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Title: The impact of physical activity and exercise on aerobic capacity in individuals with spinal cord injury: A systematic review with meta-analysis and meta-regression

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Running head: Exercise and fitness in SCI

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ABSTRACT

Background A low level of cardiorespiratory fitness [CRF; typically defined as peak oxygen uptake ($\dot{V}O_{2peak}$) or peak power output (PPO)] is a widely reported consequence of spinal cord injury (SCI). This systematic review with meta-analysis and meta-regression aimed to assess whether certain SCI characteristics and specific exercise considerations are moderators of changes in CRF.

Methods Eligible studies included randomised controlled trials (RCTs) and pre-post studies that conducted an exercise intervention lasting >2 weeks. The outcome measures of interest were absolute ($A\dot{V}O_{2peak}$) or relative $\dot{V}O_{2peak}$ ($R\dot{V}O_{2peak}$), and/or PPO. Four databases were searched up to July 2021. The Cochrane Risk of Bias 2 tool and the National Institute of Health Quality Assessment Tool were used to assess bias/quality. The certainty of the evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. Random effects meta-analyses and meta-regressions were conducted.

Results Ninety studies (110 independent exercise interventions) with a total of 1,191 participants were included in our primary meta-analysis. There were significant improvements in $A\dot{V}O_{2peak}$ [0.22 (0.17, 0.26) L/min, p<0.001)], $R\dot{V}O_{2peak}$ [2.8 (2.2, 3.4) mL/kg/min, p<0.001)], and PPO [11 (8, 13) W, p<0.001]. There were no subgroup differences in $A\dot{V}O_{2peak}$ or $R\dot{V}O_{2peak}$. There were subgroup differences ($p\leq0.008$) for changes in PPO based on time since injury, neurological level of injury, exercise modality, relative exercise intensity, method of exercise intensity prescription, and frequency. The meta-regression found that increased age was associated with increases in $A\dot{V}O_{2peak}$ and $R\dot{V}O_{2peak}$, and exercise intensity prescription and volume were associated with increases in PPO (p<0.05). GRADE assessments indicated a low level of certainty in the estimated effects due to study design, risk of bias, inconsistency, and imprecision.

Conclusion The pooled analysis indicates that performing exercise >2 weeks results in significant improvements in $A\dot{V}O_{2peak}$, $R\dot{V}O_{2peak}$ and PPO in individuals with SCI. Subgroup comparisons identify that upper-body aerobic exercise and resistance training appear the most effective at improving PPO. Furthermore, acutely-injured, individuals with paraplegia, exercising at a moderate-to-vigorous intensity, prescribed via a percentage of oxygen consumption or heart rate, for more than 3 sessions/week will likely experience the greatest change in PPO.

Registration PROSPERO CRD42018104342

KEYWORDS: Cardiorespiratory Fitness, Cardiopulmonary Fitness, Function, Spinal Cord Injuries, Rehabilitation, Exercise

Key Points

- Exercise interventions >2 weeks can significantly improve cardiorespiratory fitness in individuals with a spinal cord injury, by a magnitude greater than one spinal cord injury adjusted metabolic equivalent (i.e., ≥2.7 mL/kg/min). A one metabolic equivalent improvement has been associated with a reduction in cardiovascular related mortality risk in non-injured individuals.
- Our findings support the minimum 40 minutes of weekly moderate-to-vigorous intensity exercise recommended by the spinal cord injury-specific exercise guidelines to significantly improve fitness. However, a two-fold greater improvement in peak power output may be achieved with exercising ≥90 min/week in comparison to ≥40 min/week.
- Our secondary meta-analysis comparing cohort studies indicates that prolonged exercise participation benefits cardiorespiratory fitness in the long term. However, these studies are prone to confounding and are inherently biased.
- Future research should consider following the recommendations published in the exercise intervention reporting guidelines, investigate the dose-response relationship between exercise and cardiorespiratory fitness in this population, and identify whether differences in supraspinal sympathetic cardiovascular impacts changes in cardiorespiratory fitness.

1. INTRODUCTION

Spinal cord injury (SCI) is a complex neurological condition, caused by trauma, disease or degeneration, which results in sensory-motor deficits (i.e., paralysis or paresis) below the level of lesion and autonomic dysfunctions. Progressive physical deconditioning following injury results in increased health care utilisation, reliance on personal assistance services and a greater predisposition towards developing chronic diseases [1,2]. Individuals with SCI are at an increased risk of stroke, cardiovascular disease (CVD), and type-2 diabetes mellitus compared to non-injured counterparts [3–5]. The elevated incidence of these conditions in people with SCI emphasises the need for targeted interventions to address modifiable risk factors for these chronic diseases, such as cardiorespiratory fitness (CRF). In clinical populations cardiorespiratory fitness (CRF) is typically defined as an individual's peak oxygen uptake ($\dot{V}O_{2peak}$) or peak power output (PPO). $\dot{V}O_{2peak}$ and PPO are determined during graded cardiopulmonary exercise testing (CPET) to the point of volitional exhaustion, and represents the integrated functioning of different bodily systems (pulmonary, cardiovascular and skeletal) to uptake, transport and utilise oxygen for metabolic processes [6]. A number of prospective studies have indicated that CRF is at least as important, if not more so, than other traditional CVD risk factors (e.g., obesity, hypertension and smoking) and is strongly associated with mortality [7–12].

Low levels of CRF have been widely reported in the SCI-population [13], with the between-person variability partially explained by the neurological level and severity of injury (i.e., lower CRF reported in individuals with tetraplegia) [14]. SCI can damage somatic pathways involved in the voluntary control of skeletal muscles, but also sympatho-excitatory pathways involved in the autonomic control of the cardiovascular system. In individuals with cervical and upper-thoracic SCI, the diminished supra-spinal control to the heart and blood vessels in major capacitance beds can limit exercise capacity [15,16]. This may explain the minimal returns on investment highlighted in a recent systematic review on the effects of aerobic exercise interventions in individuals with tetraplegia [17]. A large proportion of the variance in CRF is also explained by physical activity [18], which is reduced in the SCI-population [19,20]. SCI is characterised by lower-limb impairments and an ensuing reliance on mobility aids that limits the engagement in sufficient levels of physical activity to achieve meaningful health benefits.

Performing regular physical activity and/or structured exercise has long been promoted for improving CRF in individuals with SCI [21,22]. In 2011, the first evidence-based exercise guidelines, specifically for individuals with SCI were developed [23], which stated that *"for important fitness benefits, adults with SCI should engage in at least 20 minutes of moderate-to-vigorous-intensity aerobic activity and strength-training exercises 2 times per week"*. This guideline has since been updated, yet remains the same with regards to CRF benefits [24]. Although this implies adults with SCI can accrue fitness benefits from volumes of activity well below that promoted in the general population, others have advocated that adults with a physical disability [25,26] and individuals with SCI [27] should aim to perform at least 150 minutes of aerobic exercise per week. For additional health benefits it has been suggested that adults should perform closer to 300 minutes per week of moderate-intensity physical activity [28,29]. While the current SCI-specific guidelines likely represent the *"minimum"* threshold required to achieve CRF benefits, it has been suggested that this creates an impression that individuals with SCI do not need to be as physically active as the general population [30]. The dose-response relationship between exercise and CRF improvements in individuals with SCI remains to be elucidated.

It is noteworthy that the aforementioned SCI-specific exercise guidelines utilise the terminology of *"moderate-to-vigorous"* to describe the desired exercise intensity. This is in contrast to accepted guidelines in the general population whereby moderate and vigorous-intensity exercise are distinguished from one another with specific thresholds (e.g., ≥150 minutes of moderate-intensity or ≥75 minutes of vigorous-intensity activity per week) [26]. Exercise intervention intensity has been shown to influence the magnitude of change in CRF in patients undergoing cardiac rehabilitation [31,32]. The feasibility/effectiveness of higher intensity exercise is also currently a topical area of research in the SCI-population [33–35]. There is the potential for vigorous-intensity exercise to be more time efficient or lead to superior health benefits, although its impact on CRF in individuals with SCI compared to moderate-intensity exercise is yet to be determined. A recent systematic review identified that exercise interventions of a specific modality yield distinct changes in certain cardiometabolic health outcomes and not others in individuals with SCI [36]. This provides rationale for wanting to investigate the efficacy of different exercise modalities on CRF in this population. Consequently, a number of research questions requiring further attention include:

1) Do injury-specific characteristics (e.g., tetraplegia vs. paraplegia, acute vs. chronic injuries, motor-complete vs. incomplete) mediate CRF responses to exercise?

2) What is the best intensity, frequency, and volume of weekly exercise?

3) Is there an optimal conditioning modality [e.g., upper-body aerobic exercise, resistance training, functional electrical stimulation (FES), hybrid or multimodal exercise interventions etc.]?

To address these questions, we performed a systematic review with meta-analysis and meta-regression to investigate the impact of different exercise interventions on changes in CRF in individuals with SCI. Moreover, we gathered evidence to determine whether key moderators (e.g., participant/injury characteristics, intervention/study characteristics and risk of bias) influence these intervention effects.

2. METHODS

This current review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [37] and was prospectively registered (PROSPERO ID CRD42018104342). Randomised and non-randomised study designs [randomised controlled trials (RCTs) and pre-post interventions without a comparison control group] were included in the primary meta-analysis of this review. Our secondary meta-analyses included cohort, cross-sectional and observational studies.

2.1. Eligibility criteria

Studies met the following inclusion criteria: 1) Adult (≥18 years) participants; 2) any acquired (traumatic, infection, cancer) SCI (*note, studies were included if >80% of the sample met these two aforementioned inclusion criteria*); 3) an exercise or physical activity intervention lasting >2 weeks (RCTs and pre-post trials included in the primary meta-analysis); 4) report a measurable exposure variable (i.e., secondary meta-analysis cohort studies: athletes vs. non-athletes or sedentary vs. active participants; and cross-sectional studies: self-reported or objectively measured habitual physical activity level) and; 5) report CRF-specific outcomes [i.e., absolute or relative $\dot{V}O_{2peak}$, evaluated via analysis of expired air during a peak (or symptom-limited) CPET or submaximal prediction, or PPO].

Studies were excluded if they met the following criteria: 1) non-human; 2) non-original work (i.e., reviews, guideline documents, editorials, viewpoints, letter-to-editor, protocol paper); 3) case-reports and

case series with a number (n) of participants <5 (to increase the robustness of our findings given the inclusion of smaller sample sizes in previous reviews [21,38,39]); 4) non-peer reviewed (i.e., conference proceeding/abstracts/posters); 5) children or adolescents (<18 years) ; 6) non-SCI (non-injured participants or other neurological conditions); 7) does not report a CRF-specific outcome; 8) single exercise sessions or an intervention <2 weeks; 9) no suitable comparison (i.e., control group or baseline data pre-intervention) or exposure variable measured; 10) no full text; and 11) not written in English. Studies with concurrent interventions (i.e., diet, lifestyle or respiratory training) were included only if the effects of exercise could be isolated.

2.2. Search strategy

A search of the following electronic databases: MEDLINE (via Pubmed), Excerpta Medica Database (EMBASE; via Ovid), Web of Science and the Cochrane Central Register of Controlled Trials (CENTRAL) was conducted from their respective inception through to July 18, 2021. Search terms were developed by the corresponding author (TN) and agreed upon by co-authors (AK, MW). The search strategy combined key words describing the following: 1) condition (e.g., SCI); 2) 'intervention or exposure variable' (e.g., rehabilitation, exercise and physical activity); and 3) 'outcome' (e.g., $\dot{V}O_{2peak}$ or PPO). Details of the complete search strategy can be found as online supplementary material (S1). Search results were collated using Endnote software (Thomson Reuters, NY) and duplicates removed.

2.3. Study selection and data extraction

The citations retrieved from the search strategy were screened by title, abstract, and full text by two independent reviewers (DH, GB). At each stage of the evaluation, studies were excluded if the inclusion criteria were not satisfied. A conservative approach was taken, whereby if insufficient information was available to warrant study exclusion during the title and abstract stages of the screening, studies were retained in the sample for full text screening. TN resolved any disagreement with regards to study inclusion.

Two authors (DH, GB) independently extracted data in duplicate using Microsoft Excel. Any disagreements were resolved via mutual consensus. Where more than one publication was apparent for the same participants, data were extracted from the study with the largest sample size to avoid

duplication. Author, year, study design, sample size, participant demographics/injury characteristics, exercise parameters (including the type, frequency, duration, intensity and weekly volume), or physical activity exposure details (training history, objective wearable device or validated self-report questionnaire) and adverse events were extracted. For RCTs, pre-post interventions and observational studies, mean ± standard deviation (SD) for $\dot{V}O_{2peak}$ and PPO outcomes at baseline and post-intervention/control or observation period were extracted to assess change in CRF. For cross-sectional studies, mean ± SD outcomes were extracted for the unique cohorts, along with the significance and magnitude of associations between CRF and habitual physical activity. Where possible, $\dot{V}O_{2peak}$ values were extracted in relative (mL/kg/min) and absolute (L/min) terms or calculated using pre- and post-intervention body mass values when provided. PPO values were extracted in watts (W) only. If there was insufficient information, the authors were contacted via email (N=12) and given a two-week window to provide additional data (responses received, N=8). Detailed notes were recorded outlining the reasons for study inclusion/exclusion and the number of studies included and excluded at each stage.

2.4. Data synthesis and analysis

A variety of methods [i.e., indices of heart rate (HR), $\dot{V}O_2$ or ratings of perceived exertion (RPE)] have been utilised in the literature to establish, prescribe and regulate exercise intensity in the SCI-population, which creates complexity when classifying the intensity of exercise. Each intervention was classified as having prescribed either light, moderate, vigorous or supramaximal-intensity aerobic exercise, based on thresholds proposed by the American College of Sports Medicine (ACSM) [40] (S2). If a study reported a progression in intensity that spanned the moderate and vigorous-intensity categories (e.g., 60-65% $\dot{V}O_{2peak}$), it was classified as 'moderate-to-vigorous'. If insufficient data were provided, studies were classified as 'mixed-intensity/cannot determine'. Furthermore, where a study reported frequency of sessions or length of interventions as a range (e.g., 6-8 weeks), the midpoint was extracted and if a study reported duration as a range (e.g., 40-45 min), the greater value was extracted. Descriptions of adverse events in the included studies were also collated. These were categorised into the following subgroups: 1) bone, joint or muscular pain, 2) autonomic or cardiovascular function, 3) skin irritation or pressure sores, and 4) other.

Means ± SD were estimated from median and interquartile range (IQR) [41] or median and range [42], where required. Where CRF data was only presented in figures, data were extrapolated using Photoshop (Adobe Inc). To combine within-study subgroups and to estimate SD of the delta (Δ) change in CRF using correlation factors, we followed guidance from the Cochrane handbook [41]. Correlation factors were calculated for $A\dot{V}O_{2peak}$, $R\dot{V}O_{2peak}$ and PPO using studies that reported pre-post SD and SD of the Δ change using the following equation:

$$Corr = \frac{(SD_{Pre})^2 + (SD_{Post})^2 - (SD_{Change})^2}{2 \times SD_{Pre} \times SD_{Post}}$$

The specific correlation factors that were calculated for each study were averaged across each study design (S3) and applied in the following equation to calculate SD of the change for studies where these values were not reported:

$$SD_{Change} = \sqrt{(SD_{Pre})^2 + (SD_{Post})^2 - 2 \times corr \times SD_{Pre} \times SD_{Post}}$$

where *corr* represents the correlation coefficient.

Since $A\dot{V}O_{2peak}$, $R\dot{V}O_{2peak}$, and PPO are continuous variables, expressed using the same units across studies, we utilised weighted mean differences (WMDs) and 95% confidence intervals (CI) as summary statistics. A primary meta-analysis was carried out in R (Version 3.5.1, R Foundation for Statistical Computing, Vienna, Austria) describing Δ in CRF outcomes in response to prospective, well-characterised exercise interventions lasting >2 weeks (e.g., combining exercise intervention-arms from RCTs and pre-post studies). Nine separate primary meta-analyses were performed to describe Δ in each CRF outcome with studies categorised into subgroups based on the following: 1) time since injury [(TSI), e.g., Acute (<1-year), chronic (≥1-year)]; 2) neurological level of injury (e.g., tetraplegia, paraplegia); 3) injury severity [e.g., grading in accordance with the American Spinal Injury Association Impairment Scale (AIS): motor-complete (AIS A-B), motor-incomplete (AIS C-D)]; 4) exercise modality [e.g., aerobic volitional upper-body, resistance training, FES, gait training, behaviour change]; 5) relative exercise intensity (e.g., light, moderate, moderate-to-vigorous, vigorous, supramaximal); 6) method used to prescribe exercise intensity (e.g., $\dot{V}O_2$, HR, RPE, workload); 7) frequency of exercise sessions (<3, ≥3

299 to <5, ≥5); 8) exercise volume [e.g., SCI-specific exercise guidelines for fitness (40 - 89 min/wk) [24],
300 SCI-specific exercise guidelines for cardiometabolic health (90 - 149 min/wk) [24], achieving general
301 population exercise guidelines (≥150 min/wk) [26], and 9) length of intervention (≤6 weeks, >6 to ≤12
302 weeks, >12 weeks). Studies were also classified as 'mixed' or 'not reported/cannot determine' subgroups
303 based on the aforementioned categories. Four secondary meta-analyses were also conducted for different
304 trial designs: 1. comparing inactive vs active participants (e.g., cross-sectional cohort studies); 2.
305 describing Δ in CRF outcomes with standard of care inpatient rehabilitation or free-living follow up (e.g.,
306 observational studies); 3. comparing Δ in CRF outcomes relative to control groups (RCTs only), and 4.
307 head-to-head comparison of different exercise intensities (RCTs with exercise interventions of differing
308 intensities). Statistical heterogeneity was assessed using the I^2 and accompanying p-value from the chi-
309 squared test. A fixed-effect model was used when no significant heterogeneity was detected among
310 studies (P>0.10, I^2<50%), otherwise, a random effect model was used. Evidence for differences in effects
311 between the subgroups was explored by comparing effects in the subgroups and the corresponding *p*-
312 values for interaction. To assess the effect of potential outlier studies, we conducted a sensitivity analysis
313 where studies were removed, and pooled WMD recalculated, when their CIs did not overlap with the CIs
314 of the pooled effect. Sensitivity analyses were also conducted by comparing the WMDs of low and high
315 risk of bias studies, as well as studies with and without imputed data (i.e., extracted from figures or where
316 mean ± SD were calculated from median, IQR or range), to confirm the robustness of our findings.
317 Potential publication bias in the dataset was assessed using funnel plots and Egger's tests in R. Data is
318 visualised in R (see Github for scripts: https://github.com/jutzca/Exercise-and-fitness-in-SCI). A 2.7
319 mL/kg/min, and thus 1 metabolic equivalent in SCI (1 SCI-MET) [43], change in $R\dot{V}O_{2peak}$ was
320 considered clinically meaningful.
321
322 To explore potential sources of heterogeneity, a random-effects meta-regression was performed using
323 preselected moderator variables in Stata (Version 13, StataCorp LLC, College Station, TX, USA),
324 adjusted for multiple testing. As per Cochrane recommendations [44], for each included covariate in the
325 model a minimum of 10 studies were required. To achieve this, and to also overcome the issue of
326 collinearity between moderators, some moderators were not included in the analysis. Moderators were
327 selected *a priori*, based on their potential to influence CRF responses. Exercise intensity prescription was
328 later added as a moderator in the meta-regression in light of a recent study challenging strategies for

prescribing exercise intensity in individuals with SCI [45]. Moderators fell into two categories: model 1) participant/injury characteristics [continuous variables: age, TSI and baseline CRF; categorical variables: sex (n=male), neurological level of injury (n=PARA), severity (n=motor-complete)]; or model 2) intervention/study characteristics [continuous variables: exercise session duration, frequency, weekly exercise volume, intervention length; categorical variables: exercise modality, exercise intensity, method of exercise intensity prescription, and risk of bias classification]. Any potential covariates of the effect of $A\dot{V}O_{2peak}$, $R\dot{V}O_{2peak}$, and PPO with $p \leq 0.10$ identified via univariate meta-regression were subsequently included in multivariate meta-regression modelling. The level of significance for multivariate meta-regression was set at $p \leq 0.10$. Because meta-regression can result in inflated false-positive rates when heterogeneity is present, or when there are few studies, a permutation test described by Higgins and Thompson [46] was used to verify the significance of the predictors in the final model, whereby 10,000 permutations were generated.

2.5. Risk of bias

Study quality was appraised by at least two independent reviewers in duplicate (DH, GB, SYC), with any conflicts resolved by a third reviewer (TN). The Cochrane Risk of Bias 2 (RoB 2) was used to assess the risk of bias of the RCTs [47]. Reviewers determined the level of bias for each domain using the RoB 2 algorithms and is presented visually using robvis [48]. Non-randomised designs were assessed using assessment tools generated by the National Institutes of Health (NIH) and National Heart, Lung and Blood Institute (NHLBI, Bethesda, MD). Pre-post studies were rated using the Quality Assessment Tool for Before-After (Pre-Post) Studies with No Control Group (12 items) and observational and cross-sectional studies were rated using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (14 items). Studies were subsequently classified as good, fair or poor quality using the guidance provided within each tool and is presented visually in online supplementary material.

2.6. Certainty on the body of the evidence assessment using the GRADE approach

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [49] was used to evaluate the certainty of the evidence for $A\dot{V}O_{2peak}$, $R\dot{V}O_{2peak}$ and PPO. Two authors (DH, SYC) independently assessed the certainty of evidence for each outcome, with any conflicts resolved by the corresponding author (TN). The certainty of the evidence was graded from ‘High’ to ‘Moderate’,

'Low' or 'Very Low'. GRADE certainty in the evidence was downgraded if one or more of the following criteria were present: 1) risk of bias, 2) inconsistency in the results for a given outcome, 3) indirectness, 4) imprecision, and 5) publication bias.

3. RESULTS

The initial database search identified 12,885 articles after removal of duplicates. Further, 11,029 studies were removed following the screening of titles and abstracts. The remaining 1,856 articles were selected for full-text review based on inclusion and exclusion criteria (S1). Of these, a total of 110 eligible studies, across each specific study design (RCT = 27, pre-post = 63, observational = 5, cross-sectional cohort = 9, cross-sectional association = 6), were included in this review. Ninety studies, comprising the RCTs and pre-post studies, were included in the primary meta-analysis. Summaries of the pooled cohorts and descriptions of the individual studies included within each secondary meta-analysis are provided as supplementary material.

[PLEASE INSERT FIGURE 1 HERE]

3.1. Primary meta-analysis: Effects of prescribed, prospective exercise intervention studies

CRF responses were pooled across 90 studies, comprising 110 exercise interventions in total, taken from 76 pre-post exercise interventions and 34 independent exercise intervention arms from RCTs. Some studies included multiple exercise intervention arms/phases, hence the greater total number of exercise interventions than studies. A summary of the demographic/injury characteristics and intervention parameters for the pooled cohort included in the primary analyses for $A\dot{V}O_{2peak}$, $R\dot{V}O_{2peak,}$ and PPO are presented in Tables 1-2.

[PLEASE INSERT TABLE 1 HERE]

3.1.1. Participants

Across the 110 exercise interventions, there were a total of 1,191 participants. Most interventions included both males and females (64% of studies), where females made up between 6-80% of the mixed cohorts. There were no female-only cohorts. Mean age ranged between 24 to 58 years and the majority

of participants had chronic injuries (69% >1-year), with mean TSI ranging between 56 days to 24 years. Sixty-three interventions included a mixed cohort of paraplegia and tetraplegia, of which individuals with paraplegia made up between 10-88% of the mixed cohorts. Four interventions recruited individuals with tetraplegia-only, 34 paraplegia-only, and nine did not specify. Participants across all AIS groups were included, of which 39 interventions were motor-complete-only, 19 were motor-incomplete-only, and 17 did not report. Thirty-five interventions recruited both motor-complete and incomplete individuals, of which 32% were motor-incomplete. Mean $A\dot{V}O_{2peak}$ and $R\dot{V}O_{2peak}$ at baseline was 1.26 (0.51-3.50) L/min and 18.0 (7.3-36.9) mL/kg/min, respectively, and PPO was 49 (0-168) W.

[PLEASE INSERT TABLE 2 HERE]

3.1.2. Exercise intervention characteristics

Length of interventions ranged from 4 to 52 weeks, and whilst most studies reported a specific, predetermined intervention length, some reported a range [50–52], a total or targeted number of sessions [51,53–57], or provided an average [56,58,59]. Exercise sessions were completed between two to seven times per week. Eleven studies reported a range (e.g., "two to three sessions") or maximum frequency (e.g., "up to three sessions/week") [51,54,57,60–67], and frequency was either not reported or could not be determined in five studies [68–72]. The remainder reported an exact frequency (e.g., three sessions per week). The duration of exercise sessions ranged from 5 to 90 minutes, with four studies reporting a range (e.g., 20-30 min) [51,73–75] and six studies reporting a progression to a target duration [54,76–80]. Duration was not reported or could not be determined in 13 studies. Based on current exercise guidelines, 22 interventions prescribed exercise within the SCI-specific exercise guidelines for fitness (40-89 min/week), 44 interventions targeted the SCI-specific exercise guidelines for cardiometabolic health (90-149 min/week), and 26 were greater than general population exercise guidelines (≥150 min/week).

Forty-one interventions utilised aerobic upper-body exercise, 5 upper-body resistance training/circuits, 22 FES, 15 gait training, 4 behaviour change, and 23 mixed/multimodal interventions. Following the ACSM thresholds, one intervention prescribed light-intensity (<1%), 15 prescribed moderate-intensity (14%), 33 prescribed moderate-to-vigorous-intensity (30%), 25 prescribed vigorous-intensity (23%), and

2 prescribed supramaximal-intensity exercise (2%). Intensity could not be determined from 34 interventions (31%). With regards to exercise intensity prescription methods, 32 interventions used HR, regulated either via HR_{peak} (%HR_{peak}, i.e., determined via a CPET; N=8), HR_{max} (%HR_{max}, i.e., age-predicted; N=11), or HR reserve (%HRR; N=13). Fourteen interventions established intensity using $\dot{V}O_{2peak}$ (%$\dot{V}O_{2peak}$; N=13) or $\dot{V}O_2$ reserve (%$\dot{V}O_{2reserve}$; N=1) calculated from the pre-intervention CPET. Thirteen interventions utilised RPE, using either the Borg CR10 scale (N=7) or the Borg 6-20 scale (N=6). Workload was used to prescribe intensity in 10 interventions, via a percentage of PPO (%PPO; N=5), one repetition maximum (%1RM; N=4), or maximal tolerated power (%MTP; N=1). Forty-one interventions either used a mixture of prescription methods or intensity could not be classified. Detail for the specific studies is presented in the forest plots in online supplementary material (S4).

3.1.3. Adverse events

Adverse events were described in 17 interventions, comprising 49/1,191 (4.1%) participants (S10). These events were related to: 1) bone, joint or muscular pain (n=10 participants), 2) autonomic or cardiovascular function (n=8 participants), 3) skin irritation or pressure sores (n=18 participants), and 4) other events including anxiety, nausea, dizziness and issues with testing equipment (n=3 participants). Adverse events were reported in three other pre-post studies. Beillot et al. [68] stated that participants experienced *"spontaneous fractures of lower limbs, occurrence of a syringomyelia and pressure sores at the foot and ankle"* (n=10), but did not define the number of participants who sustained each event. Likewise, Janssen and Pringle [61] reported *"lightheadedness in some subjects"*, and Gibbons et al. [81] stated that *"a number of participants showed some level of autonomic dysreflexia during the FES response test"*, but both studies did not quantify further.

3.1.4. Change in CRF outcomes

The summary statistics for the nine primary meta-analyses are presented in Tables 3-4 and their corresponding forest plots can be found in supplementary material (S4).

[PLEASE INSERT TABLES 3-4 HERE]

Sixty-nine exercise interventions assessed the change in $A\dot{V}O_{2peak}$, revealing a significant increase of 0.22 [0.17, 0.26] L/min (p<0.001). There were no significant subgroup differences for any of the nine meta-analyses. Seventy-four exercise interventions assessed the change in $R\dot{V}O_{2peak}$, revealing a significant increase of 2.8 [2.2, 3.4] mL/kg/min (p<0.001). There were no significant subgroup differences for any of the nine meta-analyses. Sixty-one exercise interventions assessed the change in PPO, revealing a significant increase of 11 [8, 13] W (p<0.001). There were significant subgroup differences for TSI (p<0.001), neurological level of injury (p<0.001), exercise modality (p=0.003), relative exercise intensity (p=0.003), method of exercise intensity prescription (p<0.001), and frequency (p<0.001) (Tables 3-4).

Sensitivity analyses

The removal of potential outliers resulted in no meaningful changes to the overall pooled effects for any outcome. A sensitivity analysis for risk of bias revealed no differences in the pooled effects for low and high risk of bias studies (S11). A sensitivity analysis for imputed data revealed a greater $R\dot{V}O_{2peak}$ in studies with imputed data (3.9 mL/kg/min) compared to studies without (2.5 mL/kg/min). Yet, there were no differences in the pooled effects for $A\dot{V}O_{2peak}$ or PPO (S11). An additional analysis grouped interventions into those that matched the CPET modality to the exercise intervention and those that did not. Following the adjustment for subgroup comparisons, there was a significantly greater $R\dot{V}O_{2peak}$ in studies with matched CPET and intervention modalities (p = 0.02). There were no significant differences in $A\dot{V}O_{2peak}$ or PPO (S12). A sub-analysis on gait training CPETs alone also revealed no subgroup differences in any outcome (S13).

3.1.5. Meta-regression

Model 1 - Participant and injury characteristics

Increased age was associated with increases in $A\dot{V}O_{2peak}$ (p = 0.045) and $R\dot{V}O_{2peak}$ (p = 0.025). There were no associations between other moderator variables included in this model and CRF outcomes. There were also no associations between PPO and the other moderator variables (Table 5).

Model 2 - Exercise intervention and study characteristics

There was no evidence that the exercise intervention and study characteristics included in model 2 were associated with increases in $A\dot{V}O_{2peak}$ or $R\dot{V}O_{2peak}$. However, there was evidence for an association between the method of exercise intensity prescription and increases in PPO (p<0.01). Additionally, there was evidence for an association between exercise volume and increases in PPO (p = 0.04) (Table 5).

[PLEASE INSERT TABLE 5 HERE]

3.1.6. Publication bias

There was no significant publication bias for $A\dot{V}O_{2peak}$ (Z = -1.23, p = 0.22), $R\dot{V}O_{2peak}$ (Z = -0.54, p = 0.59), or PPO (Z = 0.73, p = 0.46). Funnel plots are provided in supplementary material (S4).

3.2. Secondary Meta-Analyses

3.2.1. Cross-sectional studies

Nine studies included cross-sectional data comparing CRF outcomes in active (n=129 participants) vs. inactive (n=115 participants) individuals with SCI. Inactive participants were mainly classified as sedentary, whereas active participants varied from recreationally active wheelchair sport players to paralympic athletes. A meta-analysis of cross-sectional cohort studies revealed significantly (p<0.001) higher $A\dot{V}O_{2peak}$ [0.54 (0.44, 0.63) L/min], $R\dot{V}O_{2peak}$, [9.4 (7.0, 11.8) mL/kg/min] and PPO [37 (29, 44) W] in active compared to inactive individuals with SCI (S5). Given the significant heterogeneity in $R\dot{V}O_{2peak}$, a sensitivity analysis was conducted to compare inactive individuals with either 'active' or 'elite athletes'. There was a significantly higher $R\dot{V}O_{2peak}$ [5.4 (3.0, 7.7) mL/kg/min, p<0.001] in 'active' compared to inactive individuals, but an even higher $R\dot{V}O_{2peak}$ [11.2 (9.6, 12.9) mL/kg/min, p<0.001] in 'elite athletes' compared to inactive.

Six studies (n=380 participants) included cross-sectional data and assessed associations between habitual physical activity level (as a continuous variable) and CRF outcomes. Five studies assessed physical activity exposure using self-report methods [82–86], whereas one study used a validated wearable device [87]. The measurement period used to capture physical activity dimensions ranged from 3 to 7 days. There was considerable variability across studies with regards to the physical activity dimensions captured: hours per week of exercise/sport, minutes per day or week of mild, moderate, heavy-intensity

for the subcategories of leisure time physical activity (LTPA), lifestyle or household activity or cumulative activity (S6). Collectively, data indicates significant positive correlations of a larger magnitude between CRF/PPO outcomes and the volume of sport, exercise or LTPA rather than household activity. The only study to use a validated wearable device indicated that participants performing ≥150 min/wk of moderate-to-vigorous physical activity (MVPA) had a significantly higher CRF relative to a low activity group (performing <40 min/wk). Whereas, there was no significant difference in CRF between the low activity group and participants achieving the SCI fitness specific exercise guidelines (40 - 149 min/wk) [87]. Significant, positive correlations were reported for the amount of moderate-to-vigorous LTPA or cumulative activity with CRF/PPO outcomes, which was not the case for mild or light-intensity activity.

3.2.2. Observational inpatient rehabilitation or community free-living studies

Five studies (n=343 participants) included observational longitudinal data and assessed changes in CRF outcomes following either standard of care inpatient rehabilitation [88–90] or a period of community free-living [88,91,92]. The duration between assessments for standard of care varied, ranging from 5 to 28 weeks, whereas the follow-up period for community observations ranged from 1 to 2.9 years. Reporting on the therapies used within standard of care was poor and only one study included a measurement of physical activity during the community-based free-living follow-up (self-reported mean sport activity) [91]. There were significant improvements following standard of care, but not following community-based free-living, in absolute [0.12 (0.07, 0.17) L/min, p<0.001 vs. 0.09 (0.00, 0.19) L/min, p=0.06] and relative $\dot{V}O_{2peak}$ [2.1 (1.0, 3.2) mL/kg/min, p<0.001 vs -0.1 (-2.9, 2.7) mL/kg/min, p=0.94] (S7). Significant improvements in PPO were identified following both standard of care [6 (3, 9) W, p<0.001] and community-based free-living [7 (2, 12) W, p=0.006] (S7).

3.2.3. RCTs

Twenty RCTs assessed changes in CRF outcomes between exercise intervention (n=255 participants) and control (n=229 participants) groups. A meta-analysis of RCTs revealed a significantly higher $A\dot{V}O_{2peak}$ [0.15 (0.06, 0.24) L/min, p=0.001], $R\dot{V}O_{2peak}$ [2.9 (1.7, 4.0) mL/kg/min, p<0.001], and PPO [10 (5, 14) W, p<0.001] following an exercise intervention relative to SCI controls (S8).

Seven RCTs compared changes in CRF outcomes between moderate (n=52 participants) and vigorous (n=51 participants) exercise intensity groups. These studies utilised upper-body aerobic exercise and gait training. A meta-analysis revealed no significant differences between moderate and vigorous-intensity in $A\dot{V}O_{2peak}$ (p=0.67), $R\dot{V}O_{2peak}$ (p=0.88) or PPO (p=0.62) (S9). There were also no significant subgroup differences between studies that matched exercise volume between intensity groups and those that did not.

3.3. Risk of Bias

Full risk of bias assessments for pre-post and RCT interventions can be found in supplementary material (S4, S8, S9). Twenty-six pre-post studies were rated as having good, 25 as having fair, and 12 as having poor methodological quality. Six RCTs were rated as having a low risk of bias, 8 as having some concerns, and 13 as having a high risk of bias. The most common domains in the RCTs with either some concerns or high risk were 'bias in the measurement of the outcome' and 'bias in selection of the reported result'. Reporting was inadequate in many of the included studies, which made the assessment of risk of bias challenging. Notably, reporting of blinding, eligibility or selection criteria, as well as the enrollment of participants (i.e., a lack of CONSORT flow diagrams) was poor. Individual risk of bias assessments for each study design are provided in supplementary material (S4-9).

3.4. Evidence appraisal using GRADE

Overall, the GRADE assessment revealed a 'Low' certainty in the body of evidence for improvements in all CRF outcomes (Table 6). The certainty rating for $A\dot{V}O_{2peak}$ was downgraded due to imprecision and a lack of high quality study designs, whereas $R\dot{V}O_{2peak}$ was downgraded as a result of imprecision and a high risk of bias in the RCTs. The confidence rating for PPO was downgraded due to imprecision and inconsistency, resulting from considerable heterogeneity in the included exercise interventions.

[PLEASE INSERT TABLE 6 HERE]

4. DISCUSSION

This review provides a large evidence-based summary and appraisal on the effects of prescribed and prospective exercise interventions >2 weeks on CRF in individuals with SCI. The results from the meta-

analysis support the role of exercise in improving CRF in this population by 0.22 L/min and 11W in $A\dot{V}O_{2peak}$ and PPO, respectively. The meta-analysis also indicates a clinically meaningful change in $R\dot{V}O_{2peak}$ of 2.8 mL/kg/min. However, the GRADE assessment revealed 'Low' certainty in the evidence for significant improvements in $A\dot{V}O_{2peak}$, $R\dot{V}O_{2peak}$, and PPO. Subgroup analyses revealed no effects of injury characteristics or exercise intervention parameters on $A\dot{V}O_{2peak}$ or $R\dot{V}O_{2peak}$. However, there were significant subgroup differences for PPO based on TSI, neurological level of injury, exercise modality, exercise intensity, method of exercise intensity prescription, and frequency of sessions.

4.1. Impact of injury characteristics

4.1.1. Time since injury

Following exercise interventions $\dot{V}O_{2peak}$ improves in individuals with both acute and chronic SCI. However, this review highlights the need for more exercise interventions in the acute phase post-SCI. Indeed, a recent review by Van der Scheer et al. [38] rated the confidence in the evidence base for exercise in acute SCI as 'Very Low', and called for more RCTs to control for the deteriorations in fitness and health occurring almost immediately following SCI. With regards to PPO in the current review, subgroup analysis based on TSI reveals that individuals with acute SCI exhibit a greater change than individuals with chronic SCI. This could be due to spontaneous motor recovery in the first few months following SCI [93], or speculatively, a familiarisation effect to novel modalities of exercise or additive upper-limb physiological adaptations in response to concurrent inpatient rehabilitation. To support this point, the secondary meta-analysis with longitudinal observational studies indicates a 6W improvement in PPO with standard of care inpatient rehabilitation during the subacute period. Ultimately, more rigorous RCTs are required in the subacute phase post-SCI that compare standard of care versus standard of care plus a specific exercise intervention to truly quantify improvements in CRF outcomes.

4.1.2. Neurological level of injury

Exercise results in improved $\dot{V}O_{2peak}$ regardless of the neurological level of injury. In particular, this review reveals a pooled improvement of 5.9 mL/kg/min in studies that included only individuals with tetraplegia (N=3). For comparison, there is a considerably larger evidence-base for studies including only individuals with paraplegia (N=28). A recent systematic review suggested that aerobic exercise results in minimal returns on investment in individuals with tetraplegia, with $\dot{V}O_{2peak}$ improving on average only

9% following 10-37 weeks of training [17]. However, their review excluded studies with a sample size <10. Consequently, the Dicarlo study [94], which reported a 94% increase in $R\dot{V}O_{2peak}$ was excluded from their analysis. Whilst the inclusion of this study in the current analysis may have augmented the overall effect, our findings indicate that exercise improves CRF in individuals with tetraplegia and that the magnitude of change is not significantly different to individuals with paraplegia. However, this meta-analysis highlights that individuals with paraplegia (16W) are likely to accrue greater absolute changes in PPO than those with tetraplegia (9W). Typically, higher neurological levels of injury result in a loss of trunk control, motor impairments in the upper-limbs and reduced mechanical efficiency, compared to lower levels of injury [95,96]. Therefore, individuals with tetraplegia may not have the physical or motor capacity to adapt as effectively as individuals with paraplegia, and thus could experience a ceiling effect with training. Indeed, a recent study identified lesion level as a significant predictor of PPO in a group of handcyclists with SCI [97]. To account for baseline motor function differences between individuals with tetraplegia and paraplegia, we determined relative percentage change for studies that included upper-body aerobic exercise interventions only. The relative percentage change was similar between neurological level of injury classifications: 46% tetraplegia (N=1) vs. 53% paraplegia (N=9). While only one tetraplegia-only intervention was included in this subgroup analysis [98], normalising for baseline values seems to indicate similar relative magnitudes of change in PPO.

Williams et al. [99] demonstrated that individuals with a lower level of injury (<T6) significantly improved PPO compared to individuals with a higher level of injury (≥T6), suggesting a potential role of disrupted cardiovascular control in mediating changes in PPO. Whilst methods for ameliorating the reduction in sympathetic cardiovascular control typically associated with injuries ≥T6 have been investigated (e.g., abdominal binding [100], lower-body positive pressure [101], and midodrine [102]), the evidence for an improved CRF is still mixed. A recent case-report has indicated that epidural spinal cord stimulation (SCS) can safely and effectively restore cardiovascular control and improve CRF [103]. With an explosion in SCS studies over the last few years [104], particularly including transcutaneous SCS, the pairing of exercise with novel and non-invasive neuromodulatory approaches will likely continue to receive considerable research attention. Future, adequately powered, research may want to consider separating participants into paraplegia and tetraplegia groups or dichotomize by injuries above and below T6 to account for differences in sympathetic cardiovascular control. Currently, there is a

paucity of studies analysing data in this fashion, which limits our understanding of how neurological level of injury and the degree of impaired sympathetic cardiovascular control influences the magnitude of change in CRF following an exercise intervention. Researchers may want to consider conducting a battery of autonomic nervous system stress tests at baseline (e.g., Valsalva manoeuvre, head-up tilt, sympathetic skin responses etc. [105]), to determine the degree of supraspinal sympathetic disruption rather than relying on a neurological level of injury derived from a motor-sensory examination. This is important as recent research has indicated that cardiovascular instability cannot be predicted by motor-sensory level and completeness of SCI [106].

4.1.3. Injury severity

There were no significant subgroup differences in CRF. However, the subgroup analysis suggests that individuals with a motor-incomplete SCI may not yield PPO improvements of the same magnitude as individuals with a motor-complete SCI. This is most likely due to the majority of motor-incomplete studies implementing gait training as its exercise modality, which we reveal is the least effective modality for improving CRF. The gait training studies that measured PPO (N=2) used arm-crank ergometry (ACE) as the CPET modality, demonstrating no transfer effect from lower-body to upper-body exercise. During data extraction, reviewers noted a poor reporting of injury severity in a number of studies. Whilst this may be due to older studies having used now outdated severity scales (e.g., International Stoke Mandeville Games Federation or Frankel), researchers should endeavour to perform an International Standards for Neurological Classification of SCI (ISNCSCI) exam during screening, and subsequently report an AIS grade, to enable better comparisons to be made between injury severities in the future.

4.2. Impact of exercise intervention parameters

4.2.1. Exercise modality

Despite a number of recent reviews summarising the effects of specific exercise modalities on the change in CRF following SCI, including aerobic ACE [107], FES-cycling [39], and aerobic plus muscle strength training (mixed multimodal) interventions [108], this meta-analysis is the first to directly compare the effects of a wide range of exercise modalities on the change in CRF in individuals with SCI.

This review revealed there were no significant subgroup differences between exercise modalities in $A\dot{V}O_{2peak}$ or $R\dot{V}O_{2peak}$, indicating that improvements can be gained from any form of exercise intervention. The change in $R\dot{V}O_{2peak}$ in the current review (21%) is equivalent to the average 21% improvement reported in a recent systematic review on the effects of ACE in chronic SCI [107]. Whilst the current review did not exclusively investigate ACE, it is evident that aerobic, volitional upper-body exercise training can improve CRF in individuals with SCI. Activating larger amounts of skeletal muscle mass via FES exercise interventions also appears to improve $\dot{V}O_{2peak}$, yet it is noteworthy that more accessible and less expensive training modalities such as aerobic and resistance training may yield similar or even greater increases in $\dot{V}O_{2peak}$, despite utilising less muscle mass. Additionally, $\dot{V}O_{2peak}$ improves following multimodal/hybrid exercise interventions, which challenges a 2015 review reporting inconclusive findings on the effects of combined upper-body aerobic and muscle strength training on CRF [108]. Yet, as the current review included a wide range of interventions not restricted to the upper-body (e.g., aquatic treadmill [54], hybrid cycling [55,60,109], multimodal exercises [110,111], etc.), it is recommended that more research is conducted to delineate whether the improvements in $\dot{V}O_{2peak}$ with multimodal/hybrid exercise interventions are due to the combination of upper- and lower-body exercise modalities, or due to concurrent training modalities that predominantly use the upper-body (e.g., aerobic plus muscle strength training). Finally, both gait training and behaviour change interventions appear less effective at improving $\dot{V}O_{2peak}$ and PPO.

Aerobic, upper-body exercise and resistance training modalities demonstrate the greatest improvements in PPO, by 15W and 20W, respectively. It is perhaps unsurprising that resistance training resulted in the largest change in PPO given that these interventions included upper-body exercises prescribed to increase muscular strength, as shown by Jacobs et al. [112]. Ultimately, improvements in PPO have important ramifications for individuals with SCI that are dependent on performing explosive upper-body movements during transfers or wheelchair propulsion [88,92], and may lead to increased quality of life with more functional independence [113].

Several studies directly compared the effects of specific exercise modalities on the change in CRF [54,76,114]. Notably, Gorman et al. [54] demonstrated that there were no transfer effects from a robotic treadmill exercise intervention to ACE performance in a CPET. This review also demonstrates that

greater changes in R$\dot{V}O_{2peak}$ are likely achieved when the CPET modality is matched to the intervention (S12). Therefore, researchers should endeavour to match the CPET modality to their exercise intervention, or at the very least be careful when interpreting changes in CRF when using different modalities.

4.2.2. Exercise intensity

The current SCI-specific exercise guidelines recommend that exercise should be performed at a moderate-to-vigorous intensity [24]. A recent overview of systematic reviews also advocated the use of moderate-to-vigorous intensity for improving aerobic fitness [115]. The current meta-analysis demonstrates robust improvements across all CRF outcomes for interventions prescribing exercise at this particular intensity. Furthermore, the secondary meta-analysis including cross-sectional studies reveals significant associations of a greater magnitude between MVPA and CRF, as compared to lower-intensity activity. Despite this, our classification of moderate-to-vigorous exercise intensity spans two of the ACSM exercise intensity thresholds (S2). There may be considerable variation in the actual intensity performed by participants given the noticeable range across thresholds (e.g., 46-90% $\dot{V}O_{2peak}$, 64-95% HR_{peak}, 12-17 RPE etc.). Therefore, individuals with SCI and exercise practitioners should be cautious when prescribing such a broad exercise intensity.

The secondary meta-analysis comparing RCT exercise intensities reveals similar changes in CRF outcomes between moderate- and vigorous-intensity interventions. This is in agreement with a previous review [33] and supports the viewpoint from a special communication on high-intensity interval training (HIIT) [34], which suggested that vigorous-intensity exercise is more time efficient and may result in similar if not superior CRF and skeletal muscle oxidative capacity improvements in comparison to moderate-intensity exercise. Interestingly, in a response to a Letter-to-the-Editor [30], the SCI-specific exercise guideline developers acknowledge the need for shorter, effective protocols to be documented in the literature [116]. In the current review, a number of HIIT-based studies result in an improved CRF [60,109,117–121]. Furthermore, recent evidence has suggested that HIIT may be more enjoyable than moderate-intensity exercise for individuals with SCI [122]. Therefore, this form of training may offer a more time efficient and readily available alternative to moderate-intensity protocols. However, in

715 echoing the thoughts of Astorino et al. [35], research must first corroborate its safety and feasibility in
716 the SCI population before it can be recommended as an exercise strategy to improve CRF.
717
718 **4.2.3. Exercise intensity prescription methods**
719 This review reveals that $\dot{V}O_{2peak}$ improves regardless of the method used to prescribe exercise intensity.
720 With regards to PPO, the subgroup difference indicates that the magnitude of change is greater when
721 prescribing intensity via indices of HR (i.e., $\%HR_{peak}$, $\%HR_{max}$, %HRR) or $\dot{V}O_2$ (i.e., $\%\dot{V}O_{2peak}$,
722 $\%\dot{V}O_{2reserve}$), compared to RPE and workload. Previous research has revealed that RPE results in inter-
723 individual responses to exercise, with the potential for two individuals to perform the same bout of
724 exercise above or below lactate threshold despite being prescribed the same intensity, which prevents the
725 development of SCI-specific RPE recommendations [123]. The difference in PPO may also be due to
726 individuals with SCI being unaccustomed to subjective measures of exertion. Accordingly, recent
727 systematic reviews have called for better reporting of the standardisation and familiarisation procedures
728 used for RPE [124] and have only tentatively recommended its use before the evidence base is expanded
729 [125]. Therefore, it seems plausible to suggest that the blunted improvements in PPO with intensity
730 prescribed via RPE, as compared to other prescription methods, may have resulted from insufficient
731 familiarisation before an exercise intervention.
732
733 Although HR and $\dot{V}O_2$ have long been used to prescribe exercise intensity, these approaches can result
734 in large training ranges and ignore individual metabolic responses. Particularly, issues may arise with
735 using HR for individuals with a neurological level of injury ≥T6, given that these individuals typically
736 exhibit a lower HR_{peak} [126]. The use of fixed percentages (i.e, $\%HR_{peak}$, $\%\dot{V}O_{2peak}$) in the non-injured
737 population has been questioned [127] and has recently been investigated in individuals with SCI,
738 whereby Hutchinson et al. [45] showed that fixed $\%HR_{peak}$ and $\%\dot{V}O_{2peak}$ could not guarantee a
739 homogenous domain-specific exercise intensity prescription. Notably, individuals were spread across
740 moderate, heavy and severe domains at the "moderate" and "vigorous" intensity classifications; thereby
741 questioning whether the "moderate-to-vigorous" terminology used in the SCI-specific exercise
742 guidelines is suitable for adults with SCI.
743

Given that prescribing exercise intensity via HR and $\dot{V}O_2$ can typically be resource and cost-intensive, there is some scope for using RPE as a cheaper and more practical method for community-based exercise prescription. However, this may not be as effective as other objective methods. Future research should aim to identify the optimal methods of exercise intensity prescription, as well as consider revisiting the current "moderate-to-vigorous intensity" recommendations.

4.2.4. Frequency and exercise volume

Subgroup analyses based on frequency of sessions and exercise volume reveal no differences in $\dot{V}O_{2peak}$, thereby supporting the minimal volume of exercise required to attain CRF benefits in individuals with SCI. Furthermore, although there are no subgroup differences in PPO, the meta-regression identifies that a greater volume of exercise is associated with greater changes in PPO. Indeed, there is a greater magnitude of change observed for individuals exercising 90-149 min/wk in comparison to 40-89 min/wk (12W vs 6W change, respectively). A greater weekly exercise volume may therefore accrue greater changes in PPO and, as already described, may be important in improving the capacity to perform daily tasks such as bed or wheelchair transfers [88,92].

Although changes in CRF are similar between each exercise volume subgroup, and thus exercise guideline, the secondary meta-analysis on cross-sectional cohorts indicates a significant cumulative impact of prolonged participation in physical activity and exercise. To support this point, a sensitivity analysis revealed a larger difference in $R\dot{V}O_{2peak}$ between inactive individuals and elite athletes, compared to between inactive and active individuals, suggesting that those who exercise more exhibit a greater CRF. Indeed, a cross-sectional association study [87], using a wearable device to objectively monitor habitual physical activity, reported a significantly higher CRF in those performing the general population exercise guidelines (≥150 min/wk) compared to the SCI-specific fitness guidelines (40-89 min/wk). In fact, a recent study by Hoevenaars et al. [128] explored whether meeting the guidelines proposed by Tweedy et al. [27] ("≥150 min/wk of moderate or ≥60 min/wk of vigorous exercise"), which are nearly consistent with the general population exercise guidelines, is associated with greater health and fitness benefits than the current SCI-specific guidelines by Martin-Ginis et al. [24]. Individuals meeting the Tweedy guidelines had a significantly greater $A\dot{V}O_{2peak}$ and PPO than those meeting the guidelines developed by Martin-Ginis et al. [24]. Looking forward, longitudinal RCTs with multiple

intervention arms would be the best way to explore dose-response changes with regards to differing volumes of exercise, as has been done in the non-injured population [129–132].

4.3. Adverse events

Adverse events were reported for 4.1% of the total included participants, with the majority of events related to skin sores, pressure sores or ulcers. Qualitatively, there was no particular exercise modality that suggested an increased risk for an adverse event, but higher-intensity exercise appeared to reveal more adverse events, albeit being swayed by one study in particular [111]. Reporting was poor in a number of studies with reviewers at times unable to determine the exact number of events per participant. Furthermore, there is generally a lack of follow-up assessments following exercise interventions, so it is currently unknown whether there are any detrimental long-term effects of exercise in SCI.

4.4. Strengths and limitations of the review and future directions

4.4.1. Limitations of the included studies

Poor reporting of injury characteristics and exercise parameters prevented a perfect comparison of exercise interventions. Overall, studies could have provided more precise descriptions of training parameters to aid with any future refinements to the SCI-specific exercise guidelines. Reporting of adherence to interventions was also poor and should be encouraged to provide an indication of the feasibility or applicability of specific exercise interventions for individuals with SCI. Moreover, adverse events should be transparently reported, even if none occur so that practitioners are able to identify forms of exercise that are most likely to be safe for this population. Additionally, studies typically failed to utilise the training principle of progression, which during prolonged exercise interventions is essential for preventing a plateau in training adaptations and perhaps particularly important in this population for supporting the transition from an inactive lifestyle to higher levels of activity, and ultimately achieving greater CRF benefits [27]. On the whole, the reporting of $\dot{V}O_{2peak}$ attainment criteria was poor, with only 16% of the included exercise interventions using at least three criterion methods for identifying when an individual had reached peak capacity. Thus, the magnitude of change in these studies could be inflated or underestimated. Furthermore, to the best of our knowledge, only 30% of interventions had a prospectively registered clinical trial entry and only 6.4% had a protocol manuscript published. To

sustain the integrity and transparency of reporting in this field, researchers are encouraged to prospectively register any planned clinical trials using publicly available repositories.

The risk of bias assessments on pre-post studies revealed that no study conducted multiple baseline or follow-up assessments. Whilst often time-consuming and impractical with larger sample sizes, multiple assessments ensure reproducibility by accounting for any technical or biological variation, as shown previously in non-injured individuals at risk for type-2 diabetes [133]. In the SCI population, individuals are typically deconditioned and often exhibit variable responses to a CPET. This variance may be explained by profound blood pressure instability [134], including unintentional 'boosting' via episodes of autonomic dysreflexia [135]. Researchers should therefore consider performing multiple CPETs at baseline and follow-up to attain reliable assessments of CRF.

There are also several limitations with regards to the studies included in the secondary meta-analyses for this review. First, there is only one cross-sectional study using a wearable device to investigate the association between physical activity and CRF [87]. Whilst self-report questionnaires are valid tools for estimating levels of physical activity [86,136–138], there are important drawbacks including the difficulty of accurately capturing intensity, lack of questionnaires measuring activities of daily living, and recall bias. Secondly, there is a lack of RCTs comparing near-maximal, maximal or supramaximal exercise intensities to moderate-intensity exercise. The only supramaximal intervention included in this review demonstrated a 17W improvement in PPO [120]. The inclusion of more RCTs comparing vigorous-intensity to lower intensity exercise could identify whether there are, in fact, benefits to performing shorter but more vigorous-intensity exercise bouts, in comparison to longer continuous forms of exercise.

4.4.2. Strengths and limitations of the review

A major strength of the current study is that we pre-planned and prospectively registered (PROSPERO ID CRD42018104342) our systematic review. We used GRADE to assess the certainty in the body of evidence and used quality appraisal tools for the specific study designs included in this review. Our GRADE assessment demonstrates generalisability within the SCI population, through the inclusion of participants across the lifespan and with a wide range of injury characteristics. Yet, the 'Low' confidence

in the evidence across all CRF outcomes emphasises the need for more rigorous exercise interventions to address current gaps in the literature [38].

As there were not enough RCTs to perform a meta-regression on this study design specifically, we pooled pre-post and RCT exercise interventions. The changes in $R\dot{V}O_{2peak}$ and PPO in the primary meta-analysis (2.8 mL/kg/min and 11W, respectively) are somewhat similar to those reported with RCT interventions relative to controls (2.9 mL/kg/min and 10W, respectively), and thus confirms the robustness of our overall findings. Furthermore, our rigorous approach of adjusting for multiple comparisons minimises any erroneous interpretations of subgroup differences and therefore strengthens our conclusions on the available evidence.

Despite this, the categorisation of interventions within each subgroup could be considered a limitation of the current review. Whilst this was done to directly compare the effects of different subgroups (i.e., acute vs chronic, tetraplegia vs paraplegia, aerobic vs resistance vs FES etc.), it resulted in an unequal number of interventions within each classification and likely underpowered the subgroup comparisons. For example, the subgroup analysis based on exercise intensity reveals an effect of exercise intensity on PPO, yet this may be influenced by the small number of interventions for light- and supramaximal-intensity. Despite reporting some significant subgroup differences across dichotomised studies, these variables were not identified as significant moderator variables in the random-effects meta-regression, meaning these findings should be viewed with caution. It is perhaps more of a limitation of the evidence-base *per se*, rather than our meta-analysis, in that more studies should be conducted to increase the power of these subgroups and to ascertain whether there would be any significant improvements with a greater study sample size.

Another limitation is that despite our comprehensive search strategy we may have missed relevant studies as we did not search the grey literature and abstracts were not included. Finally, this review excluded studies that were not published in English, introducing a source of language bias. However, of the full texts screened for eligibility only 0.6% were excluded for being unavailable in English and is therefore highly unlikely to have influenced the overall findings.

4.4.3. Implications and future directions

Our results support the current guidelines regarding the minimal weekly volume of exercise necessary to improve CRF in the SCI population. However, our pooled analysis indicates subgroup differences for PPO based on certain exercise intervention parameters. To the best of our knowledge, there are no large scale epidemiological studies investigating the dose-response relationship between physical activity and CRF in this population using sensitive and validated methods to quantify the exposure variable (e.g. free-living physical activity). Such studies have been performed in non-injured individuals [139,140]. To identify the optimal stimulus for beneficial CRF responses in this population, dose-ranging studies, akin to those that are used in the pharmaceutical industry, should be conducted. A recent overview of systematic reviews [141] highlighted the poor reporting in exercise interventions in health and disease and called upon the inclusion of checklists [e.g., the Consensus on Exercise Reporting Template (CERT) [142] or the Template for Intervention Description and Replication (TIDieR) [143]] to improve study quality. This would ultimately lead to a better understanding of the 'dose' of exercise as medicine required to optimise CRF outcomes in this population.

Exercise interventions >2 weeks result in an overall pooled increase in $R\dot{V}O_{2peak}$ of 2.8 mL/kg/min, which is roughly equivalent to 1 MET-SCI [metabolic equivalent in SCI (2.7 mL/kg/min)] [43]. An increase in maximal aerobic capacity (an estimate of CRF) by 1 MET (3.5 mL/kg/min) in non-injured individuals is associated with a 13% and 15% reduction in all-cause and cardiovascular mortality, respectively [144]. The current review shows that individuals meeting the SCI-specific guidelines for cardiometabolic health [24] can improve $R\dot{V}O_{2peak}$ to a similar magnitude to the overall pooled effect (~1 MET-SCI), highlighting that these guidelines may offer a reduction in CVD risk, and therefore mortality. Nonetheless, an association between an improvement in CRF and a reduction in mortality is yet to be established specifically in the SCI population, and remains an important avenue of research for the future.

5. CONCLUSION

This systematic review with meta-analysis provides an updated, evidence-based summary of the effects of exercise interventions on CRF in individuals with SCI. It reveals that exercise interventions >2 weeks are associated with significant improvements to CRF, and in particular, a clinically meaningful change in $R\dot{V}O_{2peak}$. Subgroup comparisons identified that upper-body aerobic exercise and resistance training

appear the most effective at improving PPO. Furthermore, acutely-injured, paraplegic individuals, exercising at a moderate-to-vigorous intensity, prescribed via $\dot{V}O_2$ or HR, for more than 3 sessions/week will likely experience the greatest change in PPO. Importantly, there is an ever-growing need for studies to establish a dose-response relationship between exercise and CRF in the SCI population to determine the most optimal form of exercise prescription to reduce the wide-ranging consequences typically associated with SCI.

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7. DECLARATIONS

7.1. Author Contributions

Conceptualisation and study design were conducted by MW, AK and TN. Literature searches were completed by DH, GB and TN. Risk of bias and GRADE assessments were completed by DH, GB, SYC and TN. Statistical analysis and data interpretation were performed by DH, CL, CJ and TN. All authors contributed to the drafting and critical revision of the work.

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7.3. Availability of data and materials

All data included in this systematic review can be provided upon request to the corresponding author.

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950 **7.4. Ethics approval and consent to participate**

951 Not applicable.

952

953 **7.5. Consent for publication**

954 Not applicable.

955

956 **7.6. Code availability**

957 R scripts can be found on the Github repository: https://github.com/jutzca/Exercise-and-fitness-in-SCI

958

959 **7.7. Competing interests**

960 Daniel Hodgkiss, Gurjeet Bhangu, Carole Lunny, Catherine Jutzeler, Shin-Yi Chiou, Matthias Walter,
961 Samuel Lucas, Andrei Krassioukov and Tom Nightingale declare that they have no competing interests
962 relevant to the content of this article.

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8. LIST OF ABBREVIATIONS

1RM	One repetition maximum
	Arm-crank ergometry
ACSM	American College of Sports Medicine
AIS	American Spinal Injury Association Impairment Scale
A$\dot{V}O_{2peak}$	Absolute peak oxygen uptake
CENTRAL	Cochrane Central Register of Controlled Trials
CERT	Consensus on Exercise Reporting Template
CI	Confidence interval
CPET	Cardiopulmonary exercise test
CRF	Cardiorespiratory fitness
CVD	Cardiovascular disease
EMBASE	Excerpta Medica Database
FES	Functional electrical stimulation
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HIIT	High-intensity interval training
HR	Heart rate
HR_{max}	Maximum heart rate (age-predicted)
HR_{peak}	Peak heart rate
HRR	Heart rate reserve
IQR	Interquartile range
ISNCSCI	International Standards for Neurological Classification of Spinal Cord Injury
LTPA	Leisure time physical activity
MET	Metabolic equivalent
MTP	Maximal tolerated power
MVPA	Moderate-to-vigorous physical activity
PPO	Peak power output
PRISMA	Preferred Reporting Items for Systematic Reviews

RCT	Randomised-controlled trial
RoB 2	The Cochrane Risk of Bias 2 tool
RPE	Rating of perceived exertion
R$\dot{V}O_{2peak}$	Relative peak oxygen uptake
SCI	Spinal cord injury
SCS	Spinal cord stimulation
SD	Standard deviation
TIDieR	Template for Intervention Description and Replication
TSI	Time since injury
$\dot{V}O_2$	Oxygen uptake
$\dot{V}O_{2peak}$	Peak oxygen uptake
$\dot{V}O_{2reserve}$	Reserve oxygen uptake
W	Watts
WMD	Weighted mean difference

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FIGURE/TABLE LEGEND

Figure 1. PRISMA flow diagram. Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Table 1. Participant demographics and injury characteristics reported within the included studies of the primary meta-analysis.

Table 2. Exercise intervention parameters reported within the included studies of the primary meta-analysis.

Table 3. Summary statistics of the three subgroup analyses on injury characteristics describing Δ in CRF outcomes.

Table 4. Summary statistics of the three subgroup analyses on exercise parameters describing Δ in CRF outcomes.

Table 5. Meta-regression models with adjusted values for each cardiorespiratory fitness outcome.

Table 6. Grading of recommendations assessment, development and evaluation analysis for each cardiorespiratory fitness outcome.

SUPPLEMENTARY MATERIAL

Supplementary file 1 (S1): Systematic Review Search Strategy

Supplementary file 2 (S2): Description of Exercise Intensity Classifications as per the American College of Sports Medicine (ACSM) guidelines

Supplementary file 3 (S3): Calculated Correlation Factors

Supplementary file 4 (S4): Change in CRF outcomes in response to prospective, well-characterised exercise interventions lasting >2 weeks (Primary meta-analysis)

1. Summary of the individual studies included in the review
2. Forest and funnel plots for change in each CRF outcome for each subgroup comparison (time since injury, neurological level of injury, injury severity, exercise modality, length of intervention, relative exercise intensity, method of exercise intensity prescription, frequency of exercise sessions, and exercise volume)
3. Quality assessment ratings for each pre-post study included in the primary meta-analysis

4. Risk of bias for each RCT intervention arm included in the primary meta-analysis
5. References

Supplementary file 5 (S5): Cross-sectional cohort comparisons summary (secondary meta-analysis 1)

1. Overview of participant demographics and injury characteristics for the pooled cohort comparisons
2. Summary of the individual studies included in the review
3. Quality assessment rating for each study using the NIH tool for observational cohort and cross-sectional studies
4. Forest plots and funnel plots for each CRF outcome
5. Sensitivity analysis on $R\dot{V}O_{2peak}$
6. References

Supplementary file 6 (S6): Cross-sectional associations between physical activity and CRF outcomes

1. Overview of participant demographics and injury characteristics for the pooled association comparisons
2. Summary of the individual studies included in the review
3. Quality assessment rating for each study using the NIH tool for observational cohort and cross-sectional studies
4. Visualisation of correlation coefficients between physical activity dimensions and CRF outcomes across included studies
5. References

Supplementary file 7 (S7): Observational studies (secondary meta-analysis 2)

1. Overview of participant demographics and injury characteristics for the pooled observational studies
2. Summary of the individual studies included in the review

3. Quality assessment rating for each study using the NIH tool for observational cohort and cross-sectional studies
4. Forest plots for absolute and relative $\dot{V}O_{2peak}$ and peak power output
5. Funnel plots for absolute and relative $\dot{V}O_{2peak}$ and peak power output
6. References

Supplementary file 8 (S8): RCTs (secondary meta-analysis 3)

1. Overview of participant demographics and injury characteristics for the pooled RCTs (exercise intervention vs. true-world control or standard of care)
2. Summary of the individual RCTs included in the review
3. Quality assessment rating for each study using the Cochrane Risk of Bias 2 tool
4. Forest plots and funnel plots for each CRF outcome
5. References

Supplementary file 9 (S9): RCTs intensity comparisons (secondary meta-analysis 4)

1. Overview of participant demographics and injury characteristics for the pooled RCTs comparing the effects of different exercise intensities
2. Summary of the individual RCTs comparing exercise intensity included in the review
3. Quality assessment rating for each study using the Cochrane Risk of Bias 2 tool
4. Forest plots and funnel plots for each CRF outcome
5. References

Supplementary file 10 (S10): Adverse events

Supplementary file 11 (S11): Sensitivity analyses

Supplementary file 11 (S12): CPET vs. exercise intervention modality

1. Forest plots for each CRF outcome

Supplementary file 10 (S13): Gait-training sub-analysis

1. Forest plots for each CRF outcome

Table 1. Participant demographics and injury characteristics reported within the included studies of the primary meta-analysis.

	A$\dot{V}O_{2peak}$ (L/min)	**R$\dot{V}O_{2peak}$ (mL/kg/min)**	**PPO (W)**
Baseline CRF			
Total number of interventions [sum of participants] Mean (range)	69 [766] 1.26 (0.51 – 3.50)	74 [768] 18.0 (7.3 – 36.9)	61 [662] 49 (0 – 168)
Participant demographics			
Age (years)	38 (24 - 54)	39 (24 - 58)	39 (25 - 57)
Sex			
Male	22 [181]	21 [150]	20 [157]
Female	-	-	-
Mixed (% F)	43 [559] (22%)	44 [535] (24%)	39 [492] (28%)
Not reported/cannot determine	4 [26]	9 [83]	2 [13]
Injury characteristics			
Time since injury (years)	8 (0 - 21)	6 (0 - 24)	7 (0 - 21)
Acute (<1-year)	7 [111]	8 [95]	9 [117]
Chronic (>1-year)	47 [472]	48 [443]	38 [367]
Mixed (% acute)	7 [89] (13.5%)	6 [64] (17%)	7 [84] (24%)
Not reported/cannot determine	8 [94]	12 [166]	7 [94]
Neurological level of injury (TETRA/PARA)			
TETRA	2 [18]	3 [23]	3 [23]
PARA	19 [176]	27 [264]	22 [220]
Mixed (% PARA)	41 [488] (59%)	36 [398] (51%)	32 [382] (62%)
Not reported/cannot determine	7 [84]	8 [83]	4 [37]
Severity			
Motor-complete (AIS A-B)	27 [248]	29 [253]	24 [219]
Motor-incomplete (AIS C-D)	8 [102]	13 [142]	2 [14]
Mixed (% motor-incomplete)	22 [303] (32%)	21 [270] (34%)	25 [344] (35%)
Not reported/cannot determine	12 [113]	11 [103]	10 [85]

Total number of studies (N) and participants (Σ), along with descriptive characteristics for the primary meta-analysis included in this systematic review that describes Δ in CRF outcomes in response to prospective, well-characterised exercise interventions lasting >2 weeks (e.g., combining exercise intervention-arms from RCTs and pre-post studies). Continuous variables are displayed as weighted means (range: lowest – highest mean values reported from studies). Categorical variables are displayed as n (%). Weighted means were calculated to account for differences in sample size between studies using the following formula: $\Sigma n^{*}\bar{x} / \Sigma n$, where Σ = the sum of, n = number of participants in each study, and $\bar{x}$ = mean CRF outcome of each study. AIS, American Spinal Injury Association Impairment Scale; F, females; M, males; NR, not reported; PARA, paraplegia; PPO, peak power output; TETRA, tetraplegia; $\dot{V}O_{2peak}$, peak oxygen consumption; W, watts.

Table 2. Exercise intervention parameters reported within the included studies of the primary meta-analysis.

	$A\dot{V}O_{2peak}$ (L/min)	$R\dot{V}O_{2peak}$ (mL/kg/min)	PPO (W)
Baseline CRF			
Total number of interventions [sum of participants] Mean (range)	69 [766] 1.26 (0.51 – 3.50)	74 [768] 18.0 (7.3 – 36.9)	61 [662] 49 (0 – 168)
Exercise intervention parameters			
Modality			
Upper-body aerobic exercise	25 [272]	33 [299]	26 [259]
Upper-body resistance training/circuits	4 [33]	3 [29]	3 [25]
Functional electrical stimulation	17 [170]	8 [66]	14 [140]
Gait/locomotor training	10 [130]	10 [126]	2 [28]
Mixed/multimodal	10 [94]	18 [227]	12 [136]
Behaviour change	3 [67]	2 [21]	4 [74]
Relative intensity			
Light	1 [14]	-	1 [14]
Moderate	8 [58]	12 [94]	10 [73]
Moderate-to-vigorous	21 [270]	24 [305]	16 [183]
Vigorous	14 [119]	20 [194]	11 [104]
Supramaximal	-	1 [4]	1 [10]
Mixed/cannot determine	25 [305]	17 [171]	22 [278]
Relative intensity prescription method			
VO_2 (%peak, %reserve)	8 [61]	12 [112]	9 [93]
Heart rate (%HRR, $\%HR_{peak}$, $\%HR_{max}$)	16 [156]	26 [285]	14 [113]
RPE	9 [144]	8 [111]	6 [90]
Workload (%PPO, %MTP, %1RM)	9 [71]	6 [49]	7 [53]
Mixed/cannot determine	27 [334]	22 [211]	25 [313]
Session duration (min)	41 (20 - 90)	41 (15 - 90)	39 (5 - 90)
Frequency (sessions/week)	3 (2 - 7)	3 (2 - 7)	3 (2 - 7)
< 3	19 [230]	13 [168]	13 [156]
≥ 3 and < 5	35 [339]	49 [500]	38 [387]
≥ 5	11 [116]	9 [65]	5 [31]
Not reported	4 [81]	3 [35]	5 [88]
Volume (min/week)	113 (40 - 450)	116 (40 - 330)	107 (15 - 330)
SCI-specific exercise guidelines [fitness (40 – 89 min/wk)]	13 [140] 45 (40 - 84)	14 [156] 47 (40 - 88)	15 [146] 48 (15 - 88)
SCI-specific exercise guidelines [cardiometabolic (90 – 149 min/wk)]	30 [309] 99 (90 - 135)	31 [336] 102 (90 - 135)	26 [290] 113 (90 - 135)
Achieving general population exercise guidelines (≥150 min/wk)	13 [135] 229 (150 - 450)	21 [197] 206 (150 - 330)	13 [117] 212 (171 - 330)
Cannot classify	13 [182]	8 [79]	7 [109]
Length (weeks)	17 (6 - 52)	12 (4 - 52)	16 (4 - 52)
≤ 6 weeks	10 [85]	23 [215]	18 [175]
> 6 and ≤ 12 weeks	33 [368]	36 [371]	21 [223]
> 12 weeks	26 [313]	15 [182]	22 [264]
Adverse events reported			
Bone, joint or muscular pain	5 [5] [a]	6 [9] [a]	4 [4] [a]

Autonomic or cardiovascular function	3 [5]	2 [1]	4 [3]
Skin irritation or pressure sores	2 [2] [a]	5 [18] [a]	2 [2] [a]
Other [d]	2 [NR] [a,c]	4 [3] [a]	3 [1] [a,c]

Total number of studies (N) and participants, (Σ) along with descriptive characteristics for the primary meta-analysis included in this systematic review that describes Δ in CRF outcomes in response to prospective, well-characterised exercise interventions lasting >2 weeks (e.g., combining exercise intervention-arms from RCTs and pre-post studies). Continuous variables are displayed as weighted means (range: lowest – highest mean values reported from studies). Categorical variables are displayed as n (%). Weighted means were calculated to account for differences in sample size between studies using the following formula: $\Sigma n*\bar{x} / \Sigma n$, where Σ = the sum of, n = number of participants in each study, and $\bar{x}$ = mean CRF outcome of each study. F, females; HR_{max}, maximal heart rate; HR_{peak}, peak heart rate; HRR, heart rate reserve; 1RM, one repetition maximum; M, males; MTP, maximal tolerated power; NR, not reported; PPO, peak power output; $\dot{V}O_{2\ peak}$, peak oxygen consumption; W, watts. [a] Beillot et al. [68] (pre-post intervention study) reported n=10 suffered major complications including spontaneous fractures of lower limbs, occurrence of syringomyelia and pressure sores but did not specify the sum of participants for each adverse event. [b] Gibbons et al. [81] reported that some individuals experienced autonomic dysreflexia during the FES response test but did not quantify further. [c] Sum of participants experiencing adverse events were not reported by Janssen and Pringle [61]. [d] Other adverse events included: anxiety, nausea, dizziness and issues with testing equipment.

Table 3. Summary statistics of the three subgroup analyses on injury characteristics describing Δ in CRF outcomes.

	$A\dot{V}O_{2peak}$ (L/min)		$R\dot{V}O_{2peak}$ (mL/kg/min)		PPO (W)	
	N [Σ] (%)	**WMD (95% CIs) *p*-values**	**N [Σ] (%)**	**WMD (95% CIs) *p*-values**	**N [Σ] (%)**	**WMD (95% CIs) *p*-values**
Main effect	69 [696]	0.22 [0.17, 0.26] ***p* < 0.001**	74 [716]	2.8 [2.2, 3.4] ***p* < 0.001**	61 [602]	11 [8, 13] ***p* < 0.001**
Heterogeneity (I^2)	74% ($p < 0.001$)		52% ($p < 0.001$)		78% ($p < 0.001$)	
Time since injury						
Acute (<1-year)	7 [86] (10.4%)	0.23 [0.11, 0.35] ***p* < 0.001**	8 [70] (10.9%)	3.4 [1.5, 6.1] ***p* = 0.002**	9 [95] (13.6%)	16 [11, 22] ***p* < 0.001**
Chronic (≥1-year)	47 [461] (62.6%)	0.20 [0.14, 0.27) ***p* < 0.001**	48 [431] (61.8%)	2.7 [1.9, 3.5] ***p* < 0.003**	38 [343] (61.8%)	9 [6, 12] ***p* < 0.001**
Mixed	7 [79] (14%)	0.25 [0.10, 0.39] ***p* < 0.001**	6 [54] (5.9%)	1.9 [0.1, 3.7] ***p* = 0.03**	7 [75] (12.8%)	6 [5, 7] ***p* < 0.001**
Not reported/cannot determine	8 [70] (13%)	0.25 [0.11, 0.38] ***p* < 0.001**	12 [161] (21.4%)	2.6 [2.0, 3.3] ***p* < 0.003**	7 [89] (11.8%)	16 [9, 23] ***p* < 0.001**
Subgroup differences	-	$p = 0.87$	-	$p = 0.64$	-	***p* < 0.001**
Neurological level of injury						
Tetraplegia	2 [18] (5.1%)	0.45 [-0.28, 1.19] $p = 0.23$	3 [23] (8.5%)	5.9 [0.2, 11.7] ***p* = 0.04**	3 [23] (6.8%)	9 [6, 13] ***p* < 0.002**
Paraplegia	20 [174] (28.4%)	0.24 [0.17, 0.32] ***p* < 0.002**	28 [262] (45.2%)	2.8 [2.2, 3.4] ***p* < 0.003**	22 [216] (42.2%)	16 [12, 19] ***p* < 0.002**
Mixed	44 [470] (58.9%)	0.20 [0.15, 0.25] ***p* < 0.002**	41 [418] (42.5%)	2.2 [1.5, 2.8] ***p* < 0.003**	34 [350] (48.6%)	6 [4, 8] ***p* < 0.002**
Not reported/cannot determine	3 [34] (7.6%)	0.19 [0.11, 0.27] ***p* < 0.002**	2 [13] (3.8%)	2.8 [0.7, 4.8] ***p* = 0.02**	2 [13] (2.4%)	17 [7, 27] ***p* = 0.001**
Subgroup differences	-	$p = 0.65$	-	$p = 0.34$	-	***p* < 0.001**
Injury severity						
Motor-complete (AIS A-B)	27 [235] (40%)	0.21 [0.14, 0.27] ***p* < 0.002**	29 [241] (47.4%)	2.7 [2.0, 3.4] ***p* < 0.002**	24 [210] (49.2%)	11 [8, 15] ***p* < 0.002**
Motor-incomplete (AIS C-D)	8 [103] (9%)	0.10 [-0.01, 0.21] $p = 0.08$	13 [139] (12.5%)	1.6 [0.2, 2.9] ***p* = 0.02**	2 [14] (3.1%)	4 [-3, 12] $p = 0.25$
Mixed (AIS A-D)	22 [247] (26.2%)	0.18 [0.13, 0.24] ***p* < 0.002**	21 [244] (23.3%)	2.7 [1.7, 3.6] ***p* < 0.002**	25 [296] (31.1%)	10 [6, 14] ***p* < 0.002**
Not reported/cannot determine	12 [111] (24.8%)	0.32 [0.20, 0.44] ***p* < 0.002**	11 [92] (16.8%)	3.9 [1.7, 6.1] ***p* < 0.002**	10 [82] (16.6%)	11 [5, 17] ***p* < 0.002**
Subgroup differences	-	$p = 0.06$	-	$p = 0.28$	-	$p = 0.43$

Total number of interventions (N), sum of participants analysed at post-intervention (Σ), weighting of subgroups (%). Thresholds for statistically significant subgroup differences were adjusted for the number of subgroup comparisons and are highlighted in bold: time since injury (p<0.0125), neurological level of injury (p<0.0125) and injury severity (p<0.0125). Individual subgroup p-values were adjusted for multiple comparisons via the Bonferroni correction method. AIS, Americal Spinal Injury Association Impairment Scale; $A\dot{V}O_{2peak}$, absolute peak oxygen consumption; CIs, confidence intervals; PPO, peak power output; $R\dot{V}O_{2peak}$, relative peak oxygen consumption; WMD, weighted mean difference.

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Table 4. Summary statistics of the six subgroup analyses on exercise parameters describing Δ in CRF outcomes.

	$\Delta\dot{V}O_{2peak}$ (L/min)		$\Delta\dot{V}O_{2peak}$ (mL/kg/min)		PPO (W)	
	N [Σ] (%)	**WMD (95% CIs) *p*-values**	**N [Σ] (%)**	**WMD (95% CIs) *p*-values**	**N [Σ] (%)**	**WMD (95% CIs) *p*-values**
Main effect	69 [696]	0.22 [0.17, 0.26] **$p < 0.001$**	74 [716]	2.8 [2.2, 3.4] **$p < 0.001$**	61 [602]	11 [8, 13] **$p < 0.001$**
Heterogeneity (I^2)	74% ($p < 0.001$)		52% ($p < 0.001$)		78% ($p < 0.001$)	
Exercise modality						
Aerobic, volitional upper-body	25 [235] (33.5%)	0.25 [0.16, 0.34] **$p < 0.004$**	33 [264] (43.1%)	3.4 [2.4, 4.4] **$p < 0.004$**	26 [223] (32.5%)	15 [11, 19] **$p < 0.003$**
Resistance training	4 [31] (3.5%)	0.33 [0.13, 0.52] **$p = 0.003$**	3 [27] (3.9%)	5.0 [2.9, 7.0] **$p < 0.004$**	3 [25] (4.6%)	20 [12, 28] **$p < 0.003$**
Functional electrical stimulation	17 [168] (33.9%)	0.22 [0.15, 0.29] **$p < 0.004$**	8 [66] (14.4%)	2.4 [0.9, 3.9] **$p = 0.006$**	14 [138] (37.1%)	6 [3, 10] **$p < 0.003$**
Gait training	10 [127] (12%)	0.07 [-0.02, 0.17] $p = 0.14$	10 [120] (9.7%)	1.0 [-0.5, 2.6] $p = 0.40$	2 [24] (2.2%)	4 [-9, 18] $p = 0.54$
Behaviour change	3 [49] (2.5%)	0.22 [0.00, 0.44] $p = 0.10$	2 [21] (3.3%)	1.1 [-1.2, 3.5] $p = 0.35$	4 [56] (4.6%)	12 [-1, 24] $p = 0.12$
Mixed	10 [86] (14.6%)	0.21 [0.14, 0.27] **$p < 0.004$**	18 [218] (25.6%)	2.4 [1.7, 3.2] **$p < 0.004$**	12 [136] (19%)	10 [5, 16] **$p < 0.003$**
Subgroup differences	-	$p = 0.07$	-	$p = 0.02$	-	**$p = 0.003$**
Length of intervention						
≤6 weeks	10 [79] (14.5%)	0.26 [0.19, 0.39] **$p < 0.001$**	23 [206] (23.1%)	2.9 [1.9, 3.9] **$p < 0.001$**	17 [159] (26.7%)	10 [6, 14] **$p < 0.001$**
>6 – ≤12 weeks	32 [327] (46.6%)	0.21 [0.14, 0.29] **$p < 0.001$**	36 [337] (54.6%)	3.2 [2.3, 4.1] **$p < 0.001$**	22 [202] (34.5%)	13 [8, 17] **$p < 0.001$**
>12 weeks	27 [290] (38.9%)	0.22 [0.15, 0.28] **$p < 0.001$**	15 [173] (22.3%)	1.8 [1.0, 2.6] **$p < 0.001$**	22 [241] (38.8%)	9 [5, 13] **$p < 0.001$**
Subgroup differences	-	$p = 0.59$	-	$p = 0.05$	-	$p = 0.49$
Relative exercise intensity						
Light	1 [10] (0.6%)	-0.05 [-0.57, 0.47] $p = 0.85$	-	-	1 [10] (1%)	-1 [-22, 20] $p = 0.92$
Moderate	8 [58] (9.5%)	0.32 [0.09, 0.54] **$p = 0.01$**	12 [92] (18.1%)	3.2 [1.1, 5.3] **$p = 0.006$**	10 [71] (15.9%)	13 [4, 21] **$p = 0.009$**
Moderate-to-vigorous	21 [247] (33.7%)	0.21 [0.14, 0.27] **$p < 0.003$**	24 [279] (32.5%)	2.7 [2.0, 3.5] **$p < 0.003$**	16 [161] (24.1%)	17 [13, 21] **$p < 0.004$**
Vigorous	14 [109] (15.2%)	0.19 [0.14, 0.25] **$p < 0.003$**	20 [183] (21.6%)	2.2 [1.4, 3.0] **$p < 0.003$**	11 [96] (12%)	10 [7, 16] **$p < 0.004$**
Supramaximal	-	-	1 [4] (0.4%)	1.1 [-8.2, 10.4] $p = 0.82$	1 [10] (0.6%)	17 [-12, 46] $p = 0.50$
Mixed/cannot determine	25 [272] (41%)	0.21 [0.14, 0.29] **$p < 0.003$**	17 [158] (27.4%)	2.6 [1.5, 3.8] **$p < 0.003$**	22 [254] (46.4%)	8 [5, 10] **$p < 0.004$**
Subgroup differences	-	$p = 0.71$	-	$p = 0.67$	-	**$p = 0.003$**

Exercise intensity prescription						
Oxygen consumption	8 [57] (13.1%)	0.19 [0.07, 0.32] ***p* = 0.003**	12 [107] (17.9%)	2.3 [1.5, 3.2] ***p* < 0.003**	9 [89] (12.6%)	20 [15, 25] ***p* < 0.003**
Heart rate	16 [156] (20.2%)	0.28 [0.15, 0.40] ***p* < 0.002**	26 [284] (37.7%)	3.1 [2.0, 4.3] ***p* < 0.003**	14 [113] (21.8%)	14 [8, 19] ***p* < 0.003**
Rating of perceived exertion	9 [121] (12.1%)	0.18 [0.09, 0.26] ***p* < 0.002**	8 [84] (8.3%)	3.5 [1.2, 5.07] ***p* = 0.002**	6 [66] (5.7%)	9 [1, 17] ***p* = 0.03**
Workload	9 [65] (9.9%)	0.23 [0.13, 0.33] ***p* < 0.002**	6 [43] (6.5%)	3.0 [1.2, 4.8] ***p* = 0.002**	7 [49] (11.9%)	11 [4, 19] ***p* = 0.01**
Mixed/cannot determine	27 [297] (44.7%)	0.21 [0.14, 0.27] ***p* < 0.002**	22 [198] (29.6%)	2.4 [1.4, 3.3] ***p* < 0.003**	25 [285] (48%)	7 [5, 10] ***p* < 0.003**
Subgroup differences	-	$p = 0.72$	-	$p = 0.71$	-	***p* < 0.001**
Frequency of exercise sessions						
<3 sessions/wk	19 [213] (24%)	0.18 [0.12, 0.25] ***p* < 0.002**	13 [155] (15.2%)	2.8 [1.5, 4.0] ***p* < 0.002**	13 [148] (21.4%)	4 [1, 6] ***p* = 0.003**
≥3 – <5 sessions/wk	35 [306] (57.6%)	0.26 [0.19, 0.33] ***p* < 0.002**	49 [465] (65.9%)	2.8 [2.1, 3.6] ***p* < 0.002**	38 [357] (61.8%)	13 [10, 15] ***p* < 0.004**
≥5 sessions/wk	11 [118] (14.4%)	0.15 [0.07, 0.23] ***p* < 0.002**	9 [65] (14.2%)	3.6 [1.7, 5.4] ***p* < 0.002**	5 [31] (10.9%)	10 [-2, 23] $p = 0.10$
Not reported/cannot determine	4 [59] (4%)	0.13 [-0.05, 0.31] $p = 0.15$	3 [31] (4.7%)	0.8 [-1.2, 2.8] $p = 0.42$	5 [66] (5.9%)	9 [0, 18] $p = 0.10$
Subgroup differences	-	$p = 0.14$	-	$p = 0.24$	-	***p* < 0.001**
Exercise volume						
SCI-specific exercise guidelines for fitness (40 - 89 min/wk)	13 [132] (13.1%)	0.23 [0.13, 0.33] ***p* < 0.001**	14 [151] (13.9%)	3.2 [2.0, 4.5] ***p* < 0.002**	15 [138] (19.1%)	6 [2, 10] ***p* = 0.002**
SCI-specific exercise guidelines for cardiometabolic health (90 - 149 min/wk)	30 [269] (52.3%)	0.23 [0.16, 0.30] ***p* < 0.001**	31 [295] (48.3%)	2.8 [1.9, 3.8] ***p* < 0.002**	26 [260] (48.7%)	12 [9, 16] ***p* < 0.002**
Achieving general population exercise guidelines (≥150 min/wk)	13 [133] (18%)	0.18 [0.11, 0.25] ***p* < 0.001**	21 [195] (28.1%)	2.8 [1.8, 3.9] ***p* < 0.002**	13 [117] (23.9%)	11 [5, 17] ***p* < 0.002**
Not reported/cannot determine	13 [162] (16.6%)	0.24 [0.12, 0.36] ***p* < 0.001**	8 [75] (9.7%)	2.1 [0.7, 3.5] ***p* = 0.003**	7 [87] (8.3%)	10 [4, 17] ***p* = 0.002**
Subgroup differences	-	$p = 0.67$	-	$p = 0.70$	-	$p = 0.17$

Total number of interventions (N), sum of participants analysed at post-intervention (Σ), weighting of subgroups (%). Thresholds for statistically significant subgroup differences were adjusted for the number of subgroup comparisons and are highlighted in bold: exercise modality (p<0.008), length of intervention (p<0.017), relative exercise intensity [$A\dot{V}O_{2peak}$ and $R\dot{V}O_{2peak}$ (p<0.01), PPO (p<0.008)], exercise intensity prescription (p<0.01), frequency of exercise sessions (p<0.025), and exercise volume (p<0.025). Individual subgroup p-values were adjusted for multiple comparisons via the Bonferroni correction method. $A\dot{V}O_{2peak}$, absolute peak oxygen consumption; CIs, confidence intervals; PPO, peak power output; $R\dot{V}O_{2peak}$, relative peak oxygen consumption; WMD, weighted mean difference.

1499

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Table 5: Meta-regression models with adjusted values for each cardiorespiratory fitness outcome.

Covariate	Coef.	Std.Err.	t	Unadjusted P>t	95% CI	Adjusted P>t
$A\dot{V}O_{2peak}$ Model 1 (N = 69)[1] (# covariates = 5)						
Male	0.006	0.004	1.610	0.084	-0.001 to 0.013	0.322
Mean age	-0.003	0.001	-2.580	0.010	-0.006 to -0.001	0.045
TSI	0.000	0.001	0.260	0.714	-0.002 to 0.003	0.999
Neurological level of injury	-0.002	0.004	-0.470	0.584	-0.010 to 0.006	0.984
Severity	-0.005	0.003	-1.340	0.153	-0.012 to 0.002	0.534
$A\dot{V}O_{2peak}$ Model 2 (N = 69)[2] (# covariates = 6)						
Exercise modality	-0.015	0.016	-0.940	0.281	-0.048 to 0.017	0.865
Exercise intensity	-0.006	0.016	-0.390	0.666	-0.038 to 0.026	0.999
Length of intervention	0.000	0.002	0.050	0.828	-0.004 to 0.004	1.000
Duration (mins)	-0.005	0.006	-0.790	0.327	-0.018 to 0.008	0.917
Frequency	0.002	0.011	0.180	0.902	-0.019 to 0.023	1.000
Volume	-0.000	0.003	-0.040	0.929	-0.006 to 0.006	1.000
$R\dot{V}O_{2peak}$ Model 1 (N = 74)[3] (# covariates = 5)						
Male	0.084	0.047	1.790	0.84	-0.010 to 0.177	0.395
Mean age	-0.041	0.013	-3.010	0.004	-0.068 to -0.014	0.025
TSI	-0.012	0.013	-0.940	0.386	-0.039 to 0.014	0.932
Neurological level of injury	-0.043	0.042	-1.020	0.356	-0.128 to 0.042	0.907
Severity	-0.030	0.047	-0.650	0.521	-0.124 to 0.063	0.983
$R\dot{V}O_{2peak}$ Model 2 (N = 74) [4] (# covariates = 6)						
Exercise modality	-0.276	0.164	-1.680	0.110	-0.603 to 0.051	0.511
Exercise intensity	-0.076	0.200	-0.380	0.718	-0.474 to 0.323	1.00
Length of intervention	-0.024	0.033	-0.740	0.437	-0.089 to 0.041	0.982
Risk of bias	-0.057	0.350	-0.160	0.866	-0.756 to 0.642	1.000
Duration (mins)	-0.043	0.063	-0.690	0.494	-0.169 to 0.082	0.986
Frequency	0.143	0.139	1.030	0.308	-0.133 to 0.420	0.908
PPO Model 1 (N = 61) [5] (# covariates = 6)						
Male	-0.090	0.236	-0.380	0.712	-0.562 to 0.383	0.997
Mean age	-0.035	0.082	-0.420	0.694	-0.199 to 0.130	0.995
TSI	-0.149	0.077	-1.940	0.075	-0.303 to 0.005	0.296
Neurological level of injury	-0.122	0.193	-0.630	0.556	-0.509 to 0.265	0.972
Severity	-0.051	0.182	-0.280	0.796	-0.416 to 0.314	1.000
PPO Model 2 (N = 61) [6] (# covariates = 5)						
Exercise modality	-0.685	0.733	-0.930	0.068	-2.156 to 0.786	0.266
Exercise intensity prescription	-1.465	0.749	-1.960	0.001	-2.967 to 0.036	0.002
Duration (mins)	-0.170	0.361	-0.470	0.476	-0.893 to 0.554	0.945
Frequency	0.254	0.643	0.390	0.997	-1.036 to 1.543	1.00
Volume	-0.217	0.178	-1.220	0.009	-0.574 to 0.140	0.041

* Permutations = 10,000

[1] $tau^2 = 0.02339$; I^2 res = 98.61%; Adj R^2 = 13.00%; Model F (5,63) = 2.77; Prob > F = 0.0252

[2] $tau^2 = 0.2932$; I^2 res = 98.52%; Adj R^2 = -9.04%; Model F (7,61) = 0.31; Prob > F = 0.9446

[3] $tau^2 = 3.639$; I^2 res = 97.98%; Adj R^2 = 11.98%; Model F (5,68) = 2.89; Prob > F = 0.0201

[4] tau^2 = 4.108; I^2 res = 98.13%; Adj R^2 = 0.63%; Model F (7,66) = 1.04; Prob > F = 0.4124
[5] tau^2 = 65.65; I^2 res = 99.56%; Adj R^2 = 1.07%; Model F (5,55) = 1.16; Prob > F = 0.3399
[6] tau^2 = 64.86; I^2 res = 99.34%; Adj R^2 = 2.26%; Model F (7,53) = 1.17; Prob > F = 0.3333
Adj R^2, proportion of between-study variance explained; $A\dot{V}O_{2peak}$, absolute peak oxygen consumption; Coef, coefficient of variation; I^2 res, I^2 residual variation due to heterogeneity; Model F, joint test for all covariates; PP Prob > F, with Knapp-Hartung modification; $R\dot{V}O_{2peak}$, relative peak oxygen consumption; Std.Err, standard error; TSI, time since injury.

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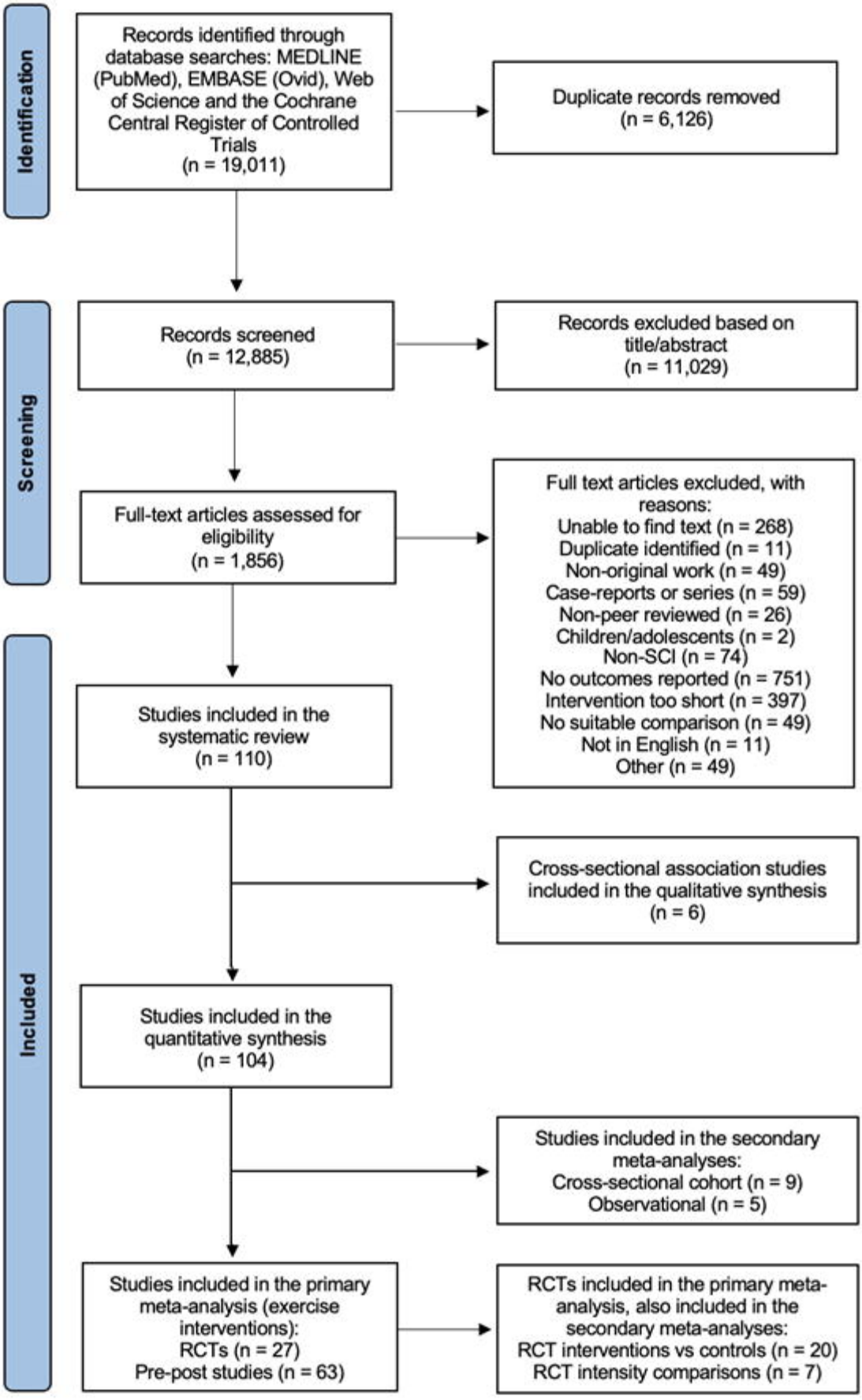
Table 6. Grading of recommendations assessment, development and evaluation analysis for each cardiorespiratory fitness outcome.

	A$\dot{V}O_{2peak}$ (L/min)	**R$\dot{V}O_{2peak}$ (mL/kg/min)**	**PPO (W)**
Summary of findings according to GRADE analysis			
GRADE	LOW	LOW	LOW
Comments	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Study design, imprecision, an unclear dose response and residual confounding reduced the Grade to Low. The evidence supporting improvements in A$\dot{V}O_{2peak}$ is predominantly in young and middle-aged males that had been injured for >1-year (chronic TSI). Participants were mostly paraplegic (70%) but there were a mixture of injury severities (AIS A-D). There were no subgroup differences in exercise intervention characteristics to suggest the optimal training parameters.	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. High risk of bias, imprecision, an unclear dose response and residual confounding reduced the Grade to Low. The evidence supporting improvements in R$\dot{V}O_{2peak}$ is predominantly in young and middle-aged males that had been injured for >1-year (chronic TSI). Participants were mostly paraplegic (70.5%) but there were a mixture of injury severities (AIS A-D). There were no subgroup differences in exercise intervention characteristics to suggest the optimal training parameters.	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Inconsistency, imprecision, an unclear dose response and residual confounding reduced the Grade to Moderate. The evidence supporting improvements in PPO is predominantly in young and middle-aged males that had been injured for >1-year (chronic TSI). Participants were mostly paraplegic (76%) but there were a mixture of injury severities (AIS A-D). Subgroup differences suggest that upper-body aerobic exercise and resistance training appear the most effective at improving PPO. Furthermore, acutely-injured, individuals with paraplegia, exercising for >3 sessions/week at a moderate-to-vigorous-intensity, prescribed via $\dot{V}O_2$ or heart rate, will likely experience the greatest change in PPO.
Lower quality criteria			
Study design	Mixture of RCTs and pre-post studies with no control groups.	Mixture of RCTs and pre-post studies with no control groups.	Mixture of RCTs and pre-post studies with no control groups.

	Overall WMDs for RCT interventions relative to controls and pre-post interventions only: RCTs (0.15 L/min) and pre-post studies (0.23 L/min). **DOWNGRADE**	Overall WMDs for RCT interventions relative to controls and pre-post interventions only: RCTs (2.9 mL/kg/min) and pre-post studies (2.9 mL/kg/min). **NO DOWNGRADE**	Overall WMDs for RCT interventions relative to controls and pre-post interventions only: RCTs (10 W) and pre-post studies (11 W). **NO DOWNGRADE**
Risk of bias (RoB)	28% of pre-post studies were rated as good, 56% as fair, and 16% as poor. 31% of RCTs had low RoB, 23% had some concerns, and 46% had high RoB. **NO DOWNGRADE**	38% of pre-post studies were rated as good, 48% as fair, and 14% as poor. 15% of RCTs had low RoB, 25% had some concerns, and 60% had high RoB. **DOWNGRADE**	26% of pre-post studies were rated as good, 59% as fair, and 15% as poor. 23% of RCTs had low RoB, 38.5% had some concerns, and 38.5% had high RoB. **NO DOWNGRADE**
Inconsistency of results	Effect estimates were consistent, with 91% of the included exercise interventions favouring an increase in $A\dot{V}O_{2peak}$, but most had a low effect estimate. $I^2 = 74\%$ **NO DOWNGRADE**	Effect estimates were consistent, with 91% of the included exercise interventions favouring an increase in $R\dot{V}O_{2peak}$, and most had a large effect estimate. $I^2 = 52\%$ **NO DOWNGRADE**	Effect estimates were consistent, with 93% of the included exercise interventions favouring an increase in PPO, and most had a large effect estimate. $I^2 = 78\%$ **DOWNGRADE**
Indirectness	Most studies (83%) included $A\dot{V}O_{2peak}$ in their main outcome measures, across a range of participant characteristics. **NO DOWNGRADE**	Most studies (72%) included $R\dot{V}O_{2peak}$ in their main outcome measures, across a range of participant characteristics. **NO DOWNGRADE**	Most studies (82%) included PPO in their main outcome measures, across a range of participant characteristics. **NO DOWNGRADE**
Imprecision	Large sample size (N=696), however, 62% of the included exercise interventions had 95% CI overlap 0. **DOWNGRADE**	Large sample size (N=716), however, 76% of the included exercise interventions had 95% CI overlap 0. **DOWNGRADE**	Large sample size (N=601), however, 67% of the included exercise interventions had 95% CI overlap 0. **DOWNGRADE**
Publication bias	An exhaustive approach was used during the search strategy (i.e., scientific databases and grey literature search). Egger's test: Z = -1.23 (p = 0.22). Visual inspection of the funnel plots, data extraction sheets and Tables 3-4 revealed no noticeable publication bias. **NO DOWNGRADE**	An exhaustive approach was used during the search strategy (i.e., scientific databases and grey literature search). Egger's test: Z = -0.54 (p = 0.59). Visual inspection of the funnel plots, data extraction sheets and Tables 3-4 revealed no noticeable publication bias. **NO DOWNGRADE**	An exhaustive approach was used during the search strategy (i.e., scientific databases and grey literature search). Egger's test: Z = 0.73 (p = 0.46). Visual inspection of the funnel plots, data extraction sheets and Tables 3-4 revealed no noticeable publication bias. **NO DOWNGRADE**
Higher quality criteria			
Large effect	Yes Z = 9.5 ($p < 0.001$) **NO UPGRADE**	Yes Z = 9.4 ($p < 0.001$) **NO UPGRADE**	Yes Z = 8.7 ($p < 0.001$) **NO UPGRADE**

Dose response	No clear dose response. **NO UPGRADE**	No clear dose response. **NO UPGRADE**	No clear dose response. **NO UPGRADE**
Residual confounding	Mixture of exercise modalities, levels of injury, etc. **NO UPGRADE**	Mixture of exercise modalities, levels of injury, etc. **NO UPGRADE**	Mixture of exercise modalities, levels of injury, etc. **NO UPGRADE**

GRADE certainty in the evidence can be 'High', 'Moderate', 'Low' or 'Very Low' according to published guidelines [34]. Risk of bias was downgraded where >50% of RCTs had a high risk of bias. Heterogeneity was also included as a measure of inconsistency, whereby an outcome with I^2 >75% was classed as considerable and resulted in a downgrade. Imprecision was downgraded where >50% of studies had confidence intervals overlap the no effect line. Indirectness would have been downgraded where <50% of studies did not include the appropriate main outcome measure or assess a range of participant characteristics. Overall effect sizes are presented as Z-scores. Statistical significance accepted as $p < 0.05$. AIS, American Spinal Injury Association Impairment Scale; $A\dot{V}O_{2peak}$, absolute peak oxygen consumption; CI, confidence intervals; CRF, cardiorespiratory fitness; PPO, peak power output; RCTs, randomised-controlled trials; RoB, risk of bias; $R\dot{V}O_{2peak}$, relative peak oxygen consumption; $\dot{V}O_2$, peak oxygen consumption.


Identification
Records identified through database searches: MEDLINE (PubMed), EMBASE (Ovid), Web of Science and the Cochrane Central Register of Controlled Trials (n = 19,011)
Duplicate records removed (n = 6,126)
Screening
Records screened (n = 12,885)
Records excluded based on title/abstract (n = 11,029)
Full-text articles assessed for eligibility (n = 1,856)
Full text articles excluded, with reasons:
Unable to find text (n = 268)
Duplicate identified (n = 11)
Non-original work (n = 49)
Case-reports or series (n = 59)
Non-peer reviewed (n = 26)
Children/adolescents (n = 2)
Non-SCI (n = 74)
No outcomes reported (n = 751)
Intervention too short (n = 397)
No suitable comparison (n = 49)
Not in English (n = 11)
Other (n = 49)
Included
Studies included in the systematic review (n = 110)
Cross-sectional association studies included in the qualitative synthesis (n = 6)
Studies included in the quantitative synthesis (n = 104)
Studies included in the secondary meta-analyses:
Cross-sectional cohort (n = 9)
Observational (n = 5)
Studies included in the primary meta-analysis (exercise interventions):
RCTs (n = 27)
Pre-post studies (n = 63)
RCTs included in the primary meta-analysis, also included in the secondary meta-analyses:
RCT interventions vs controls (n = 20)
RCT intensity comparisons (n = 7)