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The effect of exercise on cardiometabolic risk factors in adults with chronic spinal cord injury: A systematic review

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Abstract:	Objective To determine the effects of exercise on individual cardiometabolic syndrome (CMS) risk factors in adults with chronic spinal cord injury (SCI). Design Systematic review. Data sources English language searches of PubMed, Web of Science, EMBASE, and Scopus (01/01/1970 to 31/07/2019). Eligibility criteria for selecting studies (1) original articles with statistical analysis, (2) participants were adults with a SCI sustained ≥ 1-year ago, (3) exercise intervention duration ≥ 2 weeks, and (4) included any CMS risk factor as an outcome. The methodological quality of articles was assessed using the Downs and Black score. Results Sixty-five studies were included for the final analysis, including nine studies classified as high quality (≥66%), 35 studies classified as fair quality (50-66%), and 21 studies classified as low quality (<50%). Improvements in waist circumference (4/6 studies) and markers of hepatic insulin sensitivity (4/5 studies) were reported following upper-body aerobic exercise training, but no improvements in fasting glucose (8/8 studies), lipid profile (6/8 studies), systolic (8/9 studies) or diastolic blood pressure (9/9 studies) were observed. Improvements in markers of peripheral insulin sensitivity (5/6 studies) were observed following functional electrical stimulation (FES)-cycling. Improvements in lipid profile (4/5 studies) were observed following upper-body resistance training (RT) (with or without aerobic exercise). No consistent improvements in CMS risk factors were observed following assisted ambulation, FES-hybrid, FES-rowing, and FES-RT. Conclusion Upper-body aerobic exercise training (>75% maximum heart rate) appears to improve waist circumference and hepatic insulin sensitivity, but appears insufficient for improving fasting glucose, lipid profile, or resting blood pressure. The addition of RT to upper-body aerobic exercise may elicit favourable changes in the lipid profile. More high-quality studies are needed to confirm if FES-cycling is effective at improving peripheral insulin sensitivity.

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Dear Editor,

It gives us great pleasure to submit the following revised manuscript to *Archives of Physical Medicine and Rehabilitation:*

Title: **The effect of exercise on cardiometabolic risk factors in adults with chronic spinal cord injury: A systematic review**

We would like to thank Reviewer 2 for their further helpful and insightful comments and hope that you will find our responses and associated amendments have improved the quality and presentation of this Systematic Review.

Yours sincerely,

Professor James Bilzon
Professor of Human and Applied Physiology

Dear Gerald Choon-Huat Koh (Section Editor, APMR)

We would like to submit a revised version of the manuscript entitled: **The effect of exercise on cardiometabolic risk factors in adults with chronic spinal cord injury: A systematic review** *(Ref. No:* ARCHIVES-PMR-D-19-01224R1). Please see our responses below, in green font, to the reviewer's comments, in black font. All changes made to the manuscript have been recorded using track changes.

We would like to thank the reviewers for their further comments.

Reviewers Comments and Author Responses

Reviewer 1:

I congratulate the authors for their work.

Thank you.

Reviewer 2:

The authors have tried to address the issues raised in this revision. However, the reason why hand searching was done on only two journals viz. Journal of SCM and the Archives of PM&R remains unclear, when there are other accepted "most common journals" around which may yield relevant articles such as the American Journal of PM&R, European Journal of P&RM, and Journal RM.

Thank you for your further comment on this issue. We will try to clarify our approach and reassure the reviewer. The initial electronic search, included **ALL** journals listed in the PubMed database. The second phase included a search of the reference lists of all identified articles and previous systematic reviews, to identify further articles from **ALL** journals. The third and final phase included a hand-search of the two specific journals which had returned the highest proportion of articles in the initial search. We believe this to be a very thorough approach and in keeping with best practice in Systematic Reviews. Of course, it is not possible to hand-search all journals and you will see from Line 162 that this process only revealed one additional study. I have changed the text to make this systematic approach more explicit, as follows (Lines 100-104):

"The reference list of included items and previous systematic reviews were checked and further articles identified. The final step involved hand-searching the journals which had returned the highest proportion of articles in the initial search, to identify any additional studies (e.g. Journal of Spinal Cord Medicine (1982-2018) and Archives of Physical Medicine and Rehabilitation (1985-2018))."

The difference between hepatic insulin sensitivity (line 235) and peripheral insulin sensitivity (line 241) is still confusing, especially when related terms such as fasting insulin concentration, reduction in glucose and insulin, fasting glucose, fasting glycemic control keep appearing at various points (e.g. lines 236, 285, 334-8) - please clarify for the readers' benefit.

Thank you. For the benefit of the reader, we have included a new paragraph to explain these global terms (Lines 158-164):

"The terms hepatic insulin sensitivity and peripheral insulin sensitivity are used throughout this systematic review. Hepatic insulin sensitivity refers to insulin sensitivity in the fasted state and is measured by variables such as fasting insulin and/or glucose concentration and integrated indices such as HOMA-IR. Peripheral insulin sensitivity refers to insulin-mediated skeletal muscle glucose disposal and is usually measured by looking at blood glucose and insulin in responses to an oral glucose challenge (e.g. oral glucose tolerance test) and categorized using indices such as ISI-matsuda."

We have also inserted ISI-matsuda in to the list of abbreviations.

There is a small error in line 166: "reviewer's" should be "reviewers".

This has been corrected to "reviewers".

The effect of exercise on cardiometabolic risk factors in adults with chronic spinal cord injury: A systematic review

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Conflict of Interest The authors declare no conflicts of interest

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The effect of exercise on cardiometabolic risk factors in adults with chronic spinal cord injury: A systematic review

ABSTRACT

Objective To determine the effects of exercise on individual cardiometabolic syndrome (CMS) risk factors in adults with chronic spinal cord injury (SCI).

Data sources English language searches of PubMed, Web of Science, EMBASE, and Scopus (01/01/1970 to 31/07/2019).

Study Selection Articles were included if they met the following criteria: (1) original articles with statistical analysis, (2) participants were adults with a SCI sustained ≥ 1-year ago, (3) exercise intervention duration ≥ 2 weeks, and (4) included any CMS risk factor as an outcome.

Data Extraction The methodological quality of articles was assessed using the Downs and Black score.

Data Synthesis Sixty-five studies were included for the final analysis, including nine studies classified as high quality (≥66%), 35 studies classified as fair quality (50-66%), and 21 studies classified as low quality (<50%). Improvements in waist circumference (4/6 studies) and markers of hepatic insulin sensitivity (4/5 studies) were reported following upper-body aerobic exercise training, but no improvements in fasting glucose (8/8 studies), lipid profile (6/8 studies), systolic (8/9 studies) or diastolic blood pressure (9/9 studies) were observed. Improvements in markers of peripheral insulin sensitivity (5/6 studies) were observed following functional electrical stimulation (FES)-cycling. Improvements in lipid profile (4/5 studies) were observed following upper-body resistance training (RT) (with or without aerobic exercise). No consistent improvements in CMS risk factors were observed following assisted ambulation, FES-hybrid, FES-rowing, and FES-RT.

Conclusions Upper-body aerobic exercise training (>75% maximum heart rate) appears to improve waist circumference and hepatic insulin sensitivity, but appears insufficient for improving fasting glucose, lipid profile, or resting blood pressure. The addition of RT to upper-body aerobic exercise may elicit favourable changes in the lipid profile. More high-quality studies are needed to confirm if FES-cycling is effective at improving peripheral insulin sensitivity.

Key Words spinal cord injuries, exercise therapy, metabolic diseases

Abbreviations

CMS cardiometabolic syndrome

DBP diastolic blood pressure

ES effect size

FES functional electrical stimulation

HDL-C high-density lipoprotein-cholesterol

HOMA-IR homeostatic model assessment insulin resistance

HRR heart rate reserve

ISI-matsuda insulin sensitivity index

LDL-C low-density lipoprotein-cholesterol

RT resistance training

RCT randomised controlled trial

SBP systolic blood pressure

SCI spinal cord injury

TC total cholesterol

TG triglycerides

Persons with a spinal cord injury (SCI) are at an increased risk of cardiovascular disease and diabetes compared to able-bodied individuals [1, 2]. The risk of developing these chronic diseases is raised in individuals who present with a clustering of associated risk factors including: obesity, insulin resistance, dyslipidaemia, and hypertension, or as commonly referred to, cardiometabolic syndrome (CMS) [3]. The International Diabetes Federation defines CMS as central obesity (indicated by waist circumference), plus the presence (or treatment) of two of more of the following: hypertriglyceridemia (≥ 1.7 mmol/L), reduced high-density lipoprotein-cholesterol (HDL-C) (< 1.03 mmol/L for men, < 1.29 mmol/L for women), hypertension (systolic blood pressure ≥ 130 mmHg, or diastolic blood pressure ≥ 85 mmHg), and raised fasting plasma glucose (≥ 5.6 mmol/L, or diagnosed with type 2 diabetes) [4]. A waist circumference greater than 94 cm and/or a body mass index of greater than 22 kg/m^2 have been suggested as suitable cut-points to define central obesity in SCI [5, 6]. The prevalence of CMS in chronic SCI appears to be high; with the largest study to date (n=473) reporting a prevalence rate of 57.5% [7].

There is strong evidence that exercise is an effective countermeasure for the prevention of chronic disease and the treatment of CMS risk factors in the able-bodied population [8]. This has allowed national and global health organisations to produce guidelines regarding the total volume and intensity of physical activity (minimum of 150 min/week of moderate-intensity, or 75 minutes/week of vigorous-intensity) required to improve cardiometabolic health [9, 10]. However, as the most recent systematic review of the effect of exercise on health in SCI concluded, the evidence base for spinal cord injured persons "lags far behind" that for the general population [11]. This review formed the basis for the latest SCI-exercise guidelines, which recommend adults with a chronic SCI perform a minimum of 90 min/week of moderate-to-vigorous intensity aerobic exercise to improve cardiometabolic health [12]. Additional systematic reviews have also reported beneficial effects of exercise on specific CMS risk

factors, including systemic inflammation (C - reactive protein) and obesity (fat mass and waist circumference) in persons with chronic SCI [13, 14].

Since the last systematic search of the literature by van der Scheer and colleagues (search date: 1st Jan 2016), several randomised controlled trials assessing the effect of exercise training on CMS risk factors in SCI have been published. However, this systematic review did not address clinical thresholds for CMS risk factors at baseline, the magnitude of change following exercise training, and how different exercise modalities may impact specific individual CMS biomarkers. These questions are important for practitioners prescribing exercise to patients presenting with CMS risk factors, and researchers designing future studies in this field. A review which addresses these importance issues and focuses specifically on how different forms of exercise impacts on individual CMS risk factors in chronic SCI is therefore required. The aim of this systematic review is to determine the effect of different exercise modality interventions on CMS risk factors in adults with chronic SCI.

METHODS

The study inclusion criteria and planned analysis were specified in advance (PROSPERO:CRD42018105110) and the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines were followed [15]. The databases of PubMed, Web of Science, EMBASE, and Scopus (Elsevier) were searched on 22nd August 2018, using a search strategy formulated based on a similar previous systematic review [11]. The search was repeated on 31st July 2019 to identify any additional articles prior to publication. The search strategy was piloted to ensure known articles were included and reviewed by two authors (MF & TN). The full search strategy for PubMed is presented in Supplement 1 as an exemplar. Briefly, the search was performed by combining key words associated with SCI (e.g., “paraplegia”, “spinal cord lesion”), exercise, (e.g., “physical activity”, “resistance training”,

100 "functional electrical stimulation") and CMS risk factors (e.g., "glucose", "BMI", "blood
101 pressure"). The reference list of included items and previous systematic reviews were checked
102 and further articles identified. The final step involved hand-searching the journals which had
103 returned the highest proportion of articles in the initial search, to identify any additional studies
104 (e.g. Journal of Spinal Cord Medicine (1982-2018) and Archives of Physical Medicine and
105 Rehabilitation (1985-2018)).

106 Titles and abstracts of retrieved articles were independently screened for relevance by
107 two reviewers (MF & TN). The same two reviewers independently assessed the full text of
108 relevant articles for eligibility. In the event of any disagreements in article selection, a third
109 reviewer (JB) made the final decision. Articles were included if they met the criteria according
110 to the PICOS structure: i) *participants* - ≥50% of participants were aged ≥18 years old, and had
111 a chronic SCI (≥1 year post-injury), ii) *intervention* - included an exercise training programme
112 (any, or combination of: voluntary upper-body exercise, lower-body functional electrical
113 stimulation (FES), and assisted ambulation training) lasting ≥2 weeks, iii) *comparison* – studies
114 comparing exercise intervention to a control group or pre-intervention data, iv) *outcomes* -
115 study included at least one CMS risk factor as an outcome variable (see Table 1) [4], and v)
116 *study design* - study employed and reported quantitative statistical analysis to determine the
117 impact of the exercise intervention on the relevant CMS risk outcome(s) (i.e. case reports and
118 case-series were excluded), and was published in an English-language peer-reviewed journal
119 (i.e. abstracts and conference proceedings were excluded) between 1st January 1970 and the
120 final search date. Studies involving solely neuromuscular electrical stimulation (NMES) with
121 no functional movement and passive cycling were excluded on the basis that the skeletal
122 muscle contractions produced during these activities do not directly produce a functional
123 movement, and therefore cannot be classed as exercise, *per se.* Studies assessing the impact of
124 exercise on solely blood pressure amongst tetraplegics were excluded on the basis that the aim

of the exercise intervention was to increase resting blood pressure, and therefore was not reflective of a CMS risk factor (i.e. hypertension).

Two articles did not identify participants' time since injury [16, 17]. The corresponding authors were contacted by email and asked to provide clarification and given two weeks to respond. Both articles were excluded as the corresponding authors were unable to provide this information.

Two reviewers (MF and JM) independently evaluated the quality of included studies using a modified Downs and Black scale [18]. In the modified version, the scoring for question 27 (relating to statistical power) is simplified to "Yes" (1) or "No" (0). In the event of any discrepancies in scoring, discussion between the reviewers was used to reach a consensus. The total Downs & Black score for each article was expressed as a percentage of the maximum score possible (28) to allow categorisation of study quality [19]. Articles were classified as high (≥66.7%), fair (between 50.0% and 66.6%), or low (<50.0%) quality [19].

An insufficient number of studies examined the same outcomes following similar exercise modalities, precluding a meta-analysis. Therefore, a coding system [19] was used to summarise the effect of different exercise training modalities on each CMS risk factor (Table 2). If 0-33% of studies reported a statistically significant change in a specific CMS risk factor following exercise training, the result was categorised as 'no effect'. If 34-59% of studies reported a statistically significant change in a CMS risk factor following exercise training, the result was categorised as 'inconsistent'. If 60-100% of studies reported a statistically significant change in a CMS risk factor following exercise training, the result was categorised as 'positive'. If four or more studies reported the same effect, the result was highlighted in bold to indicate a consistent finding. The findings from one particular study [20] were counted as non-significant for summary coding, due to the significance being set at $p<0.10$, with actual p

values not reported. Data extraction was performed by MF, and later checked independently by TN, JM, and JB.

To aid interpretation of results, group average values at baseline for body mass index (≥22 kg/m^2) [6], waist circumference (>94 cm) [5], triglycerides (TG) (≥1.7 mmol/L), total cholesterol (TC) (≥5 mmol/L), low-density lipoprotein (LDL-C) (>3 mmol/L), HDL-C (<1.03 mmol/L), fasting glucose (≥5.6 mmol/L), systolic blood pressure (SBP) (≥130 mmHg), and diastolic blood pressure (DBP) (≥85 mmHg) [4] were highlighted to indicate that they can be classified as clinically high, according to the International Diabetes Federation and SCI-specific guidelines (Tables 3-9).

The terms hepatic insulin sensitivity and peripheral insulin sensitivity are used throughout this systematic review. Hepatic insulin sensitivity refers to insulin sensitivity in the fasted state and is measured by variables such as fasting insulin and/or glucose concentration and integrated indices such as HOMA-IR. Peripheral insulin sensitivity refers to insulin-mediated skeletal muscle glucose disposal and is usually measured by looking at blood glucose and insulin in responses to an oral glucose challenge (e.g. oral glucose tolerance test) and categorized using indices such as ISI-matsuda.

RESULTS

The initial database search yielded a total of 2450 unique records, of which 2245 were excluded following title and abstract screening. An additional 10 articles were retrieved from; hand-searching of relevant journals (n=1), relevant systematic reviews (n=2), the associated reference list of an included paper (n=4), and the updated search (n=3). Therefore, the full-text of 215 studies were subsequently assessed, three papers [21-23] contained data presented in another article, and these were removed from all analysis, leaving 65 articles for final review. The study selection process is detailed in Figure 1.

There was substantial agreement between reviewers for title and abstract screening (*k*=0.635, 95% CI: 0.581, 0.689), and almost perfect agreement for the full-text screening (*k*=0.880, 95% CI: 0.811, 0.949) [24].

We identified studies as pre-post designs (n=47), RCTs (n=15), non-randomised controlled trials (n=2), and a retrospective cohort study (n=1). Numerous studies utilised arm-cranking (n=9), wheelchair ergometry (n=3), wheelchair treadmill propulsion (n=2), or hand-cycling (n=2). These 16 studies were grouped together for analysis as voluntary upper-body aerobic exercise (Table 3). Seven studies utilised upper-body resistance training (RT) (with or without upper-body aerobic exercise) (Table 4). The most common exercise modality was FES-cycling (n=17) (Table 5). Six studies utilised FES-resistance training (FES-RT) exercise (in the form of non-isometric knee extensions), and three studies involved a combination of FES-cycling and FES-RT (Table 6). Studies which involved hybrid functional electrical stimulation (FES)-cycling (n=4) or FES-rowing (n=4) were grouped together as they both involve lower-body FES combined with voluntary upper-body aerobic exercise (Table 7). Several studies utilised solely body weight supported treadmill training (n=6), FES-walking, exoskeletal body weight supported treadmill training (n=1), or robotic body weight supported treadmill training (n=1). These 10 studies were grouped together for analysis (Table 8). Studies that involved a combination of upper-body aerobic, upper-body RT and neuromuscular stimulation (n=1), or a combination of lower-body FES-RT, and BWSTT (n=1), were not grouped for qualitative analysis (Table 9).

Intervention durations ranged from four to 52 weeks, with the most common length of 12 weeks (n=14). Training frequency ranged from 1 to 7 sessions per week, with three times per week the most common frequency of exercise performed (n=35). No serious adverse events were reported in any of the included studies.

Sample sizes ranged from four to 48. Only seven studies reported a-priori sample size calculations, and four of these met their target sample size (Table 10). There was a total of 872 participants (658 men, 110 women, 104 NR) (Table 10). There were nine studies classified as high quality, 35 studies classified as fair quality, and 21 studies classified as low quality. The most commonly assessed outcome measures for obesity, glycaemic control, dyslipidaemia, inflammation, vascular dysregulation, and thrombotic state were body mass (n=28), interleukin-6 (n=7), HDL-C (n=23), fasting glucose (n=18), PAI-1 (n=3), and systolic blood pressure (n=22), respectively. No studies reported outcome measures of hip circumference, liver fat content, apolipoprotein B, or proinsulin.

DISCUSSION

There are consistent findings that voluntary upper-body aerobic exercise (>75% HR_{MAX}) is effective in reducing waist circumference, and improving hepatic insulin sensitivity (i.e. fasting insulin concentration and HOMA-IR), however it does not appear to improve fasting glucose concentrations, lipid profile or resting blood pressure in persons with chronic SCI. The addition of upper-body RT appears to have an inconsistent effect on lipid profiles, but given the limited number of high-quality studies on combined exercise modalities, more research is needed in this area. FES-cycling may improve outcomes relating to peripheral insulin sensitivity (i.e. ability of the skeletal muscle to dispose of glucose), but more high-quality studies are required to strengthen the available evidence. There is insufficient evidence to conclude if FES-resistance training, FES-hybrid, FES-rowing, or assisted ambulation training improves any of these CMS risk factors.

Four [27, 25, 34, 33] of the six studies utilising upper-body aerobic exercise reported a reduction in supine waist circumference (-1.9 to -3.7 cm, ES: 0.26-2.67), indicating that this form of exercise is effective for reducing central obesity. A reduction in waist circumference (-2.5 cm) was achieved with as few as 64 min/week of exercise at 65-75% HRR [25], though this reduction did not translate to any change in android fat mass [25]. There was also no change in visceral adipose tissue [26] following 180 min/week at 60-65% $V\dot{O}_2peak$ of upper-body aerobic exercise. Future studies should combine both surrogate and gold-standard measures (i.e. DEXA/CT derived) of central obesity/adiposity to further elucidate changes in body composition. Given the relatively small skeletal muscle mass involved in upper-body aerobic exercise, it is perhaps unsurprising that there were consistent findings that body mass and BMI were unchanged, as reported in a previous systematic review [14]. Whilst not part of the search strategy, only one study in this category measured free-living energy intake and expenditure

during the exercise intervention [26]. In order to better understand the isolated impact of prescribed exercise interventions on energy balance and body composition, future studies should also attempt to estimate total energy intake and total energy expenditure. This would account for any compensatory changes in diet or exercise behaviours, providing a better understanding of the overall impact of exercise interventions on energy balance in SCI [90]. Guidelines for measuring these variables in persons with chronic SCI have been published elsewhere [91].

Four [25, 28, 26, 33] of the five studies that measured fasting insulin resistance by HOMA-IR and/or fasting insulin concentrations reported a reduction (22-40%, ES: 1.07-1.78) following upper-body aerobic exercise, suggesting that this form of exercise is effective at improving hepatic insulin sensitivity (i.e. ability of the liver to dispose of glucose). The single study [31] to find no statistically significant change in fasting insulin concentration following upper-body aerobic exercise, reported that all five participants had a lower insulin concentration (22-76%, ES: 0.41) post-training, indicating that the study simply lacked the statistical power to demonstrate an effect. Despite the improvement in hepatic insulin sensitivity [92] observed following upper-body aerobic exercise, the three studies [26, 28, 31] that measured outcomes relating to peripheral insulin sensitivity [93] found no changes following training. This is likely as a result of the limited skeletal muscle mass involved (i.e. limited sink for glucose disposal). Furthermore, the upper-body skeletal musculature is usually already well-conditioned from habitual wheelchair propulsion, meaning that moderate-intensity upper-body exercise is likely an insufficient stimulus to substantially promote molecular adaptations (e.g. GLUT4 translocation, mitochondrial biogenesis) associated with improved peripheral insulin sensitivity [94]. A high quality study reported no improvement in glucose or insulin area under the curve despite 180 min/week of exercise at 60-65% $V\dot{O}_2$peak [26]. This suggests that even large volumes of upper-body aerobic exercise above the

recommended guidelines of 90 min/week [12] may be insufficient to improve markers of peripheral insulin sensitivity.

There are also numerous studies indicating that upper-body aerobic exercise alone does not improve fasting glucose, resting blood pressure (SBP, DBP), or lipid profiles (TC, HDL-C, LDL-C, and TG). All eight studies [25, 26, 28, 31-35] measuring fasting glucose reported no change following upper-body aerobic exercise. However, only one study [34] reported a clinically elevated group mean glucose concentration at baseline (≥5.6 mmol/L). Nine studies [29, 35, 38, 39, 25, 26, 34, 32, 31] measured changes in resting blood pressure following upper-body aerobic exercise. The only study [34] where participants presented with clinically elevated systolic blood pressure (≥130 mmHg) at baseline reported a reduction (3 mmHg, ES: 0.66) following 10 weeks of exercise training (4 sessions/week 50-70% HRR, 60 min). Thus, a basement effect may explain the lack of significant changes in fasting glucose and resting blood pressure in participants presenting with healthy values at baseline. Eight studies measured TG, TC, HDL-C, or LDL-C [25, 26, 28, 32-35, 20] following upper-body aerobic exercise, including four with clinically high mean concentrations at baseline. Only two studies reported a significant reduction in any variable. One study [34] reported a 25% reduction (ES: 0.31) in TG in participants with a clinically elevated mean concentrations at baseline (≥1.7 mmol/L). One study reported improvements in HDL-C, LDL-C, TC: HDL-C and TG following 60 mins/week at 70-80% HRR, however the threshold for significance was set at $p<0.10$ [40]. It therefore appears that upper-body aerobic exercise may not be an adequate stimulus to improve blood lipid profile irrespective of baseline values. This is likely due to the low energy expenditure achieved through upper-body exercise, which appears to drive changes in the lipid profile [95].

Upper-body RT (with or without aerobic exercise) appears to reduce central obesity, with three [42-44] out of four studies reporting a reduction in waist circumference (-

1.0 to -2.6 cm) or waist to hip ratio (-0.02). These changes were accompanied by a decrease in whole-body fat mass and visceral adipose tissue following 120 min/week of training (3 x 10 of 50-70% 1RM, 20 min at 3-6 RPE) [42]. Upper-body RT (with or without aerobic exercise) may elicit improvements in lipid profile, with four [43-45, 40] out of the five retrieved studies reporting a beneficial effect of at least one marker (TC, HDL-C, LDL-C, TC: HDL-C, and TG). However, more studies are needed to determine this, particularly given the high-quality study reporting no change in the lipid profile following 16-weeks of twice-weekly combined training [42].

Five [50, 54, 58, 60, 62] of the six studies to measure outcomes relating to peripheral insulin sensitivity reported a significant improvement following FES-cycling. The largest of these studies (n=18) [54] reported a significant reduction in glucose and insulin at multiple time-points during a 2-h oral glucose tolerance test following 10 weeks of exercise (2-3 sessions/week, 30 min). However, four of these studies were rated as low quality, and therefore more high-quality studies are needed to confirm if FES-cycling can improve peripheral insulin sensitivity, which upper-body exercise appears unable to achieve. Surprisingly, we identified no RCT's assessing the efficacy of FES-cycling compared to a true control group (i.e. passive cycling or stretching), which should addressed in future research. Four studies reported no change in body mass following FES-hybrid or FES-rowing training. There was a distinct lack of training studies with sufficient breadth of outcomes to make any other meaningful conclusions on the effect of FES-RT, FES-hybrid, FES-rowing and assisted ambulation on CMS risk factors. Nonetheless, given that hybrid training (2 sessions/week, 18-32 min, 65-75% HRR) [25] improved a multitude of CMS risk factors (waist circumference, android fat percentage, TG, DBP), and that different exercise modalities appear to offer specific benefits to CMS risk factors, other rigorously conducted prospective studies assessing multimodal (e.g.

306 FES-cycling combined with upper-body aerobic and resistance exercise) interventions should
307 be conducted in this area of promise.

308 This review has highlighted the lack of research assessing novel markers of CMS risk,
309 including outcomes relating to inflammation, DEXA/CT derived measured of central adiposity,
310 and endothelial function. It is clear that many studies in the area recruit a convenience sample
311 of relatively active and lean individuals, who are not reflective of the wider, chronic SCI
312 population (i.e. poor metabolic health), which should be considered when interpreting results.
313 For example, individuals with SCI have a significantly lower HDL-C compared to able-bodied
314 controls (1.06 vs 1.28 mmol/L) [96], however only five of the 23 studies to measure HDL-C
315 had a clinically low mean concentration at baseline (<1.03 mmol/L). As is widely
316 acknowledged, this review has also confirmed the existing evidence base of exercise and CMS
317 risk in SCI lacks sufficiently powered (four in total identified), high-quality studies (eight in
318 total identified). However, this review identified 16 additional studies, published since the
319 previous systematic review by van der Scheer and colleagues [11] that were all categorised as
320 fair or high quality, including eight RCT's.

321

322 **Study Limitations**

323 The main limitation of this systematic review is the use of summary coding to draw
324 conclusions regarding the effect of each exercise modality on specific CMS risk factors. Due
325 to the variability in CMS risk factors measured, exercise modes and training parameters (i.e.
326 exercise intensity and volume), and participant characteristics (i.e. paraplegic vs. tetraplegic),
327 a meta-analysis was not possible. Whilst the coding system provides a useful assessment of the
328 consistency of findings in the field, it uses arbitrary classifications and does not distinguish
329 studies of differing quality. However, when studies rated as 'low-quality' were removed from
330 this analysis (Supplement 3), the conclusions remained unchanged, with the exception of

potential of FES-cycling to improve peripheral insulin sensitivity. Further, given that the vast majority of included studies lacked sufficient statistical power, there is a risk of a type II error in the conclusions formed. Finally, this review did not include acute SCI as van der Scheer and colleagues [11] determined there was an "absence of high-quality, consistent evidence" in this area, a view which still appears to be true.

CONCLUSIONS

In summary, this systematic review has provided evidence that in adults with chronic SCI, upper-body aerobic exercise improves outcomes relating to central obesity and hepatic insulin sensitivity, but is not sufficient to improve fasting glucose, lipid profiles, or resting blood pressure. Practitioners should consider prescribing moderate-to-vigorous intensity (>75% HR_{MAX}) upper-body aerobic exercise to improve fasting glycaemic control and central obesity. To elicit improvements in lipid profile, this should be combined with upper-body resistance training. More high-quality randomised controlled trials assessing novel markers of CMS and responses to combined exercise interventions (e.g. aerobic exercise with resistance training), high-intensity exercise interventions, and FES-based exercise are needed to inform and refine evidence-based exercise guidelines for the prevention and management of CMS in this population.

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667 **Figure 1.** PRISMA flow diagram

The effect of exercise on cardiometabolic risk factors in adults with chronic spinal cord injury: A systematic review

ABSTRACT

Objective To determine the effects of exercise on individual cardiometabolic syndrome (CMS) risk factors in adults with chronic spinal cord injury (SCI).

Data sources English language searches of PubMed, Web of Science, EMBASE, and Scopus (01/01/1970 to 31/07/2019).

Study Selection Articles were included if they met the following criteria: (1) original articles with statistical analysis, (2) participants were adults with a SCI sustained ≥ 1-year ago, (3) exercise intervention duration ≥ 2 weeks, and (4) included any CMS risk factor as an outcome.

Data Extraction The methodological quality of articles was assessed using the Downs and Black score.

Data Synthesis Sixty-five studies were included for the final analysis, including nine studies classified as high quality (≥66%), 35 studies classified as fair quality (50-66%), and 21 studies classified as low quality (<50%). Improvements in waist circumference (4/6 studies) and markers of hepatic insulin sensitivity (4/5 studies) were reported following upper-body aerobic exercise training, but no improvements in fasting glucose (8/8 studies), lipid profile (6/8 studies), systolic (8/9 studies) or diastolic blood pressure (9/9 studies) were observed. Improvements in markers of peripheral insulin sensitivity (5/6 studies) were observed following functional electrical stimulation (FES)-cycling. Improvements in lipid profile (4/5 studies) were observed following upper-body resistance training (RT) (with or without aerobic exercise). No consistent improvements in CMS risk factors were observed following assisted ambulation, FES-hybrid, FES-rowing, and FES-RT.

Conclusions Upper-body aerobic exercise training (>75% maximum heart rate) appears to improve waist circumference and hepatic insulin sensitivity, but appears insufficient for improving fasting glucose, lipid profile, or resting blood pressure. The addition of RT to upper-body aerobic exercise may elicit favourable changes in the lipid profile. More high-quality studies are needed to confirm if FES-cycling is effective at improving peripheral insulin sensitivity.

Key Words spinal cord injuries, exercise therapy, metabolic diseases

Abbreviations

CMS cardiometabolic syndrome

DBP diastolic blood pressure

ES effect size

FES functional electrical stimulation

HDL-C high-density lipoprotein-cholesterol

HOMA-IR homeostatic model assessment insulin resistance

HRR heart rate reserve

ISI-matsuda insulin sensitivity index

LDL-C low-density lipoprotein-cholesterol

RT resistance training

RCT randomised controlled trial

SBP systolic blood pressure

SCI spinal cord injury

TC total cholesterol

TG triglycerides

Persons with a spinal cord injury (SCI) are at an increased risk of cardiovascular disease and diabetes compared to able-bodied individuals [1, 2]. The risk of developing these chronic diseases is raised in individuals who present with a clustering of associated risk factors including: obesity, insulin resistance, dyslipidaemia, and hypertension, or as commonly referred to, cardiometabolic syndrome (CMS) [3]. The International Diabetes Federation defines CMS as central obesity (indicated by waist circumference), plus the presence (or treatment) of two of more of the following: hypertriglyceridemia (≥ 1.7 mmol/L), reduced high-density lipoprotein-cholesterol (HDL-C) (< 1.03 mmol/L for men, < 1.29 mmol/L for women), hypertension (systolic blood pressure ≥ 130 mmHg, or diastolic blood pressure ≥ 85 mmHg), and raised fasting plasma glucose (≥ 5.6 mmol/L, or diagnosed with type 2 diabetes) [4]. A waist circumference greater than 94 cm and/or a body mass index of greater than 22 kg/m^2 have been suggested as suitable cut-points to define central obesity in SCI [5, 6]. The prevalence of CMS in chronic SCI appears to be high; with the largest study to date (n=473) reporting a prevalence rate of 57.5% [7].

There is strong evidence that exercise is an effective countermeasure for the prevention of chronic disease and the treatment of CMS risk factors in the able-bodied population [8]. This has allowed national and global health organisations to produce guidelines regarding the total volume and intensity of physical activity (minimum of 150 min/week of moderate-intensity, or 75 minutes/week of vigorous-intensity) required to improve cardiometabolic health [9, 10]. However, as the most recent systematic review of the effect of exercise on health in SCI concluded, the evidence base for spinal cord injured persons "lags far behind" that for the general population [11]. This review formed the basis for the latest SCI-exercise guidelines, which recommend adults with a chronic SCI perform a minimum of 90 min/week of moderate-to-vigorous intensity aerobic exercise to improve cardiometabolic health [12]. Additional systematic reviews have also reported beneficial effects of exercise on specific CMS risk

factors, including systemic inflammation (C - reactive protein) and obesity (fat mass and waist circumference) in persons with chronic SCI [13, 14].

Since the last systematic search of the literature by van der Scheer and colleagues (search date: 1st Jan 2016), several randomised controlled trials assessing the effect of exercise training on CMS risk factors in SCI have been published. However, this systematic review did not address clinical thresholds for CMS risk factors at baseline, the magnitude of change following exercise training, and how different exercise modalities may impact specific individual CMS biomarkers. These questions are important for practitioners prescribing exercise to patients presenting with CMS risk factors, and researchers designing future studies in this field. A review which addresses these importance issues and focuses specifically on how different forms of exercise impacts on individual CMS risk factors in chronic SCI is therefore required. The aim of this systematic review is to determine the effect of different exercise modality interventions on CMS risk factors in adults with chronic SCI.

METHODS

The study inclusion criteria and planned analysis were specified in advance (PROSPERO:CRD42018105110) and the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines were followed [15]. The databases of PubMed, Web of Science, EMBASE, and Scopus (Elsevier) were searched on 22nd August 2018, using a search strategy formulated based on a similar previous systematic review [11]. The search was repeated on 31st July 2019 to identify any additional articles prior to publication. The search strategy was piloted to ensure known articles were included and reviewed by two authors (MF & TN). The full search strategy for PubMed is presented in Supplement 1 as an exemplar. Briefly, the search was performed by combining key words associated with SCI (e.g., "paraplegia", "spinal cord lesion"), exercise, (e.g., "physical activity", "resistance training",

"functional electrical stimulation") and CMS risk factors (e.g., "glucose", "BMI", "blood pressure"). The reference list of included items and previous systematic reviews were checked and further articles identified. The final step involved hand-searching the journals which had returned the highest proportion of articles in the initial search, to identify any additional studies (e.g. Journal of Spinal Cord Medicine (1982-2018) and Archives of Physical Medicine and Rehabilitation (1985-2018)).

Titles and abstracts of retrieved articles were independently screened for relevance by two reviewers (MF & TN). The same two reviewers independently assessed the full text of relevant articles for eligibility. In the event of any disagreements in article selection, a third reviewer (JB) made the final decision. Articles were included if they met the criteria according to the PICOS structure: i) *participants* - ≥50% of participants were aged ≥18 years old, and had a chronic SCI (≥1 year post-injury), ii) *intervention* - included an exercise training programme (any, or combination of: voluntary upper-body exercise, lower-body functional electrical stimulation (FES), and assisted ambulation training) lasting ≥2 weeks, iii) *comparison* – studies comparing exercise intervention to a control group or pre-intervention data, iv) *outcomes* - study included at least one CMS risk factor as an outcome variable (see Table 1) [4], and v) *study design* - study employed and reported quantitative statistical analysis to determine the impact of the exercise intervention on the relevant CMS risk outcome(s) (i.e. case reports and case-series were excluded), and was published in an English-language peer-reviewed journal (i.e. abstracts and conference proceedings were excluded) between 1st January 1970 and the final search date. Studies involving solely neuromuscular electrical stimulation (NMES) with no functional movement and passive cycling were excluded on the basis that the skeletal muscle contractions produced during these activities do not directly produce a functional movement, and therefore cannot be classed as exercise, *per se.* Studies assessing the impact of exercise on solely blood pressure amongst tetraplegics were excluded on the basis that the aim

125 of the exercise intervention was to increase resting blood pressure, and therefore was not
126 reflective of a CMS risk factor (i.e. hypertension).

127 Two articles did not identify participants' time since injury [16, 17]. The corresponding
128 authors were contacted by email and asked to provide clarification and given two weeks to
129 respond. Both articles were excluded as the corresponding authors were unable to provide this
130 information.

131 Two reviewers (MF and JM) independently evaluated the quality of included studies
132 using a modified Downs and Black scale [18]. In the modified version, the scoring for question
133 27 (relating to statistical power) is simplified to "Yes" (1) or "No" (0). In the event of any
134 discrepancies in scoring, discussion between the reviewers was used to reach a consensus. The
135 total Downs & Black score for each article was expressed as a percentage of the maximum
136 score possible (28) to allow categorisation of study quality [19]. Articles were classified as
137 high (≥66.7%), fair (between 50.0% and 66.6%), or low (<50.0%) quality [19].

138 An insufficient number of studies examined the same outcomes following similar
139 exercise modalities, precluding a meta-analysis. Therefore, a coding system [19] was used to
140 summarise the effect of different exercise training modalities on each CMS risk factor (Table
141 2). If 0-33% of studies reported a statistically significant change in a specific CMS risk factor
142 following exercise training, the result was categorised as 'no effect'. If 34-59% of studies
143 reported a statistically significant change in a CMS risk factor following exercise training, the
144 result was categorised as 'inconsistent'. If 60-100% of studies reported a statistically significant
145 change in a CMS risk factor following exercise training, the result was categorised as
146 'positive'. If four or more studies reported the same effect, the result was highlighted in bold
147 to indicate a consistent finding. The findings from one particular study [20] were counted as
148 non-significant for summary coding, due to the significance being set at $p<0.10$, with actual p

values not reported. Data extraction was performed by MF, and later checked independently by TN, JM, and JB.

To aid interpretation of results, group average values at baseline for body mass index (≥22 kg/m^2) [6], waist circumference (>94 cm) [5], triglycerides (TG) (≥1.7 mmol/L), total cholesterol (TC) (≥5 mmol/L), low-density lipoprotein (LDL-C) (>3 mmol/L), HDL-C (<1.03 mmol/L), fasting glucose (≥5.6 mmol/L), systolic blood pressure (SBP) (≥130 mmHg), and diastolic blood pressure (DBP) (≥85 mmHg) [4] were highlighted to indicate that they can be classified as clinically high, according to the International Diabetes Federation and SCI-specific guidelines (Tables 3-9).

The terms hepatic insulin sensitivity and peripheral insulin sensitivity are used throughout this systematic review. Hepatic insulin sensitivity refers to insulin sensitivity in the fasted state and is measured by variables such as fasting insulin and/or glucose concentration and integrated indices such as HOMA-IR. Peripheral insulin sensitivity refers to insulin-mediated skeletal muscle glucose disposal and is usually measured by looking at blood glucose and insulin in responses to an oral glucose challenge (e.g. oral glucose tolerance test) and categorized using indices such as ISI-matsuda.

RESULTS

The initial database search yielded a total of 2450 unique records, of which 2245 were excluded following title and abstract screening. An additional 10 articles were retrieved from; hand-searching of relevant journals (n=1), relevant systematic reviews (n=2), the associated reference list of an included paper (n=4), and the updated search (n=3). Therefore, the full-text of 215 studies were subsequently assessed, three papers [21-23] contained data presented in another article, and these were removed from all analysis, leaving 65 articles for final review. The study selection process is detailed in Figure 1.

There was substantial agreement between reviewers for title and abstract screening (*k*=0.635, 95% CI: 0.581, 0.689), and almost perfect agreement for the full-text screening (*k*=0.880, 95% CI: 0.811, 0.949) [24].

We identified studies as pre-post designs (n=47), RCTs (n=15), non-randomised controlled trials (n=2), and a retrospective cohort study (n=1). Numerous studies utilised arm-cranking (n=9), wheelchair ergometry (n=3), wheelchair treadmill propulsion (n=2), or hand-cycling (n=2). These 16 studies were grouped together for analysis as voluntary upper-body aerobic exercise (Table 3). Seven studies utilised upper-body resistance training (RT) (with or without upper-body aerobic exercise) (Table 4). The most common exercise modality was FES-cycling (n=17) (Table 5). Six studies utilised FES-resistance training (FES-RT) exercise (in the form of non-isometric knee extensions), and three studies involved a combination of FES-cycling and FES-RT (Table 6). Studies which involved hybrid functional electrical stimulation (FES)-cycling (n=4) or FES-rowing (n=4) were grouped together as they both involve lower-body FES combined with voluntary upper-body aerobic exercise (Table 7). Several studies utilised solely body weight supported treadmill training (n=6), FES-walking, exoskeletal body weight supported treadmill training (n=1), or robotic body weight supported treadmill training (n=1). These 10 studies were grouped together for analysis (Table 8). Studies that involved a combination of upper-body aerobic, upper-body RT and neuromuscular stimulation (n=1), or a combination of lower-body FES-RT, and BWSTT (n=1), were not grouped for qualitative analysis (Table 9).

Intervention durations ranged from four to 52 weeks, with the most common length of 12 weeks (n=14). Training frequency ranged from 1 to 7 sessions per week, with three times per week the most common frequency of exercise performed (n=35). No serious adverse events were reported in any of the included studies.

Sample sizes ranged from four to 48. Only seven studies reported a-priori sample size calculations, and four of these met their target sample size (Table 10). There was a total of 872 participants (658 men, 110 women, 104 NR) (Table 10). There were nine studies classified as high quality, 35 studies classified as fair quality, and 21 studies classified as low quality. The most commonly assessed outcome measures for obesity, glycaemic control, dyslipidaemia, inflammation, vascular dysregulation, and thrombotic state were body mass (n=28), interleukin-6 (n=7), HDL-C (n=23), fasting glucose (n=18), PAI-1 (n=3), and systolic blood pressure (n=22), respectively. No studies reported outcome measures of hip circumference, liver fat content, apolipoprotein B, or proinsulin.

DISCUSSION

There are consistent findings that voluntary upper-body aerobic exercise (>75% HR_{MAX}) is effective in reducing waist circumference, and improving hepatic insulin sensitivity (i.e. fasting insulin concentration and HOMA-IR), however it does not appear to improve fasting glucose concentrations, lipid profile or resting blood pressure in persons with chronic SCI. The addition of upper-body RT appears to have an inconsistent effect on lipid profiles, but given the limited number of high-quality studies on combined exercise modalities, more research is needed in this area. FES-cycling may improve outcomes relating to peripheral insulin sensitivity (i.e. ability of the skeletal muscle to dispose of glucose), but more high-quality studies are required to strengthen the available evidence. There is insufficient evidence to conclude if FES-resistance training, FES-hybrid, FES-rowing, or assisted ambulation training improves any of these CMS risk factors.

Four [27, 25, 34, 33] of the six studies utilising upper-body aerobic exercise reported a reduction in supine waist circumference (-1.9 to -3.7 cm, ES: 0.26-2.67), indicating that this form of exercise is effective for reducing central obesity. A reduction in waist circumference (-2.5 cm) was achieved with as few as 64 min/week of exercise at 65-75% HRR [25], though this reduction did not translate to any change in android fat mass [25]. There was also no change in visceral adipose tissue [26] following 180 min/week at 60-65% $V\dot{O}_2$peak of upper-body aerobic exercise. Future studies should combine both surrogate and gold-standard measures (i.e. DEXA/CT derived) of central obesity/adiposity to further elucidate changes in body composition. Given the relatively small skeletal muscle mass involved in upper-body aerobic exercise, it is perhaps unsurprising that there were consistent findings that body mass and BMI were unchanged, as reported in a previous systematic review [14]. Whilst not part of the search strategy, only one study in this category measured free-living energy intake and expenditure

during the exercise intervention [26]. In order to better understand the isolated impact of prescribed exercise interventions on energy balance and body composition, future studies should also attempt to estimate total energy intake and total energy expenditure. This would account for any compensatory changes in diet or exercise behaviours, providing a better understanding of the overall impact of exercise interventions on energy balance in SCI [90]. Guidelines for measuring these variables in persons with chronic SCI have been published elsewhere [91].

Four [25, 28, 26, 33] of the five studies that measured fasting insulin resistance by HOMA-IR and/or fasting insulin concentrations reported a reduction (22-40%, ES: 1.07-1.78) following upper-body aerobic exercise, suggesting that this form of exercise is effective at improving hepatic insulin sensitivity (i.e. ability of the liver to dispose of glucose). The single study [31] to find no statistically significant change in fasting insulin concentration following upper-body aerobic exercise, reported that all five participants had a lower insulin concentration (22-76%, ES: 0.41) post-training, indicating that the study simply lacked the statistical power to demonstrate an effect. Despite the improvement in hepatic insulin sensitivity [92] observed following upper-body aerobic exercise, the three studies [26, 28, 31] that measured outcomes relating to peripheral insulin sensitivity [93] found no changes following training. This is likely as a result of the limited skeletal muscle mass involved (i.e. limited sink for glucose disposal). Furthermore, the upper-body skeletal musculature is usually already well-conditioned from habitual wheelchair propulsion, meaning that moderate-intensity upper-body exercise is likely an insufficient stimulus to substantially promote molecular adaptations (e.g. GLUT4 translocation, mitochondrial biogenesis) associated with improved peripheral insulin sensitivity [94]. A high quality study reported no improvement in glucose or insulin area under the curve despite 180 min/week of exercise at 60-65% $V\dot{O}_2$peak [26]. This suggests that even large volumes of upper-body aerobic exercise above the

recommended guidelines of 90 min/week [12] may be insufficient to improve markers of peripheral insulin sensitivity.

There are also numerous studies indicating that upper-body aerobic exercise alone does not improve fasting glucose, resting blood pressure (SBP, DBP), or lipid profiles (TC, HDL-C, LDL-C, and TG). All eight studies [25, 26, 28, 31-35] measuring fasting glucose reported no change following upper-body aerobic exercise. However, only one study [34] reported a clinically elevated group mean glucose concentration at baseline (≥5.6 mmol/L). Nine studies [29, 35, 38, 39, 25, 26, 34, 32, 31] measured changes in resting blood pressure following upper-body aerobic exercise. The only study [34] where participants presented with clinically elevated systolic blood pressure (≥130 mmHg) at baseline reported a reduction (3 mmHg, ES: 0.66) following 10 weeks of exercise training (4 sessions/week 50-70% HRR, 60 min). Thus, a basement effect may explain the lack of significant changes in fasting glucose and resting blood pressure in participants presenting with healthy values at baseline. Eight studies measured TG, TC, HDL-C, or LDL-C [25, 26, 28, 32-35, 20] following upper-body aerobic exercise, including four with clinically high mean concentrations at baseline. Only two studies reported a significant reduction in any variable. One study [34] reported a 25% reduction (ES: 0.31) in TG in participants with a clinically elevated mean concentrations at baseline (≥1.7 mmol/L). One study reported improvements in HDL-C, LDL-C, TC: HDL-C and TG following 60 mins/week at 70-80% HRR, however the threshold for significance was set at $p<0.10$ [40]. It therefore appears that upper-body aerobic exercise may not be an adequate stimulus to improve blood lipid profile irrespective of baseline values. This is likely due to the low energy expenditure achieved through upper-body exercise, which appears to drive changes in the lipid profile [95].

Upper-body RT (with or without aerobic exercise) appears to reduce central obesity, with three [42-44] out of four studies reporting a reduction in waist circumference (-

1.0 to -2.6 cm) or waist to hip ratio (-0.02). These changes were accompanied by a decrease in whole-body fat mass and visceral adipose tissue following 120 min/week of training (3 x 10 of 50-70% 1RM, 20 min at 3-6 RPE) [42]. Upper-body RT (with or without aerobic exercise) may elicit improvements in lipid profile, with four [43-45, 40] out of the five retrieved studies reporting a beneficial effect of at least one marker (TC, HDL-C, LDL-C, TC: HDL-C, and TG). However, more studies are needed to determine this, particularly given the high-quality study reporting no change in the lipid profile following 16-weeks of twice-weekly combined training [42].

Five [50, 54, 58, 60, 62] of the six studies to measure outcomes relating to peripheral insulin sensitivity reported a significant improvement following FES-cycling. The largest of these studies (n=18) [54] reported a significant reduction in glucose and insulin at multiple time-points during a 2-h oral glucose tolerance test following 10 weeks of exercise (2-3 sessions/week, 30 min). However, four of these studies were rated as low quality, and therefore more high-quality studies are needed to confirm if FES-cycling can improve peripheral insulin sensitivity, which upper-body exercise appears unable to achieve. Surprisingly, we identified no RCT's assessing the efficacy of FES-cycling compared to a true control group (i.e. passive cycling or stretching), which should addressed in future research. Four studies reported no change in body mass following FES-hybrid or FES-rowing training. There was a distinct lack of training studies with sufficient breadth of outcomes to make any other meaningful conclusions on the effect of FES-RT, FES-hybrid, FES-rowing and assisted ambulation on CMS risk factors. Nonetheless, given that hybrid training (2 sessions/week, 18-32 min, 65-75% HRR) [25] improved a multitude of CMS risk factors (waist circumference, android fat percentage, TG, DBP), and that different exercise modalities appear to offer specific benefits to CMS risk factors, other rigorously conducted prospective studies assessing multimodal (e.g.

306 FES-cycling combined with upper-body aerobic and resistance exercise) interventions should
307 be conducted in this area of promise.

308 This review has highlighted the lack of research assessing novel markers of CMS risk,
309 including outcomes relating to inflammation, DEXA/CT derived measured of central adiposity,
310 and endothelial function. It is clear that many studies in the area recruit a convenience sample
311 of relatively active and lean individuals, who are not reflective of the wider, chronic SCI
312 population (i.e. poor metabolic health), which should be considered when interpreting results.
313 For example, individuals with SCI have a significantly lower HDL-C compared to able-bodied
314 controls (1.06 vs 1.28 mmol/L) [96], however only five of the 23 studies to measure HDL-C
315 had a clinically low mean concentration at baseline (<1.03 mmol/L). As is widely
316 acknowledged, this review has also confirmed the existing evidence base of exercise and CMS
317 risk in SCI lacks sufficiently powered (four in total identified), high-quality studies (eight in
318 total identified). However, this review identified 16 additional studies, published since the
319 previous systematic review by van der Scheer and colleagues [11] that were all categorised as
320 fair or high quality, including eight RCT's.

321

322 **Study Limitations**

323 The main limitation of this systematic review is the use of summary coding to draw
324 conclusions regarding the effect of each exercise modality on specific CMS risk factors. Due
325 to the variability in CMS risk factors measured, exercise modes and training parameters (i.e.
326 exercise intensity and volume), and participant characteristics (i.e. paraplegic vs. tetraplegic),
327 a meta-analysis was not possible. Whilst the coding system provides a useful assessment of the
328 consistency of findings in the field, it uses arbitrary classifications and does not distinguish
329 studies of differing quality. However, when studies rated as 'low-quality' were removed from
330 this analysis (Supplement 3), the conclusions remained unchanged, with the exception of

potential of FES-cycling to improve peripheral insulin sensitivity. Further, given that the vast majority of included studies lacked sufficient statistical power, there is a risk of a type II error in the conclusions formed. Finally, this review did not include acute SCI as van der Scheer and colleagues [11] determined there was an "absence of high-quality, consistent evidence" in this area, a view which still appears to be true.

CONCLUSIONS

In summary, this systematic review has provided evidence that in adults with chronic SCI, upper-body aerobic exercise improves outcomes relating to central obesity and hepatic insulin sensitivity, but is not sufficient to improve fasting glucose, lipid profiles, or resting blood pressure. Practitioners should consider prescribing moderate-to-vigorous intensity (>75% HR_{MAX}) upper-body aerobic exercise to improve fasting glycaemic control and central obesity. To elicit improvements in lipid profile, this should be combined with upper-body resistance training. More high-quality randomised controlled trials assessing novel markers of CMS and responses to combined exercise interventions (e.g. aerobic exercise with resistance training), high-intensity exercise interventions, and FES-based exercise are needed to inform and refine evidence-based exercise guidelines for the prevention and management of CMS in this population.

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667 **Figure 1.** PRISMA flow diagram

Appendix 1

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Appendix

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Appendix 2

Figure 1

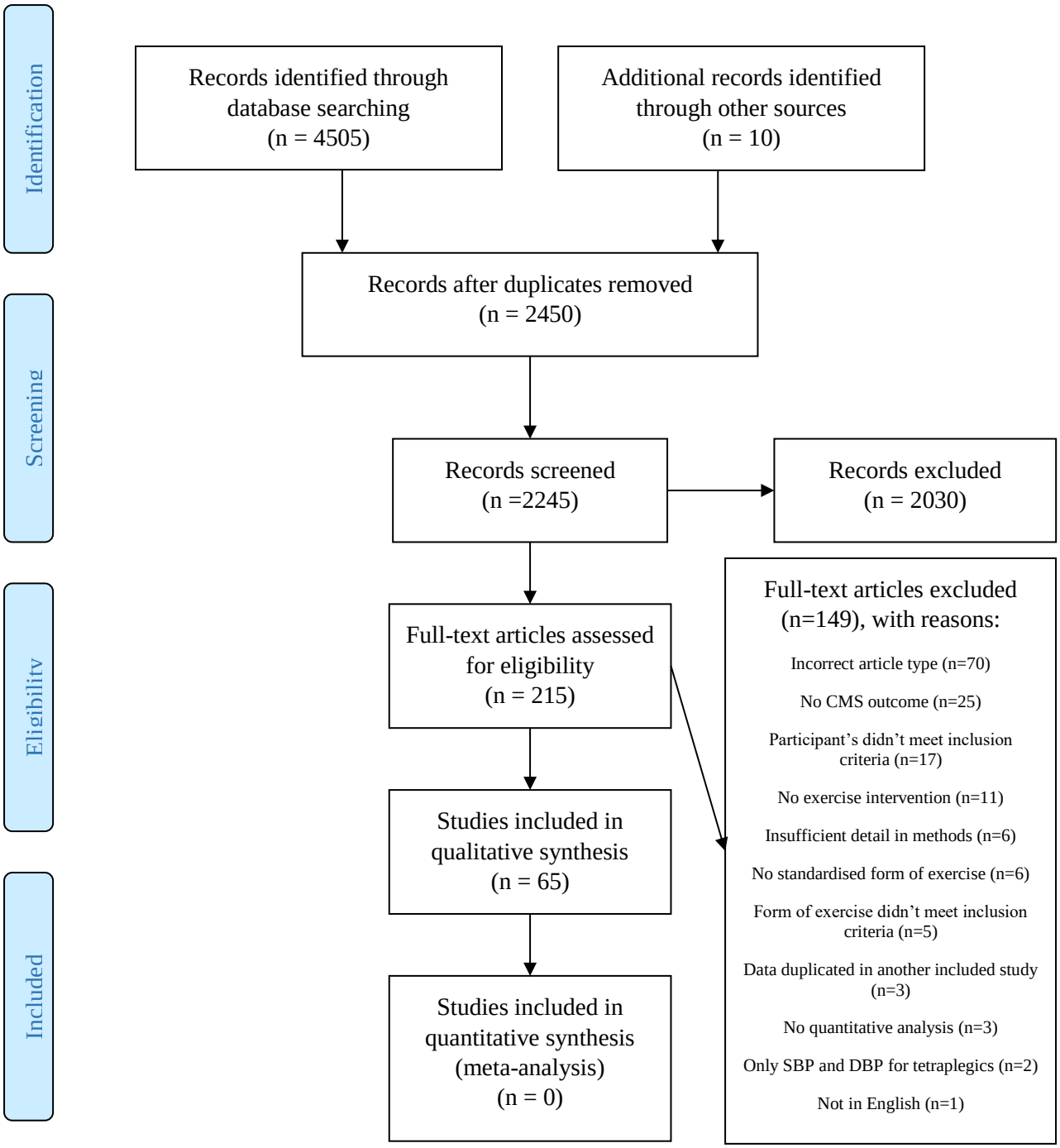
Identification
Screening
Eligibility
Included
Records identified through database searching (n = 4505)
Additional records identified through other sources (n = 10)
Records after duplicates removed (n = 2450)
Records screened (n =2245)
Records excluded (n = 2030)
Full-text articles assessed for eligibility (n = 215)
Full-text articles excluded (n=149), with reasons:
Incorrect article type (n=70)
No CMS outcome (n=25)
Participant's didn't meet inclusion criteria (n=17)
No exercise intervention (n=11)
Insufficient detail in methods (n=6)
No standardised form of exercise (n=6)
Form of exercise didn't meet inclusion criteria (n=5)
Data duplicated in another included study (n=3)
No quantitative analysis (n=3)
Only SBP and DBP for tetraplegics (n=2)
Not in English (n=1)
Studies included in qualitative synthesis (n = 65)
Studies included in quantitative synthesis (meta-analysis) (n = 0)

Table 1

Table 1. CMS outcome measures

Central Adiposity/Obesity	Body Mass Index (BMI) Body Mass (BM) Waist Circumference (Waist) Hip Circumference Waist to Hip Ratio (WHR) Body Fat Percentage (BF%) (assessed via DEXA/CT) Fat Mass (FM) (assessed via DEXA/CT) Android Fat Mass Visceral Adipose Tissue (VAT) Liver Fat Content Leptin
Glycaemic Control	Fasting insulin and glucose Glucose to insulin ratio Fasting proinsulin Glycosylated haemoglobin (HbA1c) Fasting/postprandial insulin sensitivity measures C-peptide
Dyslipidaemia	Triglycerides (TG) Low-density lipoprotein-cholesterol (LDL-C) High-density lipoprotein-cholesterol (HDL-C) Total cholesterol (TC) ~~DL, HDL, TC,~~ TC: HDL-C Non-esterified fatty acids (NEFA) Free-fatty acids (FFA) Apolipoprotein B
Inflammation	C-reactive Protein (CRP) Interleukin-6 (IL-6) Tumour necrosis factor-alpha (TNF-α) Adiponectin
Vascular Dysregulation	Systolic Blood Pressure (SBP) Diastolic Blood Pressure (DBP) Pulse wave velocity (PWV) Flow-mediated dilation (FMD) Microalbuminuria
Thrombotic State	Fibrinogen Plasminogen activator inhibitor-1 (PAI-1)

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Table 2

Table 2. Summary coding of studies examining the effect of exercise on CMS outcome measures.

		Aerobic	Aerobic + RT	Ambulation	Hybrid and Rowing	FES-cycling	FES-RT/Combined
Central Adiposity/Obesity	BM	**1/9 (11%)**	1/2 (50%)	1/3 (33%)	**0/5 (0%)**	1/4 (25%)	**0/4 (0%)**
	BMI	1/4 (25%)	1/4 (25%)	1/1 (100%)	0/1 (0%)	0/2 (0%)	1/3 (33%)*
	Waist	**4/6 (66%)**	2/3 (67%)	-	1/2 (50%)	-	-
	WHR	-	1/1 (100%)	-	-	-	-
	BF%	0/2 (0%)	-	2/2 (100%)	0/2 (0%)	1/2 (50%)	0/2 (0%)
	FM	0/3 (0%)	1/2 (50%)	0/2 (0%)	-	1/2 (50%)	0/2 (0%)
	Android FM	0/1 (0%)	-	-	0/1 (0%)	-	-
	Abdominal AT	-	-	-	--	0/1 (0%)	-
	VAT	0/1 (0%)	1/1 (100%)	-	--	-	0/2 (0%)
	Leptin	1/1 (100%)	0/1 (0%)	-	1/1 (100%)	-	-
Inflammation	CRP	0/1 (0%)	--	1/1 (100%)	0/1 (0%)	1/2 (50%)	0/1 (0%)
	IL-6	1/2 (50%)	0/1 (0%)	-	0/1 (0%)	1/2 (50%)	0/1 (0%)
	TNF-α	1/1 (100%)	0/1 (0%)	-	-	1/2 (50%)	0/1 (0%)
	Adiponectin	0/1 (0%)	0/1 (0%)	-	-	-	1/1 (100%)
Dyslipidaemia	TG	**1/6 (17%)**	2/4 (50%)	0/2 (0%)	1/1 (100%)	1/3 (33%)	1/3 (33%)
	FFA	-	-	-	-	0/1 (0%)	0/1 (0%)
	NEFA	0/1 (0%)	-	-	-	-	-
	TC	**1/6 (17%)**	2/5 (40%)	1/2 (50%)	0/1 (0%)	0/2 (0%)	1/3 (33%)
	HDL-C	**0/7 (0%)**	**1/5 (20%)**	0/2 (0%)	0/2 (0%)	1/3 (33%)	1/3 (33%)
	LDL-C	**0/5 (0%)**	2/5 (40%)	1/2 (50%)	0/1 (0%)	1/3 (33%)	0/3 (0%)
	TC: HDL-C	0/1 (0%)	1/2 (50%)	1/1 (100%)	-	1/1 (100%)	1/2 (50%)
Glycaemic Control	Fasting Glucose	**0/8 (0%)**	0/3 (0%)	0/1 (0%)	1/2 (50%)	0/1 (0%)	0/2 (0%)
	Fasting Insulin	**4/5 (80%)**	1/3 (33%)	-	0/2 (0%)	0/3 (0%)	0/1 (0%)
	HbA1c	0/1 (0%)	0/1 (0%)	-	-	-	-
	HOMA-IR	**4/4 (100%)**	2/2 (100%)	-	0/2 (0%)	-	0/2 (0%)
	HOMA-%S	1/1 (100%)	-	-	-	-	0/1 (0%)
	HOMA-%β	0/2 (0%)	-	-	-	-	0/1 (0%)
	ISI-Matsuda	0/2 (0%)	-	-	-	-	-
	Glucose OGTT	0/2 (0%)	-	1/1 (100%)	0/1 (0%)	2/3 (66%)	0/3 (0%)
	Insulin OGTT	0/2 (0%)	-	1/1 (100%)	-	1/3 (33%)	0/2 (0%)
	IVGTT Si	0/1 (0%)	-	-	-	0/2 (0%)	0/1 (0%)
	Cederholm Index	-	-	-	-	1/1 (100%)	-
	HEC Si	-	-	-	-	1/1 (100%)	-
	HEC Glucose	-	-	-	-	1/1 (100%)	-

Thrombotic State	PAI-1	1/2 (50%)	0/1 (0%)	-	-	-	-
	Fibrinogen	0/1 (0%)	-	-	-	0/1 (0%)	-
Vascular Dysregulation	SBP	**1/9 (11%)**	0/3 (0%)	0/3 (0%)	0/2 (0%)	1/4 (25%)	0/1 (0%)
	DBP	**0/9 (0%)**	0/3 (0%)	0/3 (0%)	1/2 (50%)	1/3 (33%)	0/1 (0%)
	FMD	-	0/1 (0%)	-	1/2 (50%)	-	1/1 (100%)
	PWV	-	0/1 (0%)	-	-	0/1 (0%)	-
	Albumin	-	-	-	-	-	0/1 (0%)

Black fill, white text: 0-33% of studies reported significant differences; grey fill, black text: 34-59% of studies reported significance differences; grey fill, white text: 60-100% of studies demonstrated positive significance differences, bold writing: ≥4 studies demonstrate the same effect. *one study reported a significant increase in BMI. NA; not applicable

HOMA-IR; *homeostatic model assessment insulin resistance*, HOMA-%S; *insulin sensitivity*; HOMA-%β; *beta cell function*, ISI-Matsuda*; insulin sensitivity index-Matsuda*. OGTT; *oral glucose tolerance test*, IVGTT Si; intravenous glucose tolerance test insulin sensitivity, HEC Si; *hypereuglycaemic clamp insulin sensitivity*.

Table 3

Table 3. Detailed findings from voluntary upper-body aerobic exercise studies included in this review.

Study Design D&B Quality	***n***	**Intervention**	**CMS Outcome**	**Group Baseline** *Intervention (Control)* Mean ± SD	**Change** *Intervention (Control)*	***p* value***	**ES**
[25] Pre-post† 20 High	10	Hand-cycle 16 weeks 2 sessions/week 65-75% HRR 18-32 mins	**Waist (cm)** Android Fat Mass (kg) Android Fat (%) TG (mmol/L) HDL-C (mmol/L) Fasting Glucose (mmol/L) **Fasting Insulin (pmol/L)** **HOMA-IR** SBP (mmHg) DBP (mmHg) CRP (mg/L) IL-6 (pg/mL)	**89.7 ± 3.5** 2.6 ± 0.4 38.6 ± 3.7 1.2 ± 0.2 1.4 ± 0.2 5.3 ± 0.2 **54.6 ± 8.5** **1.9 ± 0.3** 119 ± 4 72 ± 3 2.86 ± 1.36 2.40 ± 0.57	**-2.5** 0.0 -1.3 -0.1 0.0 -0.2 **-14.3** **-0.5** +4 -3 -0.39 -0.64	**0.03** 0.85 0.26 0.67 0.94 0.30 **0.01** **0.02** 0.30 0.34 0.23 0.10	**0.75** 0.00 0.40 0.63 0.00 1.00 **1.78** **2.35** 1.13 0.57 0.28 0.56
[26] RCT 19 High	21	ACE 6 weeks 4 sessions/week 60-65% $\dot{V}O_{2PEAK}$ 45 mins	Body Mass (kg) Fat Mass (kg) VAT (cm^2) TG (mmol/L) TC (mmol/L) HDL-C (mmol/L) LDL-C (mmol/L) NEFA (mmol/L) Fasting Glucose (mmol/L) **Fasting Insulin (pmol/L)** **HOMA2-IR** HOMA2-%ß (%) ISI-Matsuda Glucose OGTT (%) Insulin OGTT (%) SBP (mmHg) DBP (mmHg)	76.8 ± 13.3 (76.8 ± 11.3) 27.6 ± 10.0 (25.5 ± 6.6) 181 ± 85 (186 ± 47) 1.2 ± 0.5 (1.3 ± 0.5) 4.9 ± 1.0 (5.1 ± 0.9) 1.1 ± 0.3 (1.0 ± 0.2) 3.2 ± 0.9 (3.5 ± 0.8) 0.6 ± 0.3 (0.7 ± 0.6) 5.3 ± 0.5 (5.7 ± 1.3) **54.8 ± 30.1 (41.3 ± 18.1)** **1.03 ± 0.57 (0.80 ± 0.35)** 87 ± 31 (66 ± 23) 4.8 ± 2.2 (6.4 ± 3.1) - - 128 ± 23 (128 ± 15) 77 ± 15 (81 ± 13)	-1.1 (-0.7) -0.6 (0.0) -22 (-3) -0.1 (+0.5) -0.1 (+0.1) +0.1 (0.0) 0.0 (-0.2) +0.3 (-0.1) 0.0 (0.0) **-12.7 (+3.1)** **-0.24 (+0.06)** -14 (+1) +0.3 (-0.7) +8 (-9) -8 (+6) -3 (-2) -1 (-4)	NS NS NS NS NS NS NS NS NS **0.03** **0.04** NS NS NS NS NS NS	- - - 1.02 0.17 0.07 0.05 0.40 - 0.54 0.49 0.58 - - - - -
[27] RCT 19 High	17	ACE 12 weeks 3 sessions/week 50-65% HRR 20-30 mins	BMI (kg/m^2) **Waist (cm)** **Leptin (ng/mL)** PAI-1 (ng/mL) **IL-6 (pg/mL)** **TNF-α (pg/mL)** Adiponectin (ng/mL)	27.6 ± 4.1 (27.8 ± 4.4) **98.1 ± 6.6 (98.4 ± 6.7)** **9.6 ± 2.7 (9.8 ± 2.8)** 29.8 ± 6.2 (30.2 ± 6.1) **6.7 ± 2.2 (6.9 ± 2.3)** **23.3 ± 5.6 (23.6 ± 5.5)** 18.8 ± 4.1 (18.5 ± 4.2)	-0.2 (NR) **-3.7 (NR)** **-2.1 (+0.1)** -0.7 (-0.1) **-2.6 (+0.1)** **-2.7 (-0.1)** +0.6 (+0.1)	0.72 **0.05** **<0.05** NS **<0.05** **<0.05** NS	- - **0.71** 0.09 **1.08** **0.47** 0.11
[28] Pre-post 17 Fair	10	ACE 10 weeks 3 sessions/week 70% $\dot{V}O_{2PEAK}$ 30 mins	BF (%) Fat Mass (kg) TC (mmol/L) HDL-C (mmol/L) LDL-C (mmol/L) Fasting Glucose (mmol/L) **Fasting Insulin (pmol/L)** **Glucose: Insulin** Glucose OGTT (AUC) Insulin OGTT (AUC) **HOMA-IR** HOMA-%ß (%) **HOMA%S (%)** ISI-Matsuda	34.9 ± 34.9 25.1 ± 11.9 4.50 ± 0.58 0.94 ± 0.16 2.71 ± 0.39 5.54 ± 0.82 **84.9 ± 38.8** **9.77 ± 4.49** - - **1.6 ± 0.7** 111.4 ± 48.7 **73.3 ± 31.6** 3.4 ± 1.6	0.0 -0.3 +0.04 -0.06 +0.31 -0.05 **-31.8** **+3.92** +6% +5% **-0.6** -29.0 **+32.3** +0.2	0.35 0.75 0.75 0.07 0.12 0.92 **0.03** **0.03** 0.25 0.92 **0.05** 0.12 **0.05** 0.35	0.01 0.02 0.08 0.22 0.72 0.06 **1.07** **1.00** 0.29 0.13 **1.11** 0.78 **1.10** 0.16
[29] Pre-post 17 Fair	5	ACE 12 weeks 3 sessions/week Anaerobic Threshold 30 mins	Body Mass (kg) BMI (kg/m^2) SBP (mmHg) DBP (mmHg)	65.6 ± 6.6 23.5 ± 3.4 110 ± 25 66 ± 12	+2.3 +0.8 +1 +2	0.18 0.18 0.13 0.80	0.33 0.22 0.04 0.11
[30] Pre-post 17 Fair	14	ACE 10 weeks 3 sessions/week 25-35 mins	Body Mass (kg)	69.2	-2	NS	-

		60% W_{PEAK}					
[31] Pre-post† 16 Fair	4	ACE 16 weeks 5 sessions/week 75% HR_{MAX} 40 mins	Body Mass (kg) BMI (kg/m^2) BF (%) Fat Mass (kg) Fasting Glucose (mmol/L) Fasting Insulin (pmol/L) IVGTT Insulin Sensitivity IVGTT Glucose Effectiveness SBP (mmHg) DBP (mmHg)	80 ± 12 28 ± 4 40 ± 3.7 31 ± 7 5.27 ± 0.50 76.4 ± 62.5 - - 119 ± 13 75 ± 5	0 0 -2 -2 -0.06 -23.6 +62.5% +35% -1 +2	NS NS NS NS 0.9 NS NS NS NS NS	0.00 0.00 0.52 0.31 0.08 0.41 0.64 0.70 0.08 0.36
[32] RCT 16 Fair	33	ACE 12 weeks 3 sessions/week 50-70% $\dot{V}O_{2PEAK}$ 30 mins	Waist (cm) TG (mmol/L) TC (mmol/L) HDL-C (mmol/L) LDL-C (mmol/L) Fasting Glucose (mmol/L) SBP (mmHg) DBP (mmHg)	86.5 (94.5) 1.50 (1.38) 4.57 (4.60) 0.96 (1.05) 2.87 (2.91) 4.44 (4.47) 100 (100) 60 (60)	+4.75 (+1.5) +0.06 (+0.29) +0.26 (+0.05) 0.0 (+0.14) 0.0 (0.09) -0.19 (+0.14) 0 (0) 0 (0)	NS NS NS NS NS NS NS NS	- - - - - - - -
[33] RCT 15 Fair	16	Hand-cycle 6 weeks 3 sessions/week 70-80% HR_{PEAK} 44 mins	**BMI (kg/m^2)** **Waist (cm)** TG (mmol/L) TC (mmol/L) HDL-C (mmol/L) LDL-C (mmol/L) Fasting Glucose (mmol/L) **Fasting Insulin (pmol/L)** **HOMA-IR**	**22.0 ± 3.7 (20.8 ± 2.7)** **88.3 ± 13.1 (81.7 ± 9.0)** 1.16 ± 0.47 (1.09 ± 0.56) 4.56 ± 0.92 (4.73 ± 0.55) 1.10 ± 0.30 (1.17 ± 0.18) 2.93 ± 0.67 (3.07 ± 0.62) 4.36 ± 0.46 (4.92 ± 0.60) **37.5 ± 16.7 (34.0 ± 20.1)** **1.0 ± 0.6 (1.1 ± 0.8)**	**-0.2 (+0.3)** **-2.6 (+0.8)** -0.01 (-0.12) +0.03 (-0.09) +0.09 (-0.01) -0.06 (-0.03) -0.09 (+0.04) **-13.9 (+11.8)** **-0.4 (0.4)**	**<0.01** **<0.01** 0.95 0.81 0.29 0.99 0.32 **<0.01** **<0.01**	**1.58** **2.67** 0.25 0.25 0.82 0.09 0.39 **1.57** **1.40**
[34] Pre-post 14 Fair	9	ACE 10 weeks 4 sessions/week 50-70% HRR 60 mins	**Body Mass (kg)** **Waist (cm)** **TG (mmol/L)** TC (mmol/L) HDL-C (mmol/L) LDL-C (mmol/L) Fasting Glucose (mmol/L) HbA1c (%) **PAI-1 (g/L)** Fibrinogen (g/L) **SBP (mmHg)** DBP (mmHg)	**61.0 ± 7.0** **85.5 ± 6.2** **1.74 ± 0.78** 5.25 ± 0.88 1.45 ± 0.18 2.95 ± 0.62 5.66 ± 1.39 4.9 ± 0.6 **5.2 ± 1.1** 2.97 ± 5.7 **136 ± 5** 75 ± 8	**-1.9** **-1.9** **-0.43** -0.18 +0.05 -0.10 -0.17 -0.10 **-1.4** -0.7 **-3** -2	**<0.05** **<0.05** **<0.05** NS NS NS NS NS **<0.05** NS **<0.05** NS	**0.26** **0.26** **0.31** 0.14 0.20 0.15 0.10 0.14 **1.22** 0.14 **0.66** 0.30
[35] Pre-post 14 Fair	12	WCE 10 weeks 2-3 sessions/week Intensity NR 20-30 mins	Body Mass (kg) TG (mmol/L) **TC (mmol/L)** HDL-C (mmol/L) TC: HDL-C Fasting Glucose (mmol/L) SBP (mmHg) DBP (mmHg)	74 ± 10 1.32 ± 0.59 **4.78 ± 1.09** 1.24 ± 0.26 4 ± 1 4.77 ± 1.94 124 ± 10 85 ± 7	+2.0 -0.08 **-0.39** 0.0 -0.2 -1.0 0 -3	NS NS **0.04** NS NS NS NS NS	0.20 0.12 **0.40** 0.00 0.20 0.03 0.00 0.35
[36] Pre-post 14 Fair	12	WCT 12 weeks 14 sessions/week 60-70% HR_{PEAK}	Body Mass (kg)	41.8 ± 5.8	0.0	NS	0.00
[37] Pre-post 13 Low	9	WCT 7 weeks 5 sessions/week Intensity NR Duration NR	Body Mass (kg) Waist (cm)	82.1 ± 14.6 109.6 ± 12.2	+1.2 +4.1	NS NS	0.09 0.28
[38] Pre-post 12 Low	11	WCE 5 weeks 2 sessions/week <80% HR_{PEAK} 30 mins	SBP (mmHg) DBP (mmHg)	126 ± 12 82 ± 6	-2 -2	NS NS	0.16 0.29
[39] Non-randomised	14	ACE 16 weeks 3 sessions/week	SBP (mmHg) DBP (mmHg)	122 ± 5 (114 ± 6) 78 ± 5 (81 ± 4)	+4 (+18) -2 (+6)	NS NS	- -

controlled trial 11 Low		50 or 70% $\dot{V}O_{2PEAK}$ 20 or 40 mins					
[40] Pre-post 11 Low	11	WCE 8 weeks 3 sessions/week 70-80% HRR (or 50-60% HRR) 20 mins	**TG (mmol/L)** **TC (mmol/L)** **HDL-C (mmol/L)** **LDL-C (mmol/L)** **TC: HDL-C**	**1.08 ± 0.32 (0.88 ± 0.26)** **5.04 ± 0.91 (4.81 ± 0.70)** **1.01 ± 0.28 (1.27 ± 0.28)** **3.54 ± 0.67 (3.15 ± 0.44)** **5 ± 0.9 (4 ± 0.7)**	**-0.20 (-0.04)** **-0.41 (+0.16)** **+0.21 (-0.18)** **-0.54 (0.16)** **-1 (+1)**	**<0.1 (NS)** **NS (NS)** **<0.1 (NS)** **<0.1 (NS)** **<0.1 (NS)**	**0.76 (0.15)** **0.63 (0.28)** **0.83 (0.46)** **1.12 (0.37)** **1.37 (0.67)**

Red font clinically high group average, *bold font* significant difference following intervention reported, *ES* effect size.
ACE *arm-crank ergometry*, WCE *wheelchair ergometer*, WCT *wheelchair treadmill ergometry*, HRR heart rate reserve, $\dot{V}O_{2PEAK}$ *peak oxygen uptake*, W_{PEAK} *peak power output*, HR_{PEAK} *peak heart rate*, HR_{MAX} *age-predicted maximum heart rate*, BF *body fat*, HOMA-IR *homeostatic model assessment of insulin resistance*, OGTT *oral glucose tolerance test*, AUC *area under the curve*, IVGTT *intravenous glucose tolerance test*, NS *non-significant*, NR *not reported*
*Group x time interaction for RCT and non-randomised controlled trial, or pre-post change for pre-post study designs.
† True study design is RCT, presented as pre-post due to two different exercise modalities being tested.

Table 4

Table 4. Detailed findings from upper-body RT (with or without aerobic training) studies included in this review.

Study Design D&B Quality	***n***	**Intervention**	**CMS Outcome**	**Group Baseline** *Intervention (Control)* Mean ± SD	**Change** *Intervention (Control)*	***p* value ***	**ES**
[41] Pre-post† 23 High	17	16 weeks 3 sessions/week **RT:** 20-25 mins, 2-3 sets at 12-15 repetition max resistance **Aerobic:** 20-25 mins, 3-5 RPE	Fat Mass (kg)	23.2 ± 10.8	-0.2	NS	0.02
[42] RCT 19 High	23	16 weeks 2 sessions/week **RT:** 3 x 10, 50-70% 1RM **Aerobic:** >20 mins, 3-6 RPE	**Body Mass (kg)** **BMI (kg/m^2)** **Waist (cm)** **Fat Mass (kg)** **VAT (kg)** Leptin (ng/mL) TG (mmol/L) TC (mmol/L) HDL-C (mmol/L) LDL-C (mmol/L) TC: HDL-C Fasting Insulin (pmol/L) HbA1c (mmol/L) PAI-1 (ng/mL) SBP (mmHg) DBP (mmHg) Brachial FMD Femoral FMD PWV – Central IL-6 (pg/mL) TNF-α (pg/mL) Adiponectin (µg/mL)	**83.4 ± 18.9 (78.6 ± 15.7)** **27.3 ± 5.2 (25.7 ± 4.9)** **96.2 ± 14.9 (89.6 ± 11.7)** **- (-)** **- (-)** 10.12 ± 13.25 (10.2 ± 12.8) 1.3 ± 0.6 (1.1 ± 0.7) 4.5 ± 0.9 (4.1 ± 0.9) 1.01 ± 0.2 (1.13 ± 0.2) 2.9 ± 0.9 (2.5 ± 0.7) 4.6 ± 0.9 (3.8 ± 1.1) 39.2 ± 29.5 (68.2 ± 77.9) 1.01 ± 0.2 (1.13 ± 0.3) 30.4 ± 17.7 (31.1 ± 22.7) 116 ± 18 (118 ± 18) 68 ± 9 (74 ± 13) - - - 2.5 ± 2.2 (3.7 ± 2.1) 4.7 ± 1.8 (4.1 ± 2.2) 76.7 ± 64.0 (82.02 ± 38.28)	**↓** **-0.3 (+0.9)** **-1.0 (+3.5)** **↓** **↓** +1.0 (+4.1) +0.1 (-0.1) -0.2 (0.0) 0.0 (+0.04) -0.2 (-0.1) -0.2 (-0.2) +9.5 (+10.3) +0.9 (-0.2) +11.6 (+15.5) 0 (-2) -1 (-2) - - - -1.0 (+1.8) -0.3 (-0.1) +13.4 (+35.67)	**0.03** **0.02** **0.03** **0.04** **0.04** NS NS NS NS NS NS NS NS NS NS NS 0.31 0.66 0.526 NS NS NS	**1.07** **1.14** **1.02** **1.00** **1.02** - - - - - - - - - - - - - - - - -
[43] RCT 17 Fair	20	8 weeks 3 sessions/week **RT:** 60-80% 1RM, 5 exercises.	BMI (kg/m^2) **Waist: Hip** **TG (mmol/L)** **TC (mmol/L)** HDL-C (mmol/L) **LDL-C (mmol/L)** Fasting Glucose (mmol/L) Fasting Insulin (pmol/L) **HOMA-IR**	25.3 ± 1.4 (24.9 ± 1.0) **0.83 ± 0.02 (0.83 ± 0.14)** **1.77 ± 0.07 (1.80 ± 0.11)** **4.66 ± 0.18 (4.78 ± 0.10)** 1.12 ± 0.06 (1.15 ± 0.11) 2.81 ± 0.10 (2.82 ± 0.12) 5.46 ± 1.34 (5.45 ± 1.42) 110.6 ± 19.5 (116.7 ± 24.9) **6.92 ± 1.27 (7.27 ± 2.09)**	-0.6 (+0.2) **-0.02 (+0.01)** **-0.27 (+0.02)** **-0.38 (+0.04)** +0.12 (+0.01) -0.12 (+0.05) -0.38 (-0.01) -2.4 (-3.5) **-0.62 (-0.25)**	NS **0.03** **0.001** **0.001** NS **0.001** NS NS **0.03**	- - - - - - - - -
[44] RCT 17 Fair	17	6 weeks 3 sessions/week **RT:** 1-3 x 10-20 **Aerobic:** 10-20 mins, 4-8 RPE or 65-85% HR_{MAX}	BMI (kg/m^2) **Waist (cm)** TC (mmol/L) **HDL-C (mmol/L)** LDL-C (mmol/L) Fasting Glucose (mmol/L) **Fasting Insulin (pmol/L)** **HOMA-IR**	21.8 ± 2.9 (20.8 ± 1.9) **84.1 ± 11.9 (79.4 ± 6.6)** 4.20 ± 0.88 (1.96 ± 0.09) **1.26 ± 0.55 (1.32 ± 0.27)** 2.42 ± 0.81 (3.25 ± 0.76) 4.50 ± 0.30 (4.20 ± 0.20) **52.1 ± 32.6 (20.1 ± 7.6)** **1.5 ± 1.0 (0.5 ± 0.2)**	-0.4 (-0.1) **-2.6 (-0.2)** -0.04 (+0.05) **+0.14 (-0.04)** -0.12 (+0.36) -0.09 (+0.10) **-20.1 (+2.1)** **-0.6 (+0.06)**	0.08 **0.02** 0.46 **0.05** 0.12 0.23 **0.05** **0.05**	1.17 **1.94** 0.40 **1.24** 0.85 0.62 **1.24** **1.33**
[45] Pre-post 15 Fair	16	12 weeks 3 sessions/week **RT:** 2 x 8 to 3 x 12. **Aerobic:** 60-75% HRR 20-60 mins	Body Mass (kg) BMI (kg/m^2) Waist (cm) **TG (mmol/L)** **TC (mmol/L)** HDL-C (mmol/L) LDL-C (mmol/L) Fasting Glucose (mmol/L) SBP (mmHg) DBP (mmHg)	74.9 ± 7.2 26.0 ± 2.6 104.1 ± 7.9 **1.41 ± 0.93** **5.66 ± 1.32** 1.26 ± 0.40 4.20 ± 1.15 5.81 ± 0.05 118 ± 20 80 ± 11	-2.9 -1.0 +1.3 **-0.30** **-0.68** +0.02 -0.19 -0.74 -5 -3	NS NS NS **<0.05** **<0.05** NS NS NS NS NS	1.19 0.33 0.17 **0.35** **0.54** 0.05 0.17 1.64 0.26 0.27
[46] RCT	34	36 weeks 2 sessions/week	SBP (mmHg)* DBP (mmHg)*	125 ± 23 (133 ± 20) 72 ± 16 (85 ± 14)	+2 (-2) +3 (-4)	NS NS	- -

15 Fair		**RT:** 70-80% 1RM, **Aerobic:** 15-30 mins, 70% HR_{MAX} or 3-4 RPE.	*Paraplegics only				
[47] Pre-post 12 Low	5	12 weeks 3 sessions/week **Circuit Training:** 50-60% 1RM 40-45 mins	TG (mmol/L) TC (mmol/L) HDL-C (mmol/L) **LDL-C (mmol/L)** **TC: HDL-C**	2.29 ± 1.35 4.73 ± 0.67 1.05 ± 0.14 **3.06 ± 0.57** **5.0 ± 1.1**	-0.14 -0.42 +0.11 **-0.79** **-1.1**	0.63 0.20 0.10 **0.05** **0.05**	0.12 0.56 0.49 **1.17** **1.19**

1RM *one-rep maximum*, RPE *rating of perceived exertion*. *Group x time interaction for RCT and non-randomised controlled trial, or pre-post change for pre-post study designs. †True study design is RCT, presented as pre-post due to two different exercise modalities being tested

Table 5

Table 5. Detailed findings of FES-cycling studies included in this review.

Study Design D&B Quality	**n**	**Intervention**	**CMS Outcome**	**Group Baseline** *Intervention (Control)* Mean ± SD	**Change** *Intervention (Control)*	**p value ***	**ES**
[48] Pre-post 16 Fair	10	FES-cycling 12 weeks 3 sessions/week 90-95% of max tolerance 1-45 mins	TG (mmol/L) TC (mmol/L) HDL-C (mmol/L) LDL-C (mmol/L) CRP (pg/mL) IL-6 (pg/mL) TNF-α (pg/mL)	0.37 ± 0.19 1.99 ± 0.46 0.48 ± 0.13 1.13 ± 0.33 12.59 ± 14.06 6.29 ± 4.65 25.62 ± 49.64	-0.01 +0.07 0.0 +0.07 -5.81 +0.61 +4.27	NS NS NS NS NS NS NS	0.06 0.15 0.00 0.22 0.55 0.13 0.07
[49] Retrospective cohort study 16 Fair	45	FES-cycling 3-168 weeks 3 sessions/week Intensity NR 45-60 mins	**TG** HDL-C **LDL-C** **TC: HDL-C**	**NR** NR **NR** **4.1 ± 1.0 (5.3 ± 1.9)**	- - - -	**<0.05** NS **<0.05** **0.03**	- - - **0.79**
[31]† Pre-post 16 Fair	9	FES-cycling 16 weeks 5 sessions/week 75% HR_{MAX} 40 mins	Body Mass (kg) BMI (kg/m^2) BF (%) Fat Mass (kg) Fasting Glucose (mmol/L) Fasting Insulin (pmol/L) IVGTT Insulin Sensitivity (%) IVGTT Glucose Effectiveness (%) SBP (mmHg) DBP (mmHg)	79 ± 12 26 ± 5 38 ± 5.7 29 ± 8.6 5.00 ± 0.11 97.2 ± 118.1 - - 123 ± 8 79 ± 5	+6 +3 0 0 +0.33 -59.0 +129 +4 +4 +4	NS NS NS NS 0.4 0.8 NS NS >0.5 >0.5	0.59 0.82 0.00 0.00 0.65 0.70 0.69 0.19 0.44 0.36
[50] Pre-post 14 Fair	7	FES-cycling 8 weeks 3 sessions/week Max load to finish 30 min 30 min	**2-h Glucose OGTT (mmol/L)** 2-h Insulin OGTT (pmol/L)	**7.77 ± 0.89** 822 ± 296	**-0.98** -215	**0.01** NS	**2.13** 1.00
[51] Pre-post 14 Fair	9	FES-cycling 6 weeks 3 sessions/week Max load to finish 30 min 30 min	SBP (mmHg)	131 ± 20	+6	NS	0.40
[52] Pre-post 14 Fair	18	FES-cycling 8 weeks 3 sessions/week Intensity NR 30 mins	Body Mass (kg) BMI (kg/m^2)	73.8 ± 13.9 25.4 ± 3.9	+1.2 +0.3	0.06 NS	0.09 0.08
[53] Pre-post 13 Low	13	FES-cycling 12 weeks 3 sessions/week Max load to finish 30 min 30 min	**SBP (mmHg)** **DBP (mmHg)** ***paraplegics only**	- -	↓ ↓	**<0.05** **<0.05**	- -
[54] Pre-post 13 Low	18	FES-cycling 10 weeks 2-3 sessions/week Max load to finish 30 min or fatigue	**Body Mass (kg)** **Fat Mass (kg)** TG (mmol/L) TC (mmol/L) **HDL-C (mmol/L)** LDL-C (mmol/L) **2-h Glucose OGTT** **2-h Insulin OGTT** **CRP** **IL-6** **TNF-α**	**69.6 ± 4.2** **22.9 ± 2.3** 1.18 ± 0.30 4.08 ± 0.16 **0.88 ± 0.05** 2.65 ± 0.16 - - **15.92 ± 1.57** **4.91 ± 1.10** **11.82 ± 0.63**	**-2.1** **+0.6** -0.04 -0.04 **-0.10** +0.07 ↓ ↓ **-2.98** **-1.12** **-0.51**	**<0.05** **<0.05** NS NS **<0.05** NS **<0.05** **<0.05** **<0.05** **<0.05** **<0.05**	**0.12** **0.06** 0.04 0.06 **0.43** 0.12 - - **0.57** **0.31** **0.19**
[55] Pre-post 13 Low	8	FES-cycling 6 weeks 3 sessions/week Intensity NR 30 mins	SBP (mmHg) DBP (mmHg)	112 ± 6 77 ± 4	-3 -4	NS NS	0.63 1.00

[56] Pre-post 12 Low	5	FES-cycling 8 weeks 7 sessions/week Max load to finish 30 min 30 mins	**BF (%)** Fasting Insulin	**29.7 ± 2.6** NR	**-1.9** NR	**<0.05** NS	**0.80** -
[57] Pre-post 12 Low	12	FES-cycling 4 weeks 2 sessions/week Intensity NR 30 mins	Fibrinogen (mg/dL)	410 ± 78	+29	NS	0.17
[58] Pre-post 11 Low	5	FES-cycling 8 weeks 7 sessions/week Max load to finish 30 min 30 mins	**HEC Glucose Uptake (%)**	-	**+33**	**<0.05**	**0.95**
[59] Pre-post 11 Low	8	FES-cycling 8 weeks 2-3 sessions/week Max load to finish 30 min 30 mins	Hyperaemic Flow	-	↔	NS	-
[60] Pre-post 11 Low	10	FES-cycling 52 weeks 3 sessions/week Intensity NR 30 mins	FFA (mmol/L) Fasting Insulin (pmol/L) Glucose OGTT (AUC) Insulin OGTT (AUC) **HEC SSGIR Step 1 (%)** HEC SSGIR Step 2 (%)	0.68 ± 0.08 83 ± 35 - - - -	-0.03 -28 ↔ ↔ **+28** +17	NS NS NS NS **<0.05** NS	0.13 0.33 - - **0.74** 0.63
[61] Pre-post 10 Low	15	FES-cycling 26 weeks 3 sessions/week Max load to finish 30 min 30 mins	Body Mass Abdominal Adipose Tissue	NR NR	↔ ↔	NS NS	- -
[62] Pre-post 9 Low	5	FES-cycling 8 weeks 3 sessions/week Intensity NR 30 mins	**Cederholm Index**	-	↑	**<0.05**	-

*Group x time interaction for RCT and non-randomised controlled trial, or pre-post change for pre-post study designs.
†True study design is RCT, presented as pre-post due to two different interventions (vs. high-protein diet).

Table 6. Detailed findings of FES-RT and combined (FES-cycling and FES-RT) studies included in this review.

Study Design D&B Quality	**n**	**Intervention**	**CMS Outcome**	**Group Baseline** *Intervention (Control)* Mean ± SD	**Change** *Intervention (Control)*	**p value ***	**ES**
[63] RCT 21 High	22	FES-knee extensions (with testosterone replacement therapy) 16 weeks 2 sessions/week 4 x 10 ~1 kg increments every 2 sessions	Body Mass (kg) **BMI (kg/m^2)** BF (%) Fat Mass (kg) VAT (cm^2) TG FFA TC HDL-C LDL-C IVGTT Insulin Sensitivity (%) IVGTT Glucose Effectiveness (%) CRP IL-6 (pg/mL) TNF-α **Adiponectin (ng/mL)**	80.5 ± 16 (77.5 ± 9.0) **25 ± 4.5 (24.4 ± 3.6)** 32 ± 11 (33.4 ± 9) 26.7 ± 12.5 (26.1 ± 8.0) 101 ± 71 (91.5 ± 49.5) NR NR NR NR NR - - NR 5.5 ± 5.6 (5.9 ± 6.0) NR **4323 ± 1856 (3516 ± 1205)**	+2.6 (+0.2) **+1.6 (-0.4)** -1.3 (-1.4) 0.0 (-1.0) -13 (-7.0) ↔ ↔ ↔ ↔ ↔ 0.0 (0.0) 31.5 (28.6) ↔ -2.6 (-2.0) ↔ **-624 (+1291)**	NS **0.004** NS NS NS NS NS NS NS NS NS NS NS NS NS **<0.05**	- - - - - - - - - - - - - - - -
[64] RCT 16 Fair	9	FES knee-extensions 12 weeks 2 sessions/week 4 x 10 Increased by ~1kg every 2 sessions	Body Mass (kg) BMI (kg/m^2) BF (%) Fat Mass (kg) Trunk VAT CSA (cm^2) **TG (mmol/L)** FFA (mmol/L) TC (mmol/L) HDL-C (mmol/L) LDL-C (mmol/L) **TC: HDL-C** HOMA-IR (Log$_{10}$) Glucose OGTT (AUC) (%) Insulin OGTT (AUC) (%)	74 ± 14 (76 ± 8) 21 ± 5 (23 ± 3) 30 ± 8 (29 ± 3) 23.3 ± 9 (22 ± 2) 103 ± 80 (106 ± 32) **1.58 ± 1.38 (1.25 ± 0.28)** 0.58 ± 0.1 (0.53 ± 0.1) 4.19 ± 1.27 (3.93 ± 0.70) 0.78 ± 0.08 (0.83 ± 0.16) 2.72 ± 0.93 (2.53 ± 0.67) **5.6 ± 2 (5 ± 1)** 0.44 ± 0.27 (0.33 ± 0.17) - -	+1 (-1) 0 (0) -1 (-1) -0.7 (1) -9 (-14) **-0.60 (+0.16)** -0.14 (-0.11) +0.05 (+0.2) +0.08 (-0.03) +0.21 (+0.16) **-0.8 (+0.2)** -0.03 (+0.06) -6.5 (-8.5) -33.9 (+22.0)	NS NS NS NS NS **0.05** 0.3 0.1 0.07 0.5 **0.02** NS NS NS	- - - - - - - - - - - - - -
[65] Pre-post 14 Fair	12	FES knee-extensions 12 weeks 3 sessions/week 2 x 30 (25% Max), 1 x 60 (12.5% Max) Increased by 0.5 kg per session	Body Mass (kg)	67.6	-0.7	NS	-
[66] Pre-post 14 Fair	14	FES knee-extensions 16 weeks 2 sessions/week 4 x 10 Increased by 0.9 kg evert 2 successful sessions	BMI (kg/m^2) TG (mmol/L) **TC (mmol/L)** **HDL-C (mmol/L)** LDL-C (mmol/L) TC: HDL-C Fasting Glucose (mmol/L) 2-h Glucose OGTT (mmol/L) HOMA-IR HOMA%S HOMA%β	26.7 ± 4.7 1.55 ± 0.94 **4.76 ± 1.03** **1.09 ± 0.40** 2.95 ± 0.94 4.8 ± 1.8 4.94 ± 1.05 6.62 ± 4.30 1.6 ± 1.4 136.0 ± 112.0 125.0 ± 68.0	-0.3 -0.13 **-0.18** **+0.09** -0.21 -0.6 +0.22 +0.85 -0.1 +7.0 -14.0	0.70 0.36 **0.05** **0.02** 0.11 0.43 0.16 0.41 0.73 0.65 0.17	0.07 0.16 **0.16** **0.24** 0.21 0.33 0.07 0.19 0.06 0.07 0.19
[67] Pre-post 14 Fair	5	FES knee extensions 18 weeks 2 sessions/week 4 x 10 Increased by 0.9-1.8 kg every 2 sessions	Posterior Tibial FMD (when adjusted for resting diameter)	-	+3.9%	**0.03**	-
[68] Pre-post 13 Low	19	Combined 10-32 weeks 3 sessions/week	Albumin	NR	↔	NS	-

		Max load to fatigue or 45 reps (FES knee-extensions) 30 mins (FES-cycling)					
[69] Pre-post 12 Low	11	Combined 13-28 weeks 3 sessions/week Max load to fatigue or 45 reps (FES knee-extensions) Duration NR	SBP (mmHg) DBP (mmHg)	114 ± 4 71 ± 3	-16 -4	NS NS	1.21 0.40
[70] Pre-post 11 Low	5	FES knee-extensions 12 weeks 2 sessions/week 4 x 10 Increased by 0.9-1.8 kg every 2 sessions	Fasting Glucose (mmol/L) Fasting Insulin (mmol/L) 2-h Glucose OGTT (mmol/L) 2-h Insulin OGTT	4.87 ± 0.58 NR 5.98 ± 1.44 NR	0.0 ↔ -0.47 ↔	NS NS NS NS	0.00 - 0.24 -
[71] Pre-post 9 Low	4	Combined 4-12 weeks 5 sessions/week Intensity NR 15 mins each	Body Mass (kg)	67.9 ± 5.2	+4.9	NS	0.65

Table 7

Table 7. Hybrid and FES-rowing studies included in this review.

Study Design D&B Quality	***n***	**Intervention**	**CMS Outcome**	**Group Baseline** *Intervention (Control)* Mean ± SD	**Change** *Intervention (Control)*	***p* value**	**ES**
[25] 20 Pre-post† High	9	Hybrid 16 weeks 2 sessions/week 65-75% HRR 18-32 mins	**Waist (cm)** Android Fat Mass (kg) **Android Fat (%)** **TG (mmol/L)** HDL-C (mmol/L) Fasting Glucose (mmol/L) Fasting Insulin (pmol/L) HOMA-IR SBP (mmHg) **DBP (mmHg)** CRP (mg/L) IL-6 (pg/mL)	**91.8 ± 4.7** 2.0 ± 0.4 **33.4 ± 2.9** **1.7 ± 0.2** 1.1 ± 0.1 5.7 ± 0.3 72.7 ± 10.6 2.8 ± 0.5 112 ± 6 **69 ± 3** 3.91 ± 1.75 2.51 ± 0.91	**-3.9** -0.1 **-2.1** **-0.3** +0.1 +0.1 -18.9 -0.6 +5 **-6** -0.71 -0.63	**0.02** 0.34 **0.02** **0.01** 0.22 0.38 0.11 0.16 0.39 **0.04** 0.08 0.20	**0.92** 0.25 **0.76** **1.50** 1.00 0.28 1.66 1.09 0.65 **1.70** 0.41 0.83
[72] Pre-post 16 Fair	9	Hybrid 6 weeks 2 sessions/week Intensity NR 30 mins	Body Mass (kg) Relative Brachial FMD (%) **Relative Femoral FMD (%)**	74 ± 18 - -	+1 - -	0.52 0.28 **0.002**	0.06 - -
[73] Pre-post 15 Fair	12	FES-rowing 6 weeks 5 sessions/week >70% HR_{MAX} 42.5 mins	BMI (kg/m^2) Waist (cm)	23.4 ± 3.7 84.1 ± 10.3	-0.4 -2.1	0.06 0.06	0.11 0.21
[74] Pre-post 14 Fair	12	FES-rowing 26 weeks 1.8 ± 2 sessions/week 75-85% HR_{PEAK} 30 mins	Body Mass (kg)	72.5 ± 3.9	+0.8	NS	0.20
[75] Pre-post 14 Fair	10	Hybrid 4 weeks 2-3 sessions/week Intensity NR 30 mins	Body Mass (kg) SBP (mmHg) DBP (mmHg) Absolute Brachial FMD (mm) Relative Brachial FMD (%) Absolute Femoral FMD (mm) Relative Femoral FMD (%)	73 ± 10 123 ± 18 73 ± 14	0 -4 -5	0.77 0.17 0.23 0.48 0.68 0.06 0.10	0.00 0.23 0.38 - - - -
[76] Pre-post 14 Fair	10	FES-rowing 6 weeks 3 sessions/week 86 ± 8% HR_{PEAK} 30 mins	Body Mass (kg) BF (%)	85.1 ± 19.6 36.9 ± 5.9	0.0 -0.2	0.18 0.64	0.00 0.03
[77] Pre-post 14 Fair	7	FES-rowing 12 weeks 3-4 sessions/week 80% $\dot{V}O_{2PEAK}$ 200 kcal/session	Body Mass (kg) BF (%) **Leptin (ng/mL)** **Fasting Glucose (mmol/L)** Fasting Insulin (pmol/L) HOMA-IR	72.1 ± 3.6 25.5 ± 1.8 **6.9 ± 1.7** **5.73 ± 0.09** 95.1 ± 14.6 3.6 ± 0.8	-1.1 -1.1 **-2.2** **-0.12** -16.7 -0.8	NS 0.07 **0.05** **<0.05** NS NS	0.14 0.26 **0.60** **0.73** 0.49 0.65
[78] Pre-post 7 Low	8	Hybrid 6 weeks 2 or 3 sessions/week 80-90% HR_{MAX}	TC HDL-C LDL-C Glucose OGTT	NR NR NR NR	NR NR NR NR	NS NS NS NS	- - - -

HR_{PEAK} *peak heart rate*, HR_{MAX} *age-predicted maximum heart rate*, HOMA-IR *homeostatic model assessment of insulin resistance*, OGTT *oral glucose tolerance test*, NS *non-significant*, NR *not reported*

†True study design is RCT, presented as pre-post due to two different exercise modalities being tested.

Table 8. Ambulation studies included in this review.

Study Design D&B Quality	***n***	**Intervention**	**CMS Outcome**	**Group Baseline** *Intervention (Control)* Mean ± SD	**Change** *Intervention (Control)*	***p* value***	**ES**
[41] Pre-post† 23 High	17	FES-walking 16 weeks 3 sessions/week Max load without knee buckling 45 mins	Fat Mass (kg)	25.4	-1.1	NS	0.12
[79] RCT 19 High	18	Robotic BWSTT 12 weeks 3 sessions/week 80-85% HRR 20-45 mins	Body Mass (kg) BF (%)	80.8 ± 14.6 (94.3 ± 25.0) 33.6 ± 7.9 (34.2 ± 6.9)	-1.0 (-2) -1.2 (-0.9)	0.72 0.20	- -
[80] Pre-post 19 High	10	BWSTT 16 weeks 3 sessions/week Max speed without loss of gait 60 mins	SBP (mmHg) DBP (mmHg)	114 ±19 66 ± 11	-1 -2	0.90 0.62	0.05 0.19
[81] Pre-post 18 Fair	8	BWSTT 26 weeks 3 sessions/week Max load and speed without knee bucking or loss of gait 60 mins	SBP (mmHg) DBP (mmHg)	117 ± 20 73 ± 11	-2 -1	NS NS	0.12 0.15
[82] Pre-post 17 Fair	14	BWSTT 6 weeks 5 sessions/week Intensity NR 45 mins	TG (mmol/L) TC (mmol/L) HDL-C (mmol/L) LDL-C (mmol/L) Fasting Glucose (mmol/L) **CRP (NR)** SBP (mmHg) DBP (mmHg)	1.36 ± 0.17 4.67 ± 0.54 1.46 ± 0.31 2.61 ± 0.37 5.12 ± 0.67 **NR** 127 ± 10 75 ± 5	-0.20 -0.14 +0.07 -2.9 -0.19 **-0.15** -3 -3	NS NS NS NS NS **0.002** NS NS	0.33 0.28 0.26 0.21 0.54 - 0.21 0.49
[83] Pre-post 16 Fair	13	BWSTT 52 weeks 3 sessions/week Minimal load and max speed without knee buckling, losing proper weight shifting, and upright torso Up to 3 x 5-15 min bouts	Fat Mass (kg)	23.6 ± 11.0	+0.4	NS	0.04
[84] Pre-post 16 Fair	5	Robotic Exoskeleton Walking 60-70% HRR 6 weeks 3 sessions/week Up to 60 mins	**Body Mass (kg)** **BMI (kg/m^2)** **BF (%)**	**79.7 ± 12.5** **24.5 ± 1.7** **35.4 ± 7.1**	**+2.0** **+0.6** **-1.3**	**0.04** **0.04** **0.04**	**0.15** **0.32** **0.23**
[85] Pre-post 15 Fair	9	BWSTT 26 weeks 3 sessions/week Intensity NR Until self-reported fatigue	TG (mmol/L) **TC (mmol/L)** HDL-C (mmol/L) **LDL-C (mmol/L)** **TC: HDL**	1.51 ± 0.20 **4.91 ± 0.19** 1.29 ± 0.19 **3.25 ± 0.22** **3.83 ±0.33**	-0.19 **-0.55** +0.14 **-0.42** **-0.76**	0.17 **0.02** 0.19 **0.05** **0.04**	0.33 1.15 0.20 0.54 0.95
[86] Pre-post 14 Fair	9	BWSTT 24 weeks 3 sessions/week Based on self-reported fatigue Until self-reported fatigue	**Glucose OGTT (AUC)** **Insulin OGTT (AUC)**	- -	**-15%** **-33%**	**<0.05** **<0.05**	- -
[87] Pre-post 13 Low	16	FES-walking 11 weeks 3 sessions/week Comfortable intensity Up to 3 sets	Body Mass (kg)	66.0	+1.3	0.06	-

BSWTT *body-weight supported treadmill training*, HRR *heart rate reserve*, AUC *area under the curve* † True study design is RCT, presented as pre-post due to two different exercise modalities being tested. *Group x time interaction for RCT and non-randomised controlled trial, or pre-post change for pre-post study designs.

Table 9. Overview of other exercise studies included in review but not grouped for qualitative analysis.

Study Design D&B Quality	***n***	**Intervention**	**CMS Outcome**	**Group Baseline** *Intervention (Control)* Mean ± SD	**Change** *Intervention (Control)*	***p* value***	**ES**
[88] RCT 19 High	48	Lower body RT and BSWTT or FES 24 weeks 3 sessions Intensity NR Up to 180 mins	Body Mass (kg) BMI (kg/m^2) QUICKI	89.4 ± 20.3 (75.7 ± 21.0) 27.1 ± 6.4 (24.8 ± 6.6) 0.35 ± 0.04 (0.38 ± 0.06)	-0.20 (+5.03) 0.0 (+0.7) -0.002 (-0.012)	0.31 0.29 0.92	0.45 0.41 0.06
[89] Pre-post† 18 Fair	6	Combined RT, ACE, and FES 8 weeks 3 sessions/week **ACE:** 80-90% $\dot{V}O_{2PEAK}$, 15 x 1 mins **Upper-body RT:** 3 x 12 **FES-knee extensions:** 40 reps, increased by ~0.5-1 kg every 2 weeks	Body Mass (kg) Fat Mass (kg) Android Fat Mass (kg) TG (mmol/L) TC (mmol/L) HDL-C (mmol/L) LDL-C (mmol/L) **Fasting Glucose (mmol/L)** Fasting Insulin (pmol/L) Glucose OGTT (AUC) Insulin OGTT (AUC) HOMA-IR ISI-Matsuda IL-6 (pg/mL) TNF-α (pg/mL)	87.7 ± 15.0 - - 1.36 ± 0.66 4.44 ± 0.99 1.09 ± 0.16 2.73 ± 0.80 **6.12 ± 1.14** 115.3 ± 127.1 - - 4.6 ± 5.1 3.3 ± 2.0 1.7 ± 1.0 2.2 ± 0.4	↔ ↔ ↔ +0.39 -0.21 -0.05 -0.34 **-0.54** -25.7 +4% -27% -1.3 +1.3 -0.7 -0.8	NS NS NS 0.47 0.94 0.96 0.75 **0.04** 0.91 0.87 0.34 0.83 0.98 0.20 0.27	- - - 0.45 0.25 0.27 0.48 **0.56** 0.24 0.14 0.28 0.31 0.43 0.95 0.97

†True study design is RCT, presented as pre-post due to two different exercise modalities being tested
*Group x time interaction for RCT and non-randomised controlled trial, or pre-post change for pre-post study design

Table 10

Table 10. Participant characteristics, statistical power, and control group (if applicable) of included studies.

Study	Control Type	Statistical Power	N (M/F)	Age (y)	TSI (y)	LOI	ASIA
[32]	General Exercises	NR	33 (29/4)	I:33 (15-42), C:37 (19-62)	I: 1.3 (0.2-12), C: 1.3 (0.3-10)	C7-L3	A-D
[48]	N/A	NR	10 (9/1)	39±10 (26-55)	9±9 (1-21)	C4-T11	A-C
[25]	N/A	No	19 (18/1)	Hybrid: 49±3 (31-64), Hand cycle: 47±3 (30-63)	Hybrid: 21±3 (13-34), Hand cycle: 16±2 (9-21)	C2-L2	A-D
[28]	N/A	NR	10 (8/2)	37±13 (23-55)	12±14 (1-34)	C7-T5	A-B
[62]	N/A	NR	5 (4/1)	31-50	3-25	C5-T8	A
[45]	N/A	NR	16 (16/0)	45±12	12±10	Thoracic	A-C
[39]	No exercise intervention	NR	14 (14/0)	I: 30±3, C: 29±3	I: 19±3, C: 9±3	NR	NR
[42]	Instructed to maintain PA levels	NR	23 (21/2)	I: 39±11, C: 42±13	I: 15±10, C: 9±10	C1-T11	A-D
[81]	N/A	NR	8 (6/2)	28±5 (20-34)	10±8 (2-24)	C4-C5	B-C
[80]	N/A	NR	6 (4/2)	38±15	8±9	C4-T12	A-B
[53]	N/A	NR	13 (12/1)	31±5 (21-41)	8±4 (3-16)	C4-T10	A-D
[37]	N/A	NR	9 (NR)	35±11 (25-50)	12±5 (5-18)	C5-T4	NR
[51]	N/A	NR	9 (9/0)	39±11 (28-44)	11±10 (1-27)	C5-T8	A-C
[41]	N/A	NR	34 (26/8)	FES: 57±14, RT: 54±17	FES: 9±10, RT: 10±11	C2-T12	C-D
[83]	N/A	NR	14 (11/3)	29±8 (20-53)	8±7 (1-24)	C4-T12	NR
[63]	Testosterone replacement therapy only	Yes	22 (22/0)	I: 37±12, C: 35±8	I: 10±9; C: 7±6	C5-T11	A-B (ISNCSCI)
[31]	N/A	NR	9 (9/0)	ACE: 41±13 (30-61); FES-Cycling: 37±7 (29-45)	ACE: 11±9 (2-26); FES-Cycling: 7±5 (4-14)	C8-T10	A-B
[64]	Standardised diet with no exercise intervention	NR	9 (9/0)	35±9 (21-47)	13±9 (2-26)	C5-T11	A-B
[79]	Stretching (3 days/week for 20-25 mins)	NR	18 (NR)	I: 52±12 (28-66), C: 52±15 (30-72)	NR	NR	C-D
[54]	N/A	NR	18 (13/5)	40±2 (25-57)	11±3	C4-T7	NR
[29]	N/A	NR	5 (5/0)	40±7	13.9±5.0	C4-L1	A-D
[78]	N/A	NR	8 (NR)	NR	NR	NR	NR
[46]	No exercise intervention	NR	34 (NR)	I: 37±11 (19-65); C: 43±9 (29-63)	I: 8±6 (1-22); C: 12±7 (3-24)	C4-S1	A-D
[56]	N/A	NR	5 (5/0)	35±3 (28-44)	10±3 (4-23)	C5-C7	A-B
[58]	N/A	NR	5 (5/0)	35±3 (28-44)	10±3 (4-23)	C5-C7	A-B
[40]	N/A	NR	11 (6/5)	31±4 (23-36)	12±7 (2-19)	C5-T9	NR
[34]	N/A	NR	9 (9/0)	38±10	16±7	T8-L1	A-B
[77]	N/A	NR	6 (6/0)	46±5 (24-56)	NR	T4-T10	A-B
[50]	N/A	NR	7 (5/2)	45±8 (30-53)	20±14 (3-40)	C5-T10	NR
[88]	No exercise intervention	Yes	48 (30/11)	I: 42±13; C: 34±12	I: 7±10; C: 6±7	NR	C-D
[57]	N/A	NR	12 (NR)	NR	>1	C4-C8 and T1-T10	NR

[84]	N/A	NR	5 (4/1)	60±6	8±5	C7-T10	NR
[33]	No exercise intervention	NR	15 (9/6)	33±6 (22-46)	7±4 (2-16)	C5-T11	A-B
[44]	Standard Care	NR	17 (11/6)	37±7 (23-53)	10±7 (2-27)	C4-L1	A-C
[73]	N/A	NR	12 (10/2)	36±12 (16-45)	11±6 (5-24)	C6-L1	A-C
[87]	N/A	NR	16 (13/3)	28±7 (21-45)	4±3 (0.7-9)	T4-T11	NR
[59]	N/A	NR	8 (8/0)	39±3	>4	C5-T11	A-B
[52]	N/A	NR	18 (16/2)	40±11 (26-61)	3±2 (1-9)	C3-L1	B-D
[89]	N/A	NR	6 (6/0)	50±8 (36-58)	24±8 (10-30)	C6-T6	A-B
[70]	N/A	NR	5 (5/0)	36±5	13±7	C5-T10	A
[30]	N/A	NR	14 (NR)	Supine: 34±12; Sitting: 33±7	Supine: 9±13; Sitting: 14±6	CT-T1	NR
[35]	N/A	NR	12 (11/1) (2 non-SCI)	38±10 (22-58)	15±7 (4-29)	C6-L3	NR
[43]	No exercise intervention	NR	20 (20/0)	I: 25±3; C: 26±3	I: 10±4; C: 9±4	T9-T12	A
[60]	N/A	NR	10 (8/2)	35 (27-45)	12 (3-23)	C6 and T4	NR
[36]	N/A	NR	12 (12/0)	31±9 (19-45)	2±1 (1-3)	<T10	NR
[47]	N/A	NR	5 (5/0)	38±4 (34-43)	5±1 (1-7)	T6-T12	NR
[26]	No exercise intervention	Yes	21 (15/6)	I: 46±6, C: 48±10	I: 20±10; C: 14±11	T4-L3	A-D
[71]	N/A	NR	4 (4/0)	20-35	4±3 (1-8)	T4-T6	NR
[86]	N/A	NR	9 (8/1)	31±3	8±3	C4-T12	C
[69]	N/A	NR	11 (7/4)	29±15 (18-54)	6±3 (0.5-11)	C4-T6	NR
[68]	N/A	NR	19 (16/3)	19-47	2-17	C4-T10	NR
[55]	N/A	NR	8 (7/1)	32±2 (23-41)	12±2 (5-24)	C7-L1	NR
[65]	N/A	No	12 (9/3)	38±13 (19-63)	6±6 (1-17)	C4-T10	NR
[27]	No exercise intervention	NR	17 (17/0)	30±4 (I & C)	5±0	≤T5	NR
[66]	N/A	No	14 (11/3)	27±5 (28-57)	8±7 (2-22)	C4-T7	A-B
[49]	Standard Care	NR	45 (38/7)	I: 37±12; C: 35±12	I: 8 (1.5-43), C: 6 (1-27)	C1-L5	A-C
[74]	N/A	Yes	12 (11/1)	33±4 (22-60)	8±3 (0-33)	C4-T2	NR
[61]	No exercise intervention	NR	15 (15/0)	33 (21-48)	9 (1-21)	NR	A-B
[85]	N/A	NR	9 (8/1)	31±3	8±3	C4-T12	C
[67]	N/A	NR	5 (5/0)	36±5	13±7	C5-T10	A
[72]	N/A	NR	9 (8/1)	39±3 (25-52)	11±3 (1-25)	C5-T12	A, C
[75]	N/A	NR	10 (9/1)	39±9 (23-53)	11±6 (1-20)	T1-T12	A, C
[82]	N/A	NR	14 (10/4)	51±17	2-10	NR	Motor Incomplete
[76]	N/A	NR	10 (8/2)	47±18	18±14 (2-39)	T4-T12	A-C
[38]	N/A	NR	11 (11/0)	31±8 (20-49)	2±1 (0.5-4)	T8-T12	A

TSI *time since injury*, LOI *level of injury*, ASIA *American Spinal Injury Association Impairment Scale*, NR *not reported*, ISNCSCI *International Standards for Neurological Classification of Spinal Cord Injury*, ROM *range of motion; I* Intervention, *C* Control.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title Page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1-2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplement 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Tables 3-10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Tables 3-10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Tables 3-10
Synthesis of results	21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency.	Table 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9-14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13-14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	N/A

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