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Review Article

The effect of bed rest on balance control in healthy adults: A systematic scoping review

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Abstract

The objective of this study was to determine the effect of bed rest on balance control and the mechanisms responsible for these changes. Searches were conducted in six databases. Studies had to be conducted on healthy adults who were subjected to bed rest (≥5 days), with balance control measures obtained before and after bed rest in order to be included. Risk of bias was assessed using the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. After screening 9,785 articles, 18 were included for qualitative synthesis. Fifteen studies found decrements in at least one balance control measure following bed rest, either compared to baseline or controls, with eight studies observing impairments in >50% of their balance control measures. Of the 14 studies that included an intervention, four (mechanical stimuli, lower-body negative pressure, and training targeting strength, balance and/or aerobic capacity) successfully offset the majority of balance control deficits and targeted the musculoskeletal and cardiovascular systems. The findings of this review support bed rest negatively affecting balance control in healthy individuals. In clinical populations, these deficits may be further accentuated due to various comorbidities that impact balance control systems. PROSPERO Registration: CRD42018098887.

Keywords: Balance, Bed Rest, Disuse, Microgravity, Postural Control

Introduction

Bed rest is a frequently used intervention for critically ill patients and has also been used to simulate microgravity to understand the physiological consequences of space flight. Both clinical and experimental bed rest result in various physiological sequalae which can be detrimental to one's functioning. With a lack of gravitational pull and reduced physical activity, declines in muscle cross-sectional area can be observed in as little as five days into bed rest[1], declining at a rate of ~3% per week in major lower limb musculature[2]. A lack of sensory stimulation further results in the reweighting of vestibular[3] and potentially tactile[4] information. Taken together, these physiological consequences following bed rest are of concern for return to daily activity and may impact balance and mobility.

Balance control is a complex process that involves the integration of various inputs and systems, enabling one to stay upright by controlling the relationship between the centre of mass and base of support[5]. Deficits in the sensorimotor subsystems involved in controlling balance observed in the elderly such as decreases in strength, sensory reweighting, and altered perceptual orientation have been shown to impair balance control and consequently increase the risk of falls[6]. These changes to sensorimotor resources are also altered following bed rest. For example, orthostatic intolerance is a common consequence of one's altered orientation in space following bed rest whereby moving to an upright posture causes light-headedness or fainting. This is a result of a combination of cardiovascular and autonomic changes from bed rest such as decreased baroreflex sensitivity and difficulty adjusting peripheral resistance[7–9]. As mentioned

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earlier, lower limb musculature has been shown to atrophy and become weaker following even brief exposure to bed rest. Previous work has also demonstrated a strong relationship between lower limb strength, gait, and balance[10]. Additionally, a lack of sensory information during bed rest results in maladaptive brain activation and delayed sensory reflexes when testing the vestibular and sensorimotor systems[3,4,11]. While bed rest has been shown to affect these systems that control balance individually, the global influence of bedrest on balance control itself remains unclear.

Many bed rest studies have aimed to identify countermeasures that can counteract the physiological deficits that occur as a result of inactivity. One of the most commonly targeted systems is the musculoskeletal system; to offset loss of muscle mass and strength following bed rest, exercise interventions are frequently employed. Recommendations for exercise involve targeting the muscle groups in the back and lower limb with a gradual, progressive load[12]. Exercise, particularly resistance exercise, has also been recommended to attenuate bone loss induced by bed rest[13]. Other common interventions implemented to counteract balance control deficits during or following bed rest include standing[14], lower-body negative pressure[15], centrifugation[16], mechanical stimuli such as vibratory input to the soles of the feet[17], and pharmacological or nutritional supplements[18]; however, there has been no consensus on which of these countermeasures are most effective.

Physiological consequences to bed rest have been reviewed[12,19–22] and there is evidence that systems responsible for balance control are altered following bed rest. However, the literature investigating how balance, being influenced by multiple physiological systems, is affected by bed rest and bed rest countermeasures has not been thoroughly or systematically discussed. The overall objective of this study was to understand the impact of bed rest on balance control and the mechanisms responsible for these changes. Specifically, this systematic scoping review addressed the following research questions: (1) what outcome measures, bed rest models, and countermeasures have been previously used in the context of balance control following bed rest in healthy adults; (2) what is the effect of bed rest on balance control; and (3) what are the mechanisms that are responsible for balance control deficits following bed rest?

Materials and methods

Search strategy

The protocol for this systematic scoping review has been registered in PROSPERO (Registration # CRD42018098887). A research librarian advised search methods and assisted in the development of the search strategy. A search strategy was initially developed for MEDLINE (Supplement A) with all subsequent search strategies tailored to each database. Journal articles were searched in the following databases from inception to July 29, 2019, with the first search conducted on May 31, 2018: Ovid MEDLINE; Ovid Embase; Ovid Allied and Complementary Medicine (AMED); EBSCO Cumulative Index to Nursing and Allied Health Literature (CINAHL); SPORTDiscus; and Cochrane Library. On July 29, 2019 the same searches were run to update the articles included in the study. Articles were deduplicated against those found in the original search. Study selection and screening then continued as described in the subsequent section.

Study selection & screening

Records identified following database searching were uploaded into EndNote (EndNote X8, Clarivate Analytics, Philadelphia, United States) and were de-duplicated. Studies were included in the review if they met the following criteria: (1) included healthy human subjects aged 18 years or older with no reported medical conditions, (2) involved consecutive bed rest for a minimum of five days, (3) included balance control measures taken before and after bed rest, (4) had abstract and full-text available in English, and (5) were published in a peer-reviewed journal. Articles that met these criteria were included regardless of their implemented bed rest features, such as bed positioning or activity restriction, to maximize the number of included articles to broaden the scope of articles to be discussed. Articles were excluded if the study population involved individuals who had previously experienced spaceflight (e.g., astronauts) or were confined to bed rest due to medical conditions. Study titles and abstracts were imported into Microsoft Excel for initial screening following deduplication. Two reviewers (TS and SG) independently screened and selected relevant studies to include for full-text review based on the inclusion criteria. When disagreement between the two reviewers occurred, a third team member (GM) was consulted to reach consensus. In the second stage of screening, the same two reviewers independently read the full-text articles of all potentially relevant studies which were included in the first stage to confirm eligibility for inclusion in the review. If an article was not selected, a reason was provided based on one of the five inclusion criteria. If the article could be excluded for multiple reasons, the first criteria it failed to meet based on the PRISMA diagram (Figure 1) was chosen. Once the included full-text articles had been selected, Scopus was searched for articles that referenced, or were referenced by, the initially included articles. Subsequent title/abstract screening and full-text screening were performed on these articles using the methods outlined earlier. Data extraction and quality assessment were then completed on the included articles.

Quality assessment

Methodological quality of the included studies was independently assessed by both reviewers (TS and SG) using the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (for pre-post studies)[23], with discrepancies being resolved by consensus. This tool was used across all studies as pre-post measures were required

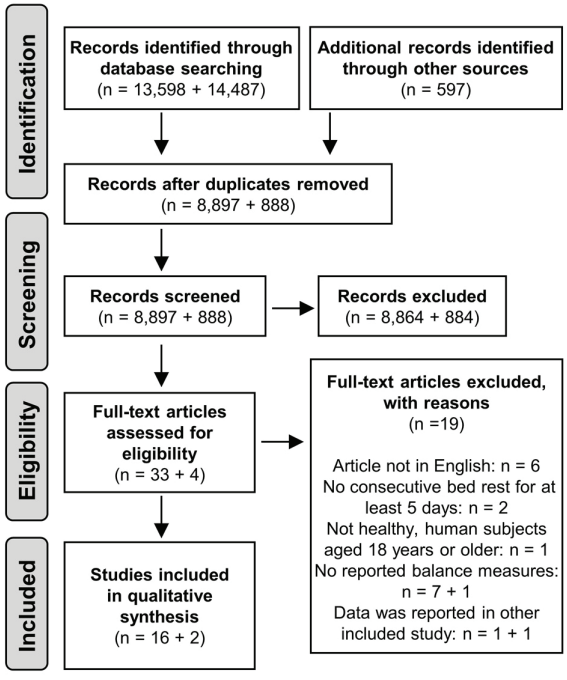

Figure 1. PRISMA diagram outlining selection process for included studies. All sections include original (May 2018) + updated (July 2019) search results.

to be included within the review and were the main outcomes of interest. Thus, the items found in the scale specifically addressed the aspects of quality that were of interest in the context of this review. The Quality Assessment Tool contained 12 questions with a Yes/No response for each question, as well as an "other" category for "cannot determine, not reported, or not available." The 12 questions in the quality assessment tool helped guide reviewers to consider key concepts aimed at evaluating internal validity; however as suggested by the developers of the scale, they were not used to create or assign a score to the study[23]. Studies were rated as good, fair, or poor and assessed based on the details reported and the concepts for minimizing bias considered. As defined by the tool, studies rated as "good" had a low risk of bias and results were considered valid. Studies rated as "fair" were considered susceptible to bias, but such that the validity of results were not compromised. Conversely, "poor" studies contained a significant risk of bias and the validity of the results were questioned[23]. No articles were excluded from the review based on the quality rating.

Data extraction & analysis

Data were extracted using a standardized and piloted data extraction form developed by the investigators. Data extracted included the following: (1) year and country of publication, (2) study design, (3) timing of outcome measures, (4) sample description (e.g., inclusion criteria, age, sex), (5) bed rest characteristics described (e.g., bed rest length, bed position, bed rest continuity), (6) interventions/countermeasures, (7) primary and secondary outcome measures, (8) authors' main conclusions, (9) limitations, and (10) any other relevant information. Due to the heterogeneity of study methodologies, the studies were grouped based on the proportion of balance control measures showing impairment (defined as significantly different at some time point following bed rest) using the following categories (1) studies that found 0 balance control measures impaired, (2) studies that had ≤50% of balance control measures impaired, and (3) studies that had >50% of balance control measures impaired. This was done to account for studies that reported a large number of balance control measures which would increase the likelihood of observing at least one impaired balance control measure. The most conservative statistical inferences reported (i.e., alpha adjusted for multiple comparisons) were used to determine these criteria. The study results were also described qualitatively.

Results

Selection of studies

A total of 13,598 articles were identified from the six databases during the original search in May 2018 and 888 new articles were found following the repeated search in July 2019. An additional 597 articles were found from the articles that referenced, or were referenced by, the initially included articles. The PRISMA flow diagram[24] of the article inclusion process through both searches is shown in Figure 1. In brief, 9,785 titles and abstracts were screened after duplicates were removed, with 37 articles accepted for full-text review. Following full-text review, 19 papers were included for data extraction and qualitative synthesis. Two of the articles, by Paloski and colleagues (2017)[25] and Reschke and colleagues (2017)[26] reported on the same study sample and balance control measures thus, data were only extracted from Paloski et al. (2017).

Study characteristics and participant demographics

Studies were conducted in five countries: France (n=3), Germany (n=2), Japan (n=3), Slovenia (n=3), and the United States (n=7). Descriptive details regarding the demographics of study participants are presented in Table 1. The mean age of participants based on 16 studies was 33.2 years (pooled standard deviation: 3.8 years). Two of the studies[15,25] did not report the mean age of participants, but the age range of the participants in these studies was 26-38 years of age. With respect to sex of the participants, 84.2% of participants in the included studies were men; 14 of the 18 studies exclusively studied men, whereas one study only examined women, and the remaining three studies had both male and female participants of approximately equal proportions. The number of participants in each study ranged from 4 to 30, with the mean number of participants who underwent bed rest in each study being 13.7 (standard deviation (SD):7.1).

Table 1. Descriptive details regarding the location and participants of the included studies (listed from most to least days in bed).

Reference	Location	Sample Size and Groups	Age, mean years(SD)	Sex (M/F)
Muir et al., 2011[29]	United States	Experimental bed rest: 17 Bed rest control: 13	35.6(7.1) 34.7(7.9)	11/6 8/5
Miller et al., 2018[38]	United States	Experimental bed rest: 9 Bed rest control: 10	33.8(5.5) 37.7(7.2)	9/0 10/0
Koppelmans et al., 2015[11]	United States	Experimental bed rest: 5 Active control: 9 Bed rest control: 5	32.1(4.5) 39.1(8.7) 33.7(5.4)	5/0 9/0 5/0
Koppelmans et al., 2017[33]	United States	Bed rest: 18 Active control: 12	41.4(9.9) 31.1(4.7)	18/0 12/0
Ritzmann et al., 2018[27]	Germany	Experimental bed rest: 12 Bed rest control: 11	30.0(7) 28.0(6)	12/0 11/0
Viguier et al., 2009[18]	France	Experimental bed rest (exercise): 8 Experimental bed rest (nutrition): 8 Bed rest control: 8	33.0(1.0) 29.0(1.0) 34.0(1.0)	0/8 0/8 0/8
Reschke et al., 2009[4]	United States	Bed rest: 13 (8 completed balance tasks)	35.9(9.6)	8/5
Dupui et al., 1992[15]	France	Bed rest: 5	28-36(range)	5/0
Šarabon et al., 2018[32]	Slovenia	Bed rest: 14	26.0(5.0)	14/0
Paloski et al., 2017[25]	United States	Experimental bed rest: 8 Bed rest control: 7	26-38(range)	8/0 7/0
Kouzaki et al., 2007[28]	Japan	Experimental bed rest: 6 Bed rest control: 6	22.7(2.9) 23.3(4.9)	6/0 6/0
Miyoshi et al., 2001[35]	Japan	Bed rest: 4	29.0(6.8)	4/0
Morishima et al., 1997[37]	Japan	Bed rest: 10	20.4(NR)	5/5
Haines, 1974[34]	United States	Bed rest: 7 Active control: 7	20.4(1.3) 20.0(0.8)	7/0 7/0
Šarabon & Rosker, 2013[30]	Slovenia	Bed rest: 16	59.6(3.4)	16/0
Šarabon & Rosker, 2015[31]	Slovenia	Bed rest: 16	59.6(3.4)	16/0
Mulder et al., 2014[14]	Germany	Bed rest: 10	29.4(5.9)	10/0
Clément et al., 2015[36]	France	Bed rest: 10	34.2(2.1)	10/0
NR=not reported, Active controls were not subject to bed rest and maintained normal daily activity				

Quality assessment

A summary of the quality ranking for the included studies is presented in Supplement B. Four studies were given a rating of "good," nine studies were rated as "fair," and five studies rated as "poor." Justification of sample size was absent in all but one study[27] and inclusion criteria were only explicitly stated in eight articles[4,25,27–32]. Bed rest length, bed positioning and countermeasures were largely described with adequate detail. Regarding study implementation, there was a lack of reporting with respect to bed rest continuity and the restrictions placed on participants in terms of activities of daily living such as bathing and toileting. In addition, for studies with multiple measurement time points before and after bed rest, there was often ambiguous rationale for the time points used for analysis, with all time points not always being considered in the statistical analyses[4,11,33]. Inappropriate statistical analyses based on the study design, failure to mention statistical tests performed, and the pooling of participants that received different interventions was also found in multiple studies[33–36].

Bed rest methodology and countermeasures

Study design details are presented in Table 2. Five of the studies used a crossover design[14,15,32,34,36], four studies[30,31,35,37] implemented a longitudinal pre-post design, and nine studies conducted a randomized experimental study with pre-post measures[4,11,18,27–29,33,38]. Three studies[14,18,34] did not provide explicit details regarding the participants' conformity to bed rest. Other studies generally confined participants to continuous bed rest positioning during daily tasks (e.g., bathing or using the bathroom), and allowed them to roll into different postures and support their heads during eating. Only three studies[11,33,34] implemented an active control group that did not participate in bed rest to account for any natural variability in the collected measures. In contrast, other studies[4,18,25,27,38] took measures on multiple days prior to bed rest to account for potential learning effects and natural variability in the balance control measures.

The median bed rest length across all studies was 21 days (interquartile range (IQR): 49 days). The majority of studies used 6° head-down tilt (HDT; n=13/18), while the others used

Reference	Bed Rest Length (Days)	Bed Rest Conformity	Bed Orientation	Description of Countermeasure	Study Design
Muir et al., 2011[29]	90	All daily function performed in HDT except Day 60 measures	6° HDT	*Low magnitude mechanical signals* delivered via foot-based vibration platform providing a 30Hz sinusoidal vibration for 10 min/day	Pre-post with bed rest and experimental bed rest groups
Miller et al., 2018[38]	70	In HDT except for propping head during eating and vertical treadmill sessions	6° HDT	*Resistance training* (squats, heel raises, leg press and hamstring curls): 3 sets for 3 times per week, with final set to failure; *continuous aerobic exercise* (cycle ergometer at ~75% peak VO_2): 3 times per week for 30 min; high *intensity interval training* (near peak VO_2 on vertical treadmill with axial unloading: 3 times per week for 15-35 minutes depending on day	Pre-post with bed rest and experimental bed rest groups
Koppelmans et al., 2015[11]	70	Participants remained in HDT except for 30 minutes head propping during meals	6° HDT	*Resistance training* (squats, heel raises, leg press and hamstring curls): 3 times per week for 35-60min; *continuous aerobic exercise* (cycle ergometer/treadmill at >75% peak VO_2): 3 times per week for 30 min; *high intensity interval training* (between 70-100% peak VO_2 on cycle ergometer/ treadmill: 3 times per week for 15-35 minutes depending on day	Pre-post with active control
Koppelmans et al., 2017[33]	70	Participants remained in HDT except for 30 minutes head propping during meals	6° HDT	*Supine exercise* with different equipment, group was pooled with bed rest control for analysis	Pre-post with active control
Ritzmann et al., 2018[27]	60	Participants were confined to 24-hour HDT for all daily tasks		*Resistance training* (plyometric jumping): performed ~ 78 jumps/hops in the horizontal plane over 48 training sessions lasting 3 min	Pre-post with bed rest and experimental bed rest groups
Viguier et al., 2009[18]	60	NR	6° HDT	*Resistance training* (lower limb inertial ergometer): every 3 days for 19 session; *supine treadmill walking* (performed in lower-body negative pressure box at -55mmHg): 29 sessions for 40 min with 10 min of lower-body negative pressure alone OR *additional protein* at 1.45g/kg	Pre-post with bed rest and experimental bed rest groups
Reschke et al., 2009[4]	42-90	Could lie in prone, supine or lateral; head elevation for 30 minutes/meal	6° HDT	NA	Pre-post
Dupui et al., 1992[15]	30	Could not raise head from plane of bed, but could perform lateral movement and roll	6° HDT	*Lower-body negative pressure* (-28 mmHg): 1-2 hours/day	Pre-post crossover
Šarabon et al., 2018[32]	21	All daily tasks were performed in horizontal lying	Horizontal	*Hypoxia* (90mmHg): constant OR *ambulatory hypoxia* (90mmHg and upright standing activating to mimic daily activity): feet had to be on ground in sitting or standing through the day	Pre-post crossover
Paloski et al., 2017[25]	21	Strict HDT	6° HDT	*Centrifugation* (1-g): 1 hour/day	Pre-post with bed rest and experimental bed rest groups
Kouzaki et al., 2007[28]	20	Prohibited from weight-bearing posture	6° HDT	*Bilateral leg press and bilateral calf raise* (5 sets of 10 reps and 60s rest at 70% max isometric force): 16/20 days of bed rest, not in HDT	Pre-post with bed rest and experimental bed rest groups
Miyoshi et al., 2001[35]	20	NR	6° HDT	NA	Pre-post
Morishima et al., 1997[37]	20	Participants spent around 30 minutes/day in wheelchair	Horizontal	NA	Pre-post
Haines, 1974[34]	14	NR	Horizontal*	*Isotonic exercise* (bicycle ergometer at 60% relative load): 1 hour/day OR *Isometric leg* exercise (25% max MVC): 1 hour/day	Pre-post crossover with active control
Šarabon & Rosker, 2013[30]	14	Reduced deviations from horizontal lying to a minimum, also during showering and toileting	Horizontal	Dynamic warm-up, 4 *strength exercises, balance training* and 30 min Nordic walking: 3 times/week for 14 days post-bed rest	Pre-post with bed rest and experimental bed rest groups
Šarabon & Rosker, 2015[31]	14	Reduced deviations from horizontal lying to a minimum, also during showering and toileting	Horizontal	Dynamic warm-up, 6 *strength exercises*, 4 *balance exercises, Nordic walking* and breathing cool down: 3 times/week for 14 days post-bed rest	Pre-post with bed rest and experimental bed rest groups
Mulder et al., 2014[14]	5	NR	6° HDT	*Standing* (stance beside bed, no activity) : 25 min/ day, *Locomotion replacement training* (heel raise and squat with 15 kg resistance, reactive jumps for 3 min): 25 min/day	Pre-post crossover
Clément et al., 2015[36]	5	Placed in horizontal lying for 1 hour, otherwise in 6° HDT	6° HDT	*Centrifugation* (1-g): Daily for continuous 30 min period (Group 1) OR daily for 6 periods of 5 mins (Group 2)	Pre-post crossover

** study was conducted before the study of 6° HDT but doesn't explicitly mention that bed rest was performed in horizontal; HDT=head-down tilt.*

Table 3. Summary of the effects of bed rest and countermeasures on balance control.

Reference, Bed Rest Length, Countermeasure	Balance control measures	Number of balance control measures significantly affected by bed rest for each condition	Number of affected balance control measures offset by countermeasure
Muir et al., 2011[29] 90 days Low magnitude mechanical signals	(1-2) Peak AP + ML COP displacement, (3) Peak AP COP velocity†, (4-5) AP + ML RMS COP displacement, (6) AP RMS velocity, (7) Mean COP velocity, (8-10) Low, Mid + High Frequency, (11) Stabilogram diffusion analysis	EO: 1/8* EC: 10/11	EC: 5/8
Miller et al., 2018[38] 70 days Aerobic/resistance training	(1) Postural settling time† (2) Mean COP sway speed† (3) Equilibrium score† (4) Tandem walk parameter†	Prone to standing: 1/1* Jump down test:1/1 EO: 1/1 Surface sway reference EC: 1/1 Tandem walk: 1/1	Prone to standing: 0/1 Jump down test:1/1 EO: 0/1 Surface sway reference EC: 0/1 Tandem walk: 0/1
Koppelmans et al., 2015[11] 70 days Aerobic/resistance training	Equilibrium score	EC w/ head erect: 0/1 EC w/ head pitch: 1/1	EC w/ head erect: 0/ EC w/ head pitch: 0/1
Koppelmans et al., 2017[33] 70 days Exercise (CD)	Equilibrium score	EC w/ head erect: 0/1 EC w/ head pitch: 1/1	EC w/ head erect: CD EC w/ head pitch: CD
Ritzmann et al., 20182[7] 60 days Resistance training	(1-4) AP + ML Centre of force displacement and velocity†, (5) Dominant frequency†, (6) Standard ellipse area†, (7) EMG co-contraction index†	Force plate measures EO:6/6* Force plate measures EC: 5/6 EMG measures EO: 4/4 EMG measures EC: 4/4	Force plate measures EO:6/6 Force plate measures EC: 5/5 EMG measures EO: 4/4 EMG measures EC: 4/4
Viguier et al., 2009[18] 60 days Aerobic/resistance training	COP displacement length†	Static EO: 1/1* Static EC: 1/1 Dynamic EO: 2/2 Dynamic EC: 2/2	Static EO: 0/1 Static EC: 0/1 Dynamic EO: 0/2 Dynamic EC: 0/2
Reschke et al., 2009[4] 42-90 days None	Equilibrium score	EO: 0/1 EC: 0/1 Visual sway reference EO: 0/1 Surface sway reference EO: 0/1 Surface sway reference EC: 0/1 Head tilt EC: CD Head pitch EC: CD Head tilt + surface sway reference EC: CD Head pitch + surface sway reference EC: CD	NA
Dupui et al., 1992[15] 30 days Lower-body negative pressure	(1) AP† + (2) ML COP displacement†	Static EO: 1/2* Static EC: 2/2 Dynamic EO: 2/2 Dynamic EC: 2/2	Static EO: 1/1 Static EC: 2/2 Dynamic EO: 1/2 Dynamic EC: 1/2
Šarabon et al., 2018[32] 21 days Hypoxia^	(1-3) EMG latency, maximal amplitude†, rate of rising† for 2 trunk muscles (4-5) AP† + ML COP velocity†	Anticipatory posture adjustments: 3/6* Reaction response: 3/6 EO: 2/2 EC: 2/2 Semi-tandem stance: 2/2	Anticipatory posture adjustments: 0/3 Reaction response: 0/3 EO: 0/2 EC: 0/2 Semi-tandem stance: 0/2
Paloski et al., 2017[25] 21 days Centrifugation	(1) Equilibrium score (2) Minimum time to boundary of AP COM position (postural sway velocity)	EO: 0/2 EC: 1/2 Visual sway reference EO: 0/2 Surface sway reference EO: 1/2 Surface sway reference EC: 1/2 Head pitch EC: 1/2 Head pitch + surface sway reference EC: 1/2	EO: 0/0 EC: 0/1 Visual sway reference EO: 0/0 Surface sway reference EO: 0/1 Surface sway reference EC: 0/1 Head pitch EC: 0/1 Head pitch + surface sway reference EC: 0/1
Kouzaki et al., 2007[28] 20 days Resistance training	(1) Mean AP COP velocity† (2) Mean of Peaks†, (3) Mean time between peaks and (4) Mean distance between peaks of COP†, (5) Low† + High (6) frequency AP COP, (7-11) Average EMG of plantar /dorsiflexors	COP measures EO: 4/6* COP measures EC: 4/6 EMG measures EO: 0/4 EMG measures EC: 0/4	COP measures EO: 0/4 COP measures EC: 0/4
Miyoshi et al., 2001[35] 20 days None	(1) Total COP sway path, (2) COP area, (3) Stabilogram diffusion coefficient, (4) EMG measures	COP measures EO: 2/3 COP measures EC: 0/3 EMG measures: CD	NA

Table 3. *(Cont. from previous page).*

Reference, Bed Rest Length, Countermeasure	Balance control measures	Number of balance control measures significantly affected by bed rest for each condition	Number of affected balance control measures offset by countermeasure
Morishima et al., 1997[37] 20 days None	(1) COP Distance, (2) Rectangle area, (3) Standard deviation area	EO: 1/3 EC: 0/3 Unipedal EO: 0/6 Unipedal EC: 2/6 Perturbation EO: 0/3 Perturbation EC: 0/3	NA
Haines, 1974[34] 14 days Resistance training	Time to complete task Task score	Floor line walk EC: 1/1 Unipedal rail balance EO: 1/2 Unipedal rail balance EC: 0/2 Sharpened Romberg floor EO: 0/1 Sharpened Romberg floor EC: 0/1 Sharpened Romberg rail EO: 0/1 Sharpened Romberg rail EC: 0/1 Rail walk EO: 1/1 Rail walk EC: 0/1	Floor line walk EC: 1/1 Unipedal rail balance EO: 0/1 Unipedal rail balance EC: 0/0 Sharpened Romberg floor EO: 0/0 Sharpened Romberg floor EC: 0/0 Sharpened Romberg rail EO: 0/0 Sharpened Romberg rail EC: 0/0 Rail walk EO: 0/1 Rail walk EC: 0/0
Šarabon & Rosker, 2013[30] 14 days Aerobic/resistance training	(1-2) AP + ML COP frequency, (2-4) AP + ML rambling frequency, (5-6) AP + ML trembling frequency, (7-8) AP + ML COP RMS†, (9-10) AP + ML rambling RMS†, (11-12) AP† + ML trembling RMS†	EO: 4/12	EO: 3/4
Šarabon & Rosker, 2015[31] 14 days Aerobic/resistance training	(1) EMG latencies of 4 trunk muscles†	Anticipatory posture adjustments: 2/4* Reaction response: 4/4	Anticipatory posture adjustments: 2/2 Reaction response: 0/4
Mulder et al., 2014[14] 5 days Standing or ambulation	Equilibrium score for 3 separate bed rest campaigns	Foam EO: 0/3 Foam EC: 0/3 Foam + head pitch EC: 1/3	Foam EO: 0/0 Foam EC: 0/0 Foam + head pitch EC: 0/1
Clément et al., 2015[36] 5 days Centrifugation	Equilibrium score	Foam EO: 0/1 Foam EC: 0/1 Foam + head pitch EC: 0/1	Foam EO: 0/0 Foam EC: 0/0 Foam + head pitch EC: 0/0

† *Indicates measures that were significantly altered for the majority of conditions following bed rest; * Indicates majority of balances measures were significantly different following or during bed rest; ^ hypothesized hypoxia would cause larger deficits in balance; NA=not applicable, CD=cannot determine, COP=centre of pressure, EO=eyes open, EC=eyes closed, EMG=electromyography, ML=mediolateral, AP=anteroposterior, RMS=root mean square, COM=centre of mass.*

horizontal bed rest. Fourteen studies incorporated at least one countermeasure, which manipulated different systems involved in balance control such as muscular, proprioceptive, and vestibular. Using broad categories, countermeasures included: exercise – aerobic and/or resistance (n=8/14), low magnitude mechanical signals (n=1/14), lower-body negative pressure (n=1/14), ambulation (n=2/14), and centrifugation (n=2/14).

Balance assessment: conditions and measures

All studies with the exception of three[31,32,37] focused on quiet stance balance control, often assessed through a variation of conditions which would manipulate sensory information and increase the challenge of the tasks during bipedal stance. The majority of studies (n=14/18) manipulated visual feedback by including eyes open and eyes closed conditions for the postures studied[4,14,35–38,15,18,25,27–29,32,34]. The vestibular system was specifically manipulated in seven studies (n=7/18) that used a combined eyes closed and dynamic head tilting condition[4,11,14,25,33,36,38]. Stance was either manipulated through semi-tandem stance[32] or unipedal stance[27,34]. A similar number of studies incorporated dynamic balance control through the use of a rocking base[15,18], rail walking[34], or a stabilizing task[38]. Šarabon and colleagues (2015, 2018) and Morishima et al., (1997) were the only studies that measured anticipatory and reactive balance control. It was reported that more difficult tasks were generally more sensitive to balance control changes following bed rest[14,15,25].

The balance control measures used in the included studies are described in Table 3. Regarding the specific measures collected to assess balance, only five studies[27,28,31,32,35] studied electromyogram (EMG) responses, reporting perturbation response latencies and magnitudes during balance control tasks. All other studies collected force plate measures and one study used a battery of balance tests and assessed performance using distance and time parameters[34]. Force plate measures could generally be separated into

either centre of pressure (COP) measures, which consisted of variables such as COP displacement and velocity, or equilibrium scores (EQ=100 x (1-(Θ/12.5)). Equilibrium scores are determined for the sensory organization test and were calculated using the anterior-posterior peak-to-peak sway angle (Θ) and the maximum theoretical peak-to-peak sway in the sagittal plane (12.5°).

Effects of bed rest on balance control

A summary of the effect of bed rest on balance control is presented in Table 3. The median bed rest length for studies that did or did not report the majority of their balance control measures being affected by bed rest was 45 days (IQR: 41.8 days) and 20 days (IQR: 40.8 days), respectively. Only three of the included studies[4,14,36] did not find balance control deficits in any of the collected measures, with two of them[14,36] implementing five days of bed rest. Surprisingly, the other study that found no balance control deficits had a longer duration of bed rest that ranged from 42 and 90 days[4]. Seven studies observed deficits in ≤50% of the reported measures. Of the 10 studies that found no balance control impairments or deficits in ≤50% of their measures, six studies measured balance using equilibrium scores[4,11,14,25,33,36], which may not have been sensitive enough to detect balance deficits. In the eight studies that identified the majority of their balance control measures to be impaired following bed rest[15,18,27–29,31,32,38], all incorporated COP measures and EMG measures in the battery of tools to assess balance control.

Effect of countermeasures on balance control

Table 3 shows the effects of countermeasures on offsetting changes in balance control. Of the 14 studies that included a countermeasure, seven demonstrated either an improvement in balance following bed rest (compared to baseline measures) or resulted in balance that was significantly better than bed rest alone in at least one of their collected measures[15,18,29–31,38]. Three countermeasures demonstrated a maintenance of balance control following bed rest in >50% of their balance control measures that were impaired: low magnitude mechanical signals[29], lower-body negative pressure[15], and training that targeted strength, balance, and/or aerobic capacity[27,30]. In the study comparing a group of subjects who received low magnitude mechanical signals as a countermeasure during 60 days of bedrest, to a control group (bedrest alone), anterior-posterior and medial-lateral peak COP displacement (eyes closed), velocity (eyes open and closed), and root-mean-square of velocity (eyes closed) were all significantly lower and closer to baseline values in the countermeasures group compared to the control group[29]. Similarly, the anterior-posterior shear forces during mid and high frequency ranges (eyes closed) as well as the Stabilogram Diffusion Analysis parameters (eyes closed) were significantly higher in the control group compared to the countermeasures group. These measures were all collected during bipedal stance. In the study conducted by Dupui and colleagues (1992), the application of lower-body negative pressure[15] resulted in significantly lower anterior-posterior COP displacement for all static balance control measures than the control group (bipedal, eyes open and closed), but not during dynamic conditions. Despite this, dynamic conditions appeared to be recovered faster in the intervention group for anterior-posterior COP displacement. In the medial-lateral direction, all conditions showed a significant difference in COP displacement between the lower-body negative pressure and control group (e.g., bipedal, rocking base, eyes open and closed). In the study by Šarabon & Rosker (2013), only four of the 12 balance control measures demonstrated impairments following bed rest, majority of which were found in the medial-lateral direction and all were root-mean-square measures of COP during bipedal, eyes open standing; three of these four measures were no longer significantly different to pre-bed rest values following two weeks of strength, balance, and aerobic training. Lastly, Ritzmann and colleagues (2018) found that plyometric jumping preserved balance control during both eyes open and eyes closed bipedal standing for all collected force plate and EMG measures.

Discussion

The overall purpose of this systematic scoping review was to understand the impact of bed rest on balance control and the sensorimotor systems which contribute to balance control. Of the 18 studies reviewed, 15 provided evidence of a deleterious effect of bed rest on balance (at least one balance control measure/condition impaired), with eight studies finding impairments in the majority of their balance control outcomes, all of which had "fair" or "good" quality, strengthening the case that bed rest does affect balance control. Low magnitude mechanical signals, lower-body negative pressure, and training that targeted balance, strength, and/or aerobic capacity were the three countermeasures that successfully offset the majority of balance impairments.

Assessing balance control following bed rest

The amount of challenge placed on the systems responsible for balance control through the types of tasks and conditions, likely influences the amount of balance control deficits reported following bed rest. While only eight studies found impairments in >50% of their balance control measures, 15 of the studies found balance control decrements in at least one measure taken during the collected conditions. Of these studies, six observed a comparable number of deficits across the various conditions and seven found greater deficits in the more difficult conditions where visual information, vestibular information, or stance was manipulated. This might suggest that while increasing the difficulty of a balance task is important, the measures used to assess balance control may be additionally important.

Various measures were used to assess balance control in the included studies. Limited deficits in balance control were

observed when equilibrium scores were reported, however COP and EMG measures appeared to be more sensitive to changes in balance control. Indeed, other calculated measures during the sensory organization test, such as the postural stability index, have been shown to better correlate to postural sway, and are more sensitive to balance control deficits and less prone to bias than equilibrium scores[39,40]; however, none of the included studies used the postural stability index to assess balance control. Many different COP measures were collected in the reviewed studies, which measured values that characterized the displacement, velocity, and variability of the COP. As highlighted in Table 3, velocity measures of COP, particularly in the anterior-posterior position, appeared to be quite sensitive in detecting balance control changes following bed rest, regardless of the condition assessed. Both Dupui and colleagues (1992) and Muir et al., (2011) found medial-lateral COP displacement and velocity, respectively, to be less disturbed by bed rest compared to the anterior-posterior direction. This is likely due to the increased coordination involved in controlling sway in the anterior-posterior direction combined with the atrophy that occurs in the antigravity muscles responsible for this control following bed rest[12,41]. With respect to EMG measures, based on the included studies it cannot be determined whether latencies or magnitudes are more sensitive to detecting balance control deficits following bed rest, with mixed results being found for both[27,28,31,32]. Based on the findings of the included studies, COP measures, particularly those that include a velocity component may be more sensitive to balance control changes following bed rest compared to equilibrium scores or EMG measures.

Effect of bed rest length on balance control

As length of bed rest increases, it may be anticipated that deficits in balance control would also become more pronounced. Studies that reported the majority of their measures being affected by bed rest had a median length of 45 days, whereas those that did not had a median of 20 days. Fourteen days may be sufficient to elicit balance control impairments for sensitive measures as Šarabon and colleagues (2015) found deficits in the majority of EMG measures during anticipatory adjustments and reactive movements. Conversely, five days in a young healthy population may not be long enough as the two studies that had participants confined to bed rest for five days found no effect of bed rest in any of the balance conditions[14,36]. As reported by Muir and colleagues (2011), there may also be a limit to the length of bed rest needed before balance control deficits plateau or improve, as a trend toward an improvement in balance control was observed between day 60 and 90 in their study; multiple baseline measures may help determine whether this was truly a meaningful trend, a plateau in balance control deficits, or the natural variability of the measure. This finding is important for future work to ensure that if studies are being conducted for longer than 60 days, multiple time points are collected before and during bed rest to ensure that important trends can be observed. This may also explain why Reschke and colleagues (2009) did not observe significant balance control deficits in their study participants who were in bed between 42 and 90 days. Despite no significant differences in their reported measures, they did qualitatively observe performance decrements during the more challenging balance tasks, highlighting the importance of needing sensitive measures to assess balance[4]. The measures used to assess balance control may also explain why Koppelmans (2015, 2017) did not find the majority of balance measures affected following 70 days of bed rest as they only included equilibrium scores which were less sensitive to bed rest effects. Based on the studies included in this review, the optimal range over which to examine the effects of bed rest on balance control can likely be limited to between 14 and 60 days with measures taken at multiple time points before and after bed rest.

Effectiveness of countermeasures

In the studies included in this review, countermeasures implemented during or immediately after bed rest were designed to promote the maintenance of bone and muscle mass, coordination, and cardiovascular functioning. The three interventions that showed the most robust maintenance of balance control following bed rest were the use of low magnitude mechanical signals[29], lower-body negative pressure[15], and training that targeted strength, balance, and/or aerobic capacity[27,30]. However, one of the studies that implemented a combination of strength, balance, and aerobic training[30] could not account for natural recovery of balance control, making the intervention's effectiveness difficult to discern.

In other studies, low magnitude mechanical signals have been shown to promote anabolic pathways in bone and muscle[42,43], providing a multi-faceted method of counteracting the effect of bed rest on the musculoskeletal system. In bed rest, individuals experiencing low magnitude mechanical signals were able to retain knee flexor, but not knee extensor, strength; however, other systems that contribute to balance control such as circulatory or vestibular function, were not measured and may have been preserved[29]. With respect to lower-body negative pressure, previous work has shown it to be effective in offsetting orthostatic intolerance and cardiovascular changes following bed rest by reducing central venous pressure and venous return, and minimizing venous pooling[44,45]. As not all balance conditions were maintained with the use of lower-body negative pressure, it was suggested that sensorimotor impairments may impact balance control greater than deficits in orthostatic tolerance. While these countermeasures may be promising, more work is needed to replicate these findings. Specifically, future work should implement randomized controlled trials with adequately powered sample sizes and sensitive balance control measures that are not prone to learning effects. The balance conditions should also be challenging enough to expose these balance control deficits.

The most commonly implemented countermeasure to offset the effect of bed rest on balance control was exercise, either in the form of aerobic training, resistance training, or a combination of both. Six of the studies implemented exercise during bed rest[11,18,27,28,34,38], while two studies employed the exercise intervention following bed rest[30,31]. Ritzmann et al., (2018) and Šarabon & Rosker (2013) found training that targeted balance, strength, and/or aerobic capacity effective in counteracting the balance control deficits that were observed. In the case of Šarabon & Rosker's study, a lack of a control group made it difficult to conclude whether this was a result of natural recovery from resuming normal activity or of the intervention, as the countermeasure was not applied until after bed rest was completed. Ritzmann et al., found that high intensity plyometric exercise preserved balance control following bed rest when studying both force plate and EMG measures compared to their bed rest control group. The authors hypothesized that this preservation was due to a maintenance in muscle mass and function, as was shown in a separate paper[46]. Despite exercise countermeasures often targeting muscles, only two studies[28,30] reported muscle strength or size before and after bed rest and exercise intervention, making it unclear whether exercise was vigorous enough to maintain muscle size or strength throughout bed rest. Kouzaki et al., (2007) found that plantar flexor muscle volume (measured with MRI) was maintained with strength training despite pervasive balance control deficits. Conversely, Šarabon and colleagues (2013) determined that 14 days of exercise following bed rest did not fully return all strength measures back to pre-bed rest, as dorsiflexor torque matching was still impaired after two weeks of training. Identifying associations between strength and balance deficits following bed rest would be advantageous in informing future studies.

Limitations of the current literature & recommendations for future work

The studies included in this review contained methodological limitations which can be improved in future work. Firstly, five of the studies were rated as "poor" based on the quality assessment tool, limiting our confidence in their findings. Importantly, none of these studies found significant balance control deficits in the majority of their reported measures. The main reasons for these ratings were related to poor description of the bed rest intervention and inappropriate or unclear statistical methods. In addition, to draw more definitive conclusions regarding the external validity of bed rest studies, features such as larger sample sizes and the inclusion of female participants is required. Notwithstanding the understandable challenges in participant recruitment for these study designs, future work should include proportions of male and female participants that reflect demographics of the target population of interest. It is worth noting that many studies involved space organizations which have historically been male dominant, thus prior focus on male subjects exclusively in older studies (e.g., pre-1980s) was expected. Furthermore, balance conditions can be subject to learning effects. This was observed in multiple studies, whereby when the condition was performed on a second occasion, balance control measures improved[11,14,33,37]. Providing a familiarization session, as well as having a non-bed rest control group may help control for learning effects on the balance tasks. The conditions used to test balance control should also be challenging, allowing for an increased likelihood of observing deficits following bed rest. In addition, using sensitive measures that incorporate COP measures, specifically velocity components during balance control may increase the ability to detect balance control deficits. While it would have been ideal to compare studies that used similar methods to measure balance control, in the context of the current literature this was not feasible thus limiting our ability to state concrete findings. This is not uncommon amongst biomechanics studies, as there are over 35 different COP-based measures alone that can be used to assess balance control in various time and frequency domains[47]. It is recommended that future studies use velocity components of COP and that a limited number of variables are calculated, as many COP-based measures are correlated to each other[47]. This will further decrease the chance of a type 1 error whereby investigators will observe balance control deficits due to the vast numbers of measures calculated. Lastly, to determine whether countermeasures are effectively targeting the body systems responsible for controlling balance, secondary measures should be taken that directly measure that system (e.g., muscle strength should be measured if targeted by the countermeasure). Implementing these suggestions in future bed rest studies should improve the quality of data and allow for further recommendations for countermeasures in both clinical and aerospace populations.

Study limitations

This review was not without its own limitations. Article selection was limited in that the review was conducted on articles written in English, resulting in six papers being excluded. In addition, due to heterogeneity in study design and reported measures, studies were categorized based on the number of balance measures impaired, which does not account for interrelated variables. Furthermore, studies were only included if bed rest was completed for a minimum of five days as this is when muscle atrophy starts to occur[1]. Despite this limitation, we did not observe balance control deficits following five days of bed rest, thus it is likely we did not eliminate studies that observed balance control deficits with less than five days of bed rest. Lastly, the included studies were limited to healthy individuals undergoing experimental bed rest; therefore, the results may not be applicable to clinical populations who have comorbidities.

Conclusions

In conclusion, approximately half of the reviewed studies found deficits as a result of bed rest in the majority of balance control measures supporting an effect of bed rest on balance control. Duration of bed rest likely played a role in its impact on balance control with 14-60 days being sufficient to elicit deficits. Interventions that counteracted the deleterious effects of bed rest on balance control were low magnitude mechanical signals[29], lower-body negative pressure[15], and training that targeted strength, balance and aerobic capacity[27,30]. The success of these interventions may point to neuromuscular and cardiovascular deficits being responsible for impairing balance control following bed rest. While the musculoskeletal system is likely a strong contributor to balance, interventions that sought to maintain physical or muscle activity and strength poorly preserved balance control. This emphasized not only the complex interaction of the systems involved in balance control, but also the vastness of physiological changes that emerge due to bed rest. Future work should focus on: implementing more sensitive and reliable measures of balance control such as COP velocity or postural stability indices[39,40,47–49], using challenging balance conditions such as eyes closed with and without head tilt, improving sample size, maintaining an accurate representation of men and women, and testing systems involved in controlling balance such as the proprioceptive and vestibular systems. This will allow for future reviews to provide stronger evidence regarding the effect of bed rest on balance control.

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TS contributed to the conception and design of the work; the acquisition, analysis, and interpretation of data for the work; drafting the work and the final approval of the version to be published. SG was involved in the acquisition, analysis, and interpretation of data for the work, revising the work, and the final approval of the version to be published. GM and AM were involved in the interpretation of the data, revising the work, and the final approval of the version. SM was involved in the conception and design of the work, interpretation of the data, revising the work, and the final approval of the version. All authors have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplement A. Search strategy implemented for Ovid MEDLINE.

1	((supin* adj3 position*) or (supin* adj3 lying)).tw,kf. (13623)
2	Supine Position/ (5560)
3	Head-Down Tilt/ (1570)
4	(head adj3 down adj3 tilt).tw,kf. (1155)
5	Weightlessness/ (6651)
6	weightless*.tw,kf. (2558)
7	microgravity.tw,kf. (5404)
8	Bed Rest/ (3788)
9	(bed* adj3 rest*).tw,kf. (5593)
10	bedrest.tw,kf. (925)
11	Postural Balance/ (19967)
12	postur*.tw,kf. (55706)
13	balanc*.tw,kf. (261740)
14	stabili*.tw,kf. (571691)
15	sway*.tw,kf. (5893)
16	((centre* or center*) adj3 (mass* or pressure* or gravit*)).tw,kf. (12990)
17	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 (34584)
18	11 or 12 or 13 or 14 or 15 or 16 (878831)
19	17 and 18 (4842)
20	exp animals/ not humans.sh. (4464699)
21	19 not 20 (4487)

Supplement B. NIH Rating of Bias.

Reference		Risk of Bias (Yes, No, other: CD -cannot determine, NA-not applicable, NR - not reported)											
Author	Year	Was the study question or objective clearly stated?	Were eligibility/selection criteria for the study population prespecified and clearly described?	Were the participants in the study representative of those who would be eligible for the test/service /intervention in the general or clinical population of interest?	Were all eligible participants that met the prespecified entry criteria enrolled?	Was the sample size sufficiently large to provide confidence in the findings?	Was the test/service/intervention clearly described and delivered consistently across the study population?	Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Were the people assessing the outcomes blinded to the participants' exposures/ interventions?	Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (e.g., did they use an interrupted time-series design)?	Quality Rating (Good, Fair, Poor)
Sarabon & Rosker	2013	Yes	Yes	No	Yes	NR/ CD	No	Yes	NR	Yes	Yes	No	Fair
Clement et al	2015	Yes	CD	No	CD	NR/ CD	No	Yes	NR	No	No	No	Poor
Dupui et al	1992	Yes	CD	No	CD	NR/ CD	Yes	Yes	NR	Yes/NR	Yes	No	Fair
Haines	1974	Yes	CD	No	CD	CD	No	No	NR	NR	No/Yes	Yes	Poor
Koppelmans et al	2015	Yes	CD	No	CD	CD	Yes	Yes	NR	NR	No	Yes	Fair
Koppelmans et al	2017	Yes	CD	No	CD	CD	No/Yes	Yes	NR	NR	No	Yes	Poor
Kouzaki et al	2007	Yes	Yes/ No	No	CD	CD	Yes	Yes	NR	NR	Yes	No	Good
Miyoshi et al	2001	Yes	No	No	CD	CD	No	Yes	NR	NR	No	No	Poor
Morishima et al	1997	Yes	No	Yes	CD	CD	Yes	Yes	NR	Yes	Yes	No	Fair
Muir et al	2011	Yes	Yes	Yes	CD	CD	Yes	Yes	No	Yes	Yes/No	No	Good
Mulder et al	2014	Yes	No	No	CD	CD	Yes	Yes	NR	NR	Yes	No	Fair
Paloski et al	2017	Yes	No/ Yes	No	CD	CD	Yes	Yes	NR	NR	Yes	Yes	Good
Reschke et al	2009	Yes	Yes	Yes	CD	CD	No	No	NR	No	No	Yes	Poor
Sarabon and Rosker	2015	Yes	Yes	No	CD	CD	Yes/No	Yes	NR	Yes	Yes	No	Fair
Sarabon et al	2018	Yes	Yes	No	CD	CD	Yes	Yes	NR	NR	Yes	No	Fair
Viguier et al	2009	Yes	No	No	No	CD	Yes	Yes	NR	NR	Yes	Yes	Fair
Ritzmann et al	2018	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Miller et al	2018	Yes	No	No	CD	CD	Yes	No	NR	NR	Yes	Yes	Fair

Question 14: "If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level," was reported as not applicable for all of the included studies and was not included in the table. Sections with a Yes/No response demonstrates disagreement amongst the reviewers.