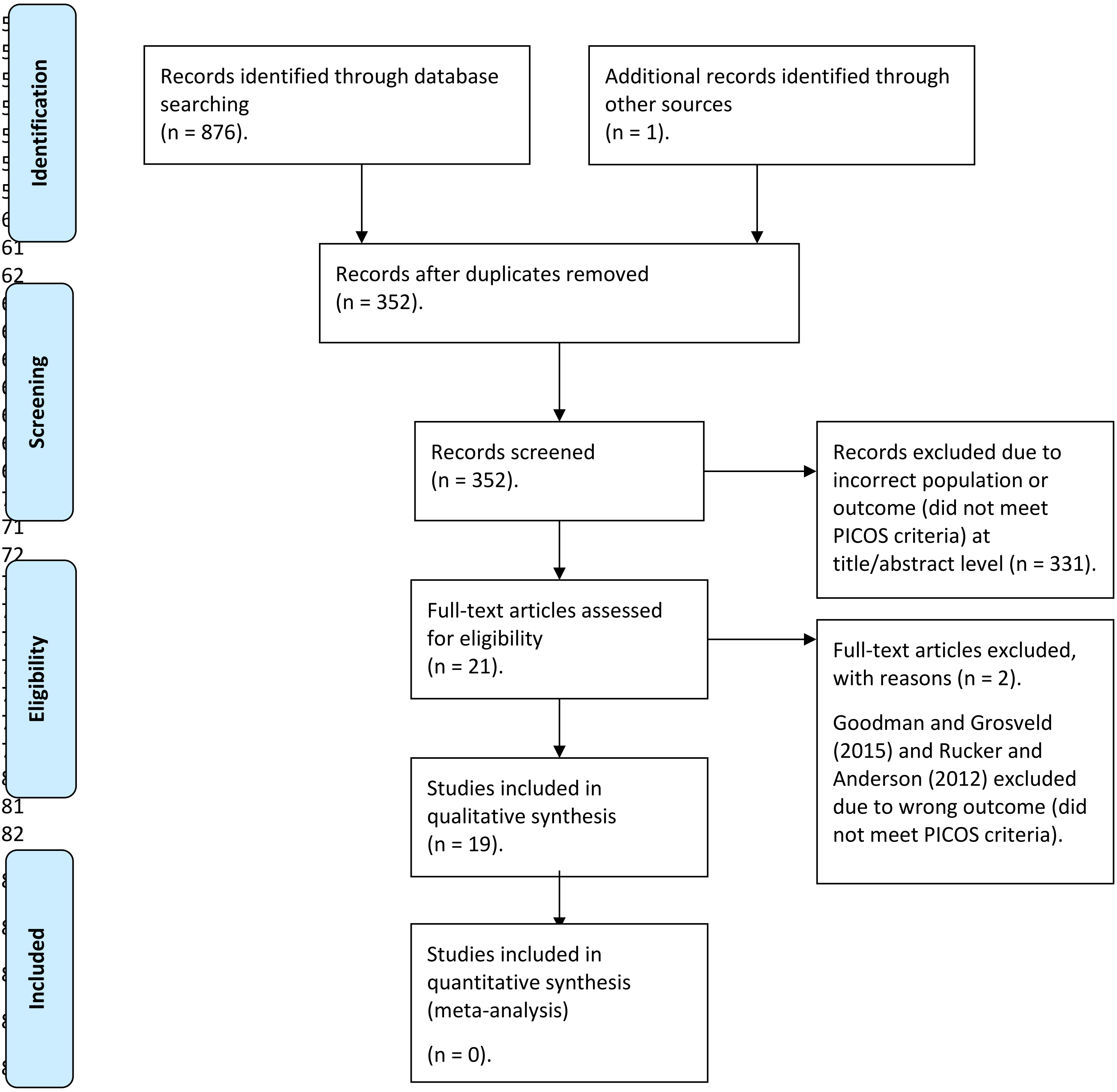

Figure 1 PRISMA flow diagram displaying search and screening results.

3.1. Characteristics of Included Documents

The characteristics of the included documents are summarised in Table 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 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

Author(s)	Document Type	Technical Constraint(s) Reported
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

Author(s)	Document Type	Technical Constraint(s) Reported
Buxton, Kalogera, and Hanson (2017)	Academic/Scientific Poster	Limited Volume of Spacecraft

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 (Thompson et al., 2014; Thompson et al., 2015) received the highest possible score of 4. Six documents received a score of 2 (De Witt et al., n.d; Downs et al., 2015; Funk et al., n.d; Moore et al., 2014; Ryder et al., 2016; Steinberg, 2015) and the remaining documents received a score of 1 (Buxton et al., 2017; Colosky, n.d; Downs et al., 2017; Downs, 2017; Gallo et al., 2016; Godfrey et al., 2017; Lewandowski et al., 2016; Moore, 2016; Perusek et al., 2015; Sheehan et al., 2016; Witt, 2016).

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 (Buxton et al., 2017; Colosky, n.d; Downs et al., 2017; Downs, 2017; Gallo et al., 2016; Godfrey et al., 2017; Lewandowski et al., 2016; Moore, 2016; Perusek et al., 2015; Sheehan et al., 2016; Witt, 2016). The highest score was 7 was met by two documents (Thompson et al., 2014; Thompson et al., 2015), with the remaining 6 documents (De Witt et al., n.d; Downs et al., 2015; Funk et al., n.d; Moore et al., 2014; Ryder et al., 2016; Steinberg, 2015) receiving a total score of 5. A summary of the overall quality scores for all documents can be seen in table 4.

Table 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.

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 5.

Table 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. Most of the included documents reported only qualitative data. Any quantitative data that was reported within the included documents is presented in Table 6.

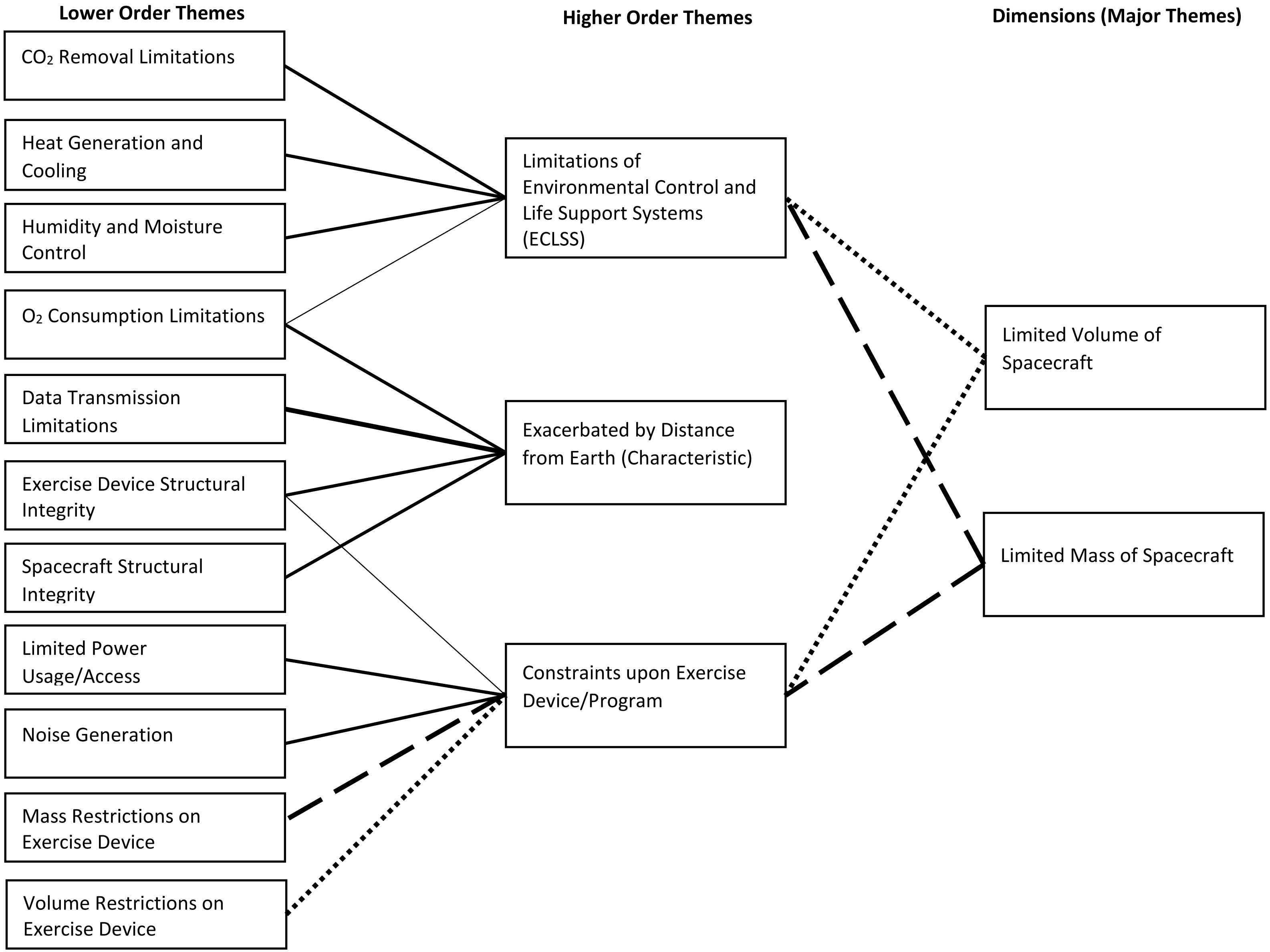

Figure 2 Thematic Map

Dotted lines indicate a relationship with “Limited Volume of Spacecraft”. Dashed lines indicate a relationship with “Limited Mass of Spacecraft”. The thickness of each line indicates the strength of the relationship between themes. “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 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 “gold standard” 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)

4. Discussion

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.

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 hours 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 smaller exploration mission 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 up 4.5 hours (270 minutes) in total (i.e. 3 x 90 minutes). Assuming the MPCV was carrying its maximum number of astronauts (four 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 hours, 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 must be limited to 30 minutes per 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.

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 typically use a restraint system, such as a harness or bungee that provides a force to keep astronauts attached to the exercise device (De Witt & Ploutz-Snyder, 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 “gold standard” 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 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 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) indicated 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 75000 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 program and raises concerns that exercise devices and programs 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.

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 programs (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 8760 litres of fluid for a crew of four.

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., 2018). 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.

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 6 in the results section summarised the quantitative data extracted from the included documents. Table 7 presents the predicted additional constraints based on the available information.

Table 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).

4.6. Space Agency Operational Insights

The discussion of this review has been based upon evidence from publically available grey literature and technical documents, however, personal communications with space agencies suggests 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 for 360 minutes 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 missions 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 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 usable 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.

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 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 is 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.

5. 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 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.

Funding

This research did not receive any specific grant or funding from funding agencies in the public, commercial, or not-for-profit sectors.

References

Allen, B., & Dubar, B. (2007). Human Needs: Sustaining Life During Exploration. Retrieved from https://www.nasa.gov/vision/earth/everydaylife/jamestown-needs-fs.html

Anderson, M. S., & Stambaugh, I. C. (2015). *Exploring Life Support Architectures for Evolution of Deep Space Human Exploration*.

Bahr, R., Ingnes, I., Vaage, O., Sejersted, O., & Newsholme, E. A. (1987). Effect of duration of exercise on excess postexercise O2 consumption. *Journal of applied physiology, 62*(2), 485-490.

Bahr, R., & Sejersted, O. M. (1991). Effect of intensity of exercise on excess postexercise O2 consumption. *Metabolism, 40*(8), 836-841.

Barber, J. R., Crooks, K. R., & Fristrup, K. M. (2010). The costs of chronic noise exposure for terrestrial organisms. *Trends in ecology & evolution, 25*(3), 180-189.

Barnett-Page, E., & Thomas, J. (2009). Methods for the synthesis of qualitative research: a critical review. *BMC medical research methodology, 9*(1), 59.

Bhasin, S., Storer, T. W., Berman, N., Callegari, C., Clevenger, B., Phillips, J., . . . Casaburi, R. (1996). The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. *New England Journal of Medicine, 335*(1), 1-7.

Braun, V., & Clarke, V. (2006). Using thematic analysis in psychology. *Qualitative research in psychology, 3*(2), 77-101.

Braun, V., Clarke, V., Hayfield, N., & Terry, G. (2019). Thematic analysis. *Handbook of Research Methods in Health Social Sciences*, 843-860.

Burns, J. O., Kring, D. A., Hopkins, J. B., Norris, S., Lazio, T. J. W., & Kasper, J. (2013). A lunar L2-farside exploration and science mission concept with the Orion Multi-Purpose Crew Vehicle and a teleoperated lander/rover. *Advances in space research, 52*(2), 306-320.

Buxton, R. E., Kalogera, K. L., & Hanson, A. M. (2017). The Evolution of Exercise Hardware on ISS: Past, Present, and Future.

Cichan, T., Norris, S. D., & Marshall, P. (2015). *Orion: EFT-1 flight test results and EM-1/2 status.* Paper presented at the AIAA SPACE 2015 Conference and Exposition.

Colosky, P. E. (n.d). The Constant Force Resistive Exercise Unit (CFREU) for Multi-Functional Exercise.

Connors, M. M., Harrison, A. A., & Akins, F. R. (1985). Living aloft: Human requirements for extended spaceflight.

Convertino, V. A., & Sandler, H. (1995). Exercise countermeasures for spaceflight. *Acta Astronautica, 35*(4-5), 253-270.

Crawford, J. (2016). Clinical results in cachexia therapeutics. *Current Opinion in Clinical Nutrition & Metabolic Care, 19*(3), 199-204.

Crawford, J., Prado, C. M., Johnston, M. A., Gralla, R. J., Taylor, R. P., Hancock, M. L., & Dalton, J. T. (2016). Study design and rationale for the phase 3 clinical development program of enobosarm, a selective androgen receptor modulator, for the prevention and treatment of muscle wasting in cancer patients (POWER trials). *Current oncology reports, 18*(6), 37.

Cuenca, E. M., & Crawford, C. L. (2011). Collaborative Center for Integrative Reviews and Evidence Summaries

(CCIRES). Retrieved from http://ccires.org/DLS/tools/CCIRES_Evidence_Leveling_System.pdf

Curley, S., Stambaugh, I., Swickrath, M., Anderson, M., & Rotter, H. (2012). *Deep space habitat ECLSS design concept.* Paper presented at the 42nd International Conference on Environmental Systems.

De la Torre, G. (2014). Cognitive neuroscience in space. *Life, 4*(3), 281-294.

De Witt, J. K., Caldwell, E. E., Fincke, R. S., Newby, N. J., & Scott- Pandorf, M. M. (n.d). Evaluation of Exercise Hardware for use in the Crew Exploration Vehicle (EORS_CEV).

De Witt, J. K., & Ploutz-Snyder, L. L. (2014). Ground reaction forces during treadmill running in microgravity. *Journal of biomechanics, 47*(10), 2339-2347.

Dillon, E. L., Sheffield-Moore, M., Durham, W. J., Ploutz-Snyder, L. L., Ryder, J. W., Danesi, C. P., . . . Urban, R. J. (2018). Efficacy of Testosterone plus NASA Exercise Countermeasures during Head-Down Bed Rest. *Medicine and science in sports and exercise, 50*(9), 1929 ‐ 1939. doi:10.1249/MSS.0000000000001616

Downs, M., Hanson, A., & Newby, N. (2015). Full body loading for small exercise devices project.

Downs, M., Kalogera, K., Newby, N., Fincke, R., DeWitt, J., Hanson, A., . . . Donnan, S. (2017). In-Flight Demonstration of the Miniature Exercise Device (MED-2).

Downs, M. E. (2017). Novel Musculoskeletal Loading and Assessment System.

Faget, M. A., Meyer, J. A. J., Chilton, R. G., Blanchard, J. W. S., Kehlet, A. B., Hammack, J. B., & Johnson, J. C. C. (1963).

Frechette, A. (August 07, 2019, 08/08/2019). [Personal Coummincation].

Funk, J., Perusek, G., Beleisath, S., Funk, N., Anderson, E., Kutnick, C., . . . Bruinsma, D. (n.d). Atlas (advanced twin lifting and aerobic system) development overview.

Gallo, C. A., Thompson, W. K., Lewandowski, B. E., & Jagodnik, K. M. (2016). Squat Biomechanical Modeling Results from Exercising on the Hybrid Ultimate Lifting Kit.

Gernand, J. M. (2004). Risk Assessment and Control through Countermeasure System Iplementation for Long-term Crew Exposure to Microgravity.

Gershon, R. R., Qureshi, K., Barrera, M., Erwin, M., & Goldsmith, F. (2005). Health and safety hazards associated with subways: a review. *Journal of Urban Health, 82*(1), 10.

Godfrey, A., Humphreys, B., Funk, J., Perusek, G., & Lewandowski, B. (2017). MPCV Exercise Operational Volume Analysis.

Goodman, J. R., & Grosveld, F. W. (2015). Acoustics and Noise Control in Space Crew Compartments.

Hallgren, E., Migeotte, P.-F., Kornilova, L., Delière, Q., Fransen, E., Glukhikh, D., . . . MacDougall, H. (2015). Dysfunctional vestibular system causes a blood pressure drop in astronauts returning from space. *Scientific Reports, 5*, 17627.

Hambleton, K. (2018). NASA's First Flight With Crew Important Step on Long-term Return to the Moon, Missions to Mars. Retrieved from https://www.nasa.gov/feature/nasa-s-first-flight-with-crew-important-step-on-long-term-return-to-the-moon-missions-to

Hardee, J. P., & Lynch, G. S. (2019). Current pharmacotherapies for sarcopenia. *Expert opinion on pharmacotherapy, 20*(13), 1645-1657.

Harden, A., Brunton, G., Fletcher, A., Oakley, A., Burchett, H., & Backhans, M. (2006). Young people, pregnancy and social exclusion: A systematic synthesis of research evidence to identify effective, appropriate and promising approaches for prevention and support.

Harden, A., Garcia, J., Oliver, S., Rees, R., Shepherd, J., Brunton, G., & Oakley, A. (2004). Applying systematic review methods to studies of people's views: an example from public health research. *Journal of Epidemiology & Community Health, 58*(9), 794-800.

Harding, C., Taylor, T., Takemoto, J., & Vargis, E. (2017). Comparison of alginate and microcarriers for in vitro modeling of microgravity-induced muscle atrophy.

Hargens, A. R., Bhattacharya, R., & Schneider, S. M. (2013). Space physiology VI: exercise, artificial gravity, and countermeasure development for prolonged space flight. *European journal of applied physiology, 113*(9), 2183-2192.

Jones, H. W., Hodgson, E. W., & Kliss, M. H. (2014). *Life Support for Deep Space and Mars*.

Jones, P. A., & Spence, B. R. (2011). Spacecraft solar array technology trends. *IEEE Aerospace and Electronic Systems Magazine, 26*(8), 17-28.

Kanas, N. (2013). From Earth's orbit to the outer planets and beyond: Psychological issues in space. In *On Orbit and Beyond* (pp. 285-296): Springer.

Kanas, N., & Manzey, D. (2008). *Space psychology and psychiatry* (Vol. 22): Springer Science & Business Media.

Kanas, N., Sandal, G., Boyd, J., Gushin, V., Manzey, D., North, R., . . . Fiedler, E. (2009). Psychology and culture during long-duration space missions. *Acta Astronautica, 64*(7-8), 659-677.

Laforgia, J., Withers, R. T., & Gore, C. J. (2006). Effects of exercise intensity and duration on the excess post-exercise oxygen consumption. *Journal of sports sciences, 24*(12), 1247-1264.

Lane, H. W., & Feeback, D. L. (2002). Water and energy dietary requirements and endocrinology of human space flight. *Nutrition, 18*(10), 820-828.

Laws, J., & Winnard, A. (2019). *Tool for Scoring the Quality of Non-Empirical Data Sources- E.G: Technical Reports*.

LeBlanc, A. D., Spector, E. R., Evans, H. J., & Sibonga, J. D. (2007). Skeletal responses to space flight and the bed rest analog: a review. *Journal of Musculoskeletal and Neuronal Interactions, 7*(1), 33.

Lewandowski, B., Jagodnik, K., Crentsil, L., Humphreys, B., Funk, J., Gallo, C., . . . Perusek, G. (2016). Supplementing biomechanical modeling with EMG analysis.

Loehr, J. A., Guilliams, M. E., Petersen, N., Hirsch, N., Kawashima, S., & Ohshima, H. (2015). Physical training for long-duration spaceflight. *Aerospace medicine and human performance, 86*(12), A14-A23.

McGregor, C. (2013). *A platform for real-time online health analytics during spaceflight.* Paper presented at the 2013 IEEE Aerospace Conference.

Metcalf, J., Peterson, L., Carrasquillo, R., & Bagdigian, R. (2012). *National Aeronautics and Space Administration (NASA) Environmental Control and Life Support (ECLS) Integrated Roadmap Development.* Paper presented at the 42nd International Conference on Environmental Systems.

Monzani, D., Galeazzi, G. M., Genovese, E., Marrara, A., & Martini, A. (2008). Psychological profile and social behaviour of working adults with mild or moderate hearing loss. *Acta Otorhinolaryngologica Italica, 28*(2), 61.

Moore, A. D., Lee, S. M., Stenger, M. B., & Platts, S. H. (2010). Cardiovascular exercise in the US space program: past, present and future. *Acta Astronautica, 66*(7-8), 974-988.

Moore, C. (2016). Planning for Crew Exercise for Exploration Mission Scenarios.

Moore, C., Howard, R. L., & Mendeck, G. (2014). *Human Health/Human Factors Considerations in Trans-Lunar Space.* Paper presented at the SpaceOps 2014 Conference.

Morphew, M. E. (2001). Psychological and human factors in long duration spaceflight. *McGill Journal of Medicine, 6*(1), 74-80.

Mulavara, A. P., Peters, B. T., Miller, C. A., Kofman, I. S., Reschke, M. F., Taylor, L. C., . . . Lee, S. M. (2018). Physiological and functional alterations after spaceflight and bed rest. *Medicine and science in sports and exercise, 50*(9), 1961.

Muta, Y., Tanaka, T., Hamaguchi, Y., Hamanoue, N., Motonaga, R., Tanabe, M., . . . Yanase, T. (2019). Selective androgen receptor modulator, S42 has anabolic and anti-catabolic effects on cultured myotubes. *Biochemistry and biophysics reports, 17*, 177-181.

Neil, D., Clark, R. V., Magee, M., Billiard, J., Chan, A., Xue, Z., & Russell, A. (2018). GSK2881078, a SARM, produces dose-dependent increases in lean mass in healthy older men and women. *The Journal of Clinical Endocrinology & Metabolism, 103*(9), 3215-3224.

Ouzzani, M., Hammady, H., Fedorowicz, Z., & Elmagarmid, A. (2016). Rayyan—a web and mobile app for systematic reviews. *Systematic reviews, 5*(1), 210.

Palinkas, L. A. (2007). Psychosocial issues in long-term space flight: overview. *Gravitational and Space Research, 14*(2).

Perusek, G., Lewandowski, B., Nall, M., Norsk, P., Linnehan, R., & Baumann, D. (2015). Human Research Program Advanced Exercise Concepts (AEC) Overview.

Petersen, N., Jaekel, P., Rosenberger, A., Weber, T., Scott, J., Castrucci, F., . . . Kozlovskaya, I. (2016). Exercise in space: the European Space Agency approach to in-flight exercise countermeasures for long-duration missions on ISS. *Extreme physiology & medicine, 5*(1), 9.

Phillipson, E. A., Bowes, G., Townsend, E. R., Duffin, J., & Cooper, J. (1981). Role of metabolic CO2 production in ventilatory response to steady-state exercise. *The Journal of clinical investigation, 68*(3), 768-774.

Ploutz-Snyder, L., Ryder, J., English, K., Haddad, F., & Baldwin, K. (2015). Risk of impaired performance due to reduced muscle mass, strength, and endurance (HRP-47072). *Retrieved from Houston, TX*.

QSR NVivo 12. (2014). NVivo qualitative data analysis software; QSR International Pty Ltd. In: Version.

Raimondi, N. (August 23, 2019).

Reddy, S. Y., Iatauro, M. J., Kürklü, E., Boyce, M. E., Frank, J. D., & Jónsson, A. K. (2008). *Planning and monitoring solar array operations on the ISS.* Paper presented at the Proc. Scheduling and Planning App. Workshop (SPARK), ICAPS.

Rehman, S., Bader, M. A., & Al-Moallem, S. A. (2007). Cost of solar energy generated using PV panels. *Renewable and sustainable energy reviews, 11*(8), 1843-1857.

Richter, C., Braunstein, B., Winnard, A., Nasser, M., & Weber, T. (2017). Human biomechanical and cardiopulmonary responses to partial gravity–a systematic review. *Frontiers in physiology, 8*, 583.

Rittweger, J. (2019). Maintaining Crew Bone Health. *Handbook of Life Support Systems for Spacecraft and Extraterrestrial Habitats*, 1-15.

Robinson, K. A., Saldanha, I. J., & Mckoy, N. A. (2011). Development of a framework to identify research gaps from systematic reviews. *Journal of clinical epidemiology, 64*(12), 1325-1330.

Rucker, M. A., & Anderson, M. (2012). Issues and design drivers for deep space habitats.

Russell, C. L. (2005). An overview of the integrative research review. *Progress in transplantation, 15*(1), 8-13.

Ryder, J. W., Scott, J., Ploutz-Snyder, R., & Ploutz-Snyder, L. L. (2016). Sweat Rates During Continuous and Interval Aerobic Exercise: Implications for NASA Multipurpose Crew Vehicle (MPCV) Missions.

Schaezler, R. N., & Cook, A. J. (2015). *Report on ISS O2 Production, Gas Supply & Partial Pressure Management*.

Scott, J. P., Weber, T., & Green, D. A. (2019). Introduction to the Frontiers Research Topic: Optimization of Exercise Countermeasures for Human Space Flight–Lessons From Terrestrial Physiology and Operational Considerations. *Frontiers in physiology, 10*.

Sheehan, C., Funk, J., Funk, N., Kutnick, G., Humphreys, B., Bruinsma, D., & Perusek, G. (2016). Closed Loop Control Compact Exercise Device for Use on MPCV.

Solomon, Z. J., Mirabal, J. R., Mazur, D. J., Kohn, T. P., Lipshultz, L. I., & Pastuszak, A. W. (2018). Selective androgen receptor modulators: current knowledge and clinical applications. *Sexual medicine reviews*.

SpaceX. (2017). Making Life Multiplanetary. Retrieved from https://www.spacex.com/mars

Steinberg, S. (2015). 2015 Bone and Muscle Risks Standing Review Panel.

Tambs, K. (2004). Moderate effects of hearing loss on mental health and subjective well-being: results from the Nord-Trøndelag Hearing Loss Study. *Psychosomatic medicine, 66*(5), 776-782.

Thomas, J., & Harden, A. (2008). Methods for the thematic synthesis of qualitative research in systematic reviews. *BMC medical research methodology, 8*(1), 45.

Thomas, J., Kavanagh, J., Tucker, H., Burchett, H., Tripney, J., & Oakley, A. (2007). Accidental injury, risk-taking behaviour and the social circumstances in which young people (aged 12-24) live: a systematic review.

Thomas, J., Sutcliffe, K., Harden, A., Oakley, A., Oliver, S., Rees, R., . . . Kavanagh, J. (2003). Children and healthy eating: a systematic review of barriers and facilitators. In *Database of Abstracts of Reviews of Effects (DARE): Quality-assessed Reviews [Internet]*: Centre for Reviews and Dissemination (UK).

Thompson, W. K., Caldwell, E. E., Newby, N. J., Humphreys, B. T., Lewandowski, B. E., Pennline, J. A., . . . Mulugeta, L. (2014). *Integrated Biomechanical Modeling of Lower Body Exercises on the Advanced Resistive Exercise Device (ARED) Using LifeMOD®*.

Thompson, W. K., Gallo, C. A., Crentsil, L., Lewandowski, B. E., Humphreys, B. T., DeWitt, J. K., . . . Mulugeta, L. (2015). Digital Astronaut Project Biomechanical Models: Biomechanical Modeling of Squat, Single-Leg Squat and Heel Raise Exercises on the Hybrid Ultimate Lifting Kit (HULK).

Van Ombergen, A., Demertzi, A., Tomilovskaya, E., Jeurissen, B., Sijbers, J., Kozlovskaya, I. B., . . . Laureys, S. (2017). The effect of spaceflight and microgravity on the human brain. *Journal of neurology, 264*(1), 18-22.

Whittemore, R., & Knafl, K. (2005). The integrative review: updated methodology. *Journal of advanced nursing, 52*(5), 546-553.

Wieland, P. (1994). Designing for human presence in space: an introduction to environmental control and life support systems.

Williams, D., Kuipers, A., Mukai, C., & Thirsk, R. (2009). Acclimation during space flight: effects on human physiology. *Cmaj, 180*(13), 1317-1323.

Winnard, A., Debuse, D., Wilkinson, M., Parmar, A., Schuren, T., & Caplan, N. (2019). Effect of time on biomechanics during exercise on the functional re-adaptive exercise device. *Journal of sports sciences*, 1-6.

Winnard, A., Nasser, M., Debuse, D., Stokes, M., Evetts, S., Wilkinson, M., . . . Caplan, N. (2017). Systematic review of countermeasures to minimise physiological changes and risk of injury to the lumbopelvic area following long-term microgravity. *Musculoskeletal Science and Practice, 27*, S5-S14.

Winnard, A., Scott, J., Waters, N., Vance, N., & Caplan, N. (2019). (in press). Effect of time on human muscle outcomes during simulated microgravity exposure without countermeasures – systematic review. *Frontiers in Physiology – Environmental, Aviation and Space Physiology*.

Witt, E. G. (2016). Introduction to Human Systems Integration (HSI).