Do physical interventions improve outcomes following concussion: a systematic review and meta-analysis?

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ABSTRACT

Objective To investigate the effect of physical interventions (subthreshold aerobic exercise, cervical, vestibular and/or oculomotor therapies) on days to recovery and symptom scores in the management of concussion.

Design A systematic review and meta-analysis.

Data sources Medline, CINAHL, Embase, SportDiscus, Cochrane library, Scopus and PEDro.

Eligibility criteria Randomised controlled trials of participants with concussion that evaluated the effect of subthreshold aerobic exercise, cervical, vestibular and/or oculomotor therapies on days to recovery/return to activity, symptom scores, balance, gait and/or exercise capacity.

Results Twelve trials met the inclusion criteria: 7 on subthreshold aerobic exercise, 1 on vestibular therapy, 1 on cervical therapy and 3 on individually tailored multimodal interventions. The trials were of fair to excellent quality on the PEDro scale. Eight trials were included in the quantitative analysis. Subthreshold aerobic exercise had a significant small to moderate effect in improving symptom scores (standardised mean difference (SMD)=0.43, 95% CI 0.18 to 0.67, p=0.001, I^2=0%) but not in reducing days to symptom recovery in both acutely concussed individuals and those with persistent symptoms (SMD=0.19, 95% CI −0.54 to 0.93, p=0.61, I^2=52%). There was limited evidence for stand-alone cervical, vestibular and oculomotor therapies. Concussed individuals with persistent symptoms (>2 weeks) were approximately 3 times more likely to have returned to sport by 8 weeks (relative risk=3.29, 95% CI 0.30 to 35.69, p=0.33, I^2=83%) if they received individually tailored, presentation-specific multimodal interventions (cervical, vestibular and oculo-motor therapy). In addition, the multimodal interventions had a moderate effect in improving symptom scores (SMD=0.63, 95% CI 0.11 to 1.15, p=0.02, I^2=0%) when compared with control.

Conclusions Subthreshold aerobic exercise appears to lower symptom scores but not time to recovery in concussed individuals. Individually tailored multimodal interventions have a worthwhile effect in providing faster return to sport and clinical improvement, specifically in those with persistent symptoms.

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INTRODUCTION

Concussion is a common injury that is often poorly identified, under-reported and undermanaged.[1] It is defined as a biomechanically induced traumatic brain injury from a direct blow to the head or a force transmitted indirectly from an impact to the body, resulting in a rapid onset of disruption to normal brain function, presenting as a range of clinical signs and symptoms.[2] Although most adults recover in 14 days, 10%–30% of individuals have persistent symptoms, negatively affecting their quality of life.[2–6] For these individuals, rehabilitation may facilitate recovery.[2 3] Tailored interventions may also be beneficial in the early stages of concussion management; however, best practice guidelines are still in their infancy. Although the latest recommendations for early management recommend a brief period (24–48 hours) of cognitive and physical rest, followed by a stepwise return to physical activity, more recently there is emerging evidence[6 7] for the use of physical interventions such as subthreshold aerobic exercise, cervical therapy, vestibular and/or oculomotor rehabilitation for individuals with ongoing concussion symptoms.[2 5 8–10] Concussion presentations are often heterogeneous, the treatment is complex and needs to address the large number of possible deficits and symptoms such as headache, dizziness, neck pain, imbalance, vestibular–oculomotor and cognitive impairments.[3 9 10]

Following the previous systematic reviews,[7 8 11–15] six new randomised controlled trials (RCTs) have been conducted[16–24] and could add high-quality support for the use of physical interventions in order to improve patient outcomes. We aim to perform a systematic review with meta-analysis to synthesise the findings from similar individual studies, and derive conclusions about best practice for managing this complex condition.

Therefore, the research questions for this systematic review were:

1. What is the effect of incorporating subthreshold aerobic exercise, cervical therapy, vestibular and/or oculomotor therapies into concussion management, for acute and ongoing symptoms?
2. What is the effect of incorporating such physical therapies as individually tailored, presentation-specific multimodal interventions into the acute and ongoing management of concussion?

METHODS

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Data sources and searches

The following databases were searched: Medline, CINAHL, SportDiscus, PEDro, Cochrane library, Embase and Scopus, from inception to 5 September

Box 1 Inclusion criteria

Design
- ► Randomised controlled trial.

Participants
- ► Individuals who have suffered a concussion or mild traumatic brain injury.
- ► All age groups, both sexes.

Intervention
- ► Subthreshold aerobic exercise, cervical therapy, vestibular therapy or oculomotor therapy.

Outcome measures
- ► Symptom severity.
- ► Days to recovery/clearance to resume sport or work.
- ► Measure of balance or gait.
- ► Physical activity.

Comparisons
- ► Sham intervention.
- ► Standard care.

2020 (online supplemental appendix 1). Appropriate search and MeSH terms were adapted and applied to each database, with the help of the University research librarian. To supplement the initial database searches, a manual search of the references listed in identified systematic reviews was also conducted.

Eligibility criteria

We included RCTs evaluating the effects of physical therapies on recovery following concussion, either acute or ongoing, sustained from any cause (box 1).

Subthreshold exercise was defined as exercise at 80%–90% of the heart rate, where symptoms were exacerbated. The search was limited to human trials published in English only. Exclusion criteria were articles published in abstract form. Duplicate studies identified as a result of searching multiple databases were removed using EndNote V.X8 software. The titles and abstracts were screened by two assessors independently (JF and SM), according to predetermined eligibility criteria. Full text articles were assessed and if there was uncertainty over the inclusion of a study, a third reviewer (SAR) was consulted until consensus was reached.

Quality assessment and data extraction

Data extracted from the full text articles included sample size, mean age of participants, gender, acute or persistent presentation, interventions, outcomes and results.

The quality of individual studies was assessed using the PEDro scale, an 11-item scale designed for rating the methodological quality of RCTs to discriminate between high-quality and low-quality trials. Items address the internal validity based on factors such as random allocation and concealment, baseline variables, blinding, outcomes obtained at baseline and intention to treat analysis, and whether the trial contains sufficient statistical information to make it interpretable.[25] Total PEDro scores of 0–4 are considered ‘poor’, 4–5 ‘fair’, 6–8 ‘good’ and 9–10 ‘excellent’.[26]

PEDro scores published on the PEDro database (www.pedro.org) were extracted for all available studies.

Data synthesis

The trials were compared for homogeneity (online supplemental table 1). Trials were grouped according to the type of intervention used (ie, exercise, vestibular, cervical or multimodal) and according to outcome measures (ie, symptom scores or days to recovery).

Meta-analysis

Meta-analysis was performed using Review Manager V.5.3 software (Cochrane Collaboration) (RevMan). Meta-analysis was performed when more than one study could be grouped for type of intervention (exercise, vestibular, cervical or multimodal) and according to outcome measures (symptom scores or days to recovery). If there was only one study in the group, then meta-analysis could not be performed and the statistics from that single study were reported. Concussed patients receiving a sham, or no intervention, were considered to be control. Standardised mean differences (SMDs) and 95% CI were calculated when outcomes were measured on different scales for continuous data, and risk ratio and 95% CIs were calculated for dichotomous variables. Post-scores were used in the RevMan analysis rather than change scores as several studies did not provide change scores or enough information to establish them.

The I^2 statistic, an expression of inconsistency of studies' results, was calculated to describe the percentage of variation across studies because of heterogeneity rather than by chance. A random-effects model was used for outcomes where studies differed in their measuring tool and a fixed-effects model when studies used the same measuring tool. Interpretation of effect size was determined using Cohen's criteria for pooled estimates, with an SMD of 0.2–0.4, considered a small effect size, 0.5–0.7, moderate, and 0.8 or higher, a large effect size.[27]

RESULTS

Study selection, risk of bias and characteristics

The electronic database search initially identified 2977 articles (figure 1), duplicates were then removed, and records screened. Thirty eight full texts were reviewed for eligibility, of which 12 trials met the eligibility criteria. A total of 647 participants (aged: 12–54 years) were included in this systematic review. Three trials reported on adults,[21 22 28] six on adolescents,[16–20 23] two on both adolescents and adults[29 30] and one did not report the age of participants.[24] Of these 12 trials, 9 trials assessed standardised treatment protocols of stand-alone interventions of subthreshold aerobic exercise, cervical or vestibular therapy. Seven of these trials evaluated subthreshold aerobic exercise,[17–19 21 23 24 29] one stand-alone cervical therapy[28] and one stand-alone vestibular therapy.[22] The other three studies[16 21 30] assessed the effect of multimodal management, which combined multiple types of intervention, including cervical, vestibular and/or oculomotor therapies, individually targeting the patient's symptoms and objective findings. Four of the 12 trials included participants with acute concussion symptoms and eight included those with persistent symptoms, in excess of 2 weeks.

Characteristics of the 12 included trials are summarised in online supplemental table 1.

All twelve RCTs had been scored by PEDro so the scores were extracted from the PEDro database (www.pedro.org) (table 1). One study was considered to be of poor quality,[24] four of fair quality[17 18 28 29] and seven were of good to excellent quality.[16 19–23 30] The majority of trials randomly allocated subjects (100%), reported between group statistics (100%), reported point measures and variability (92%) and listed

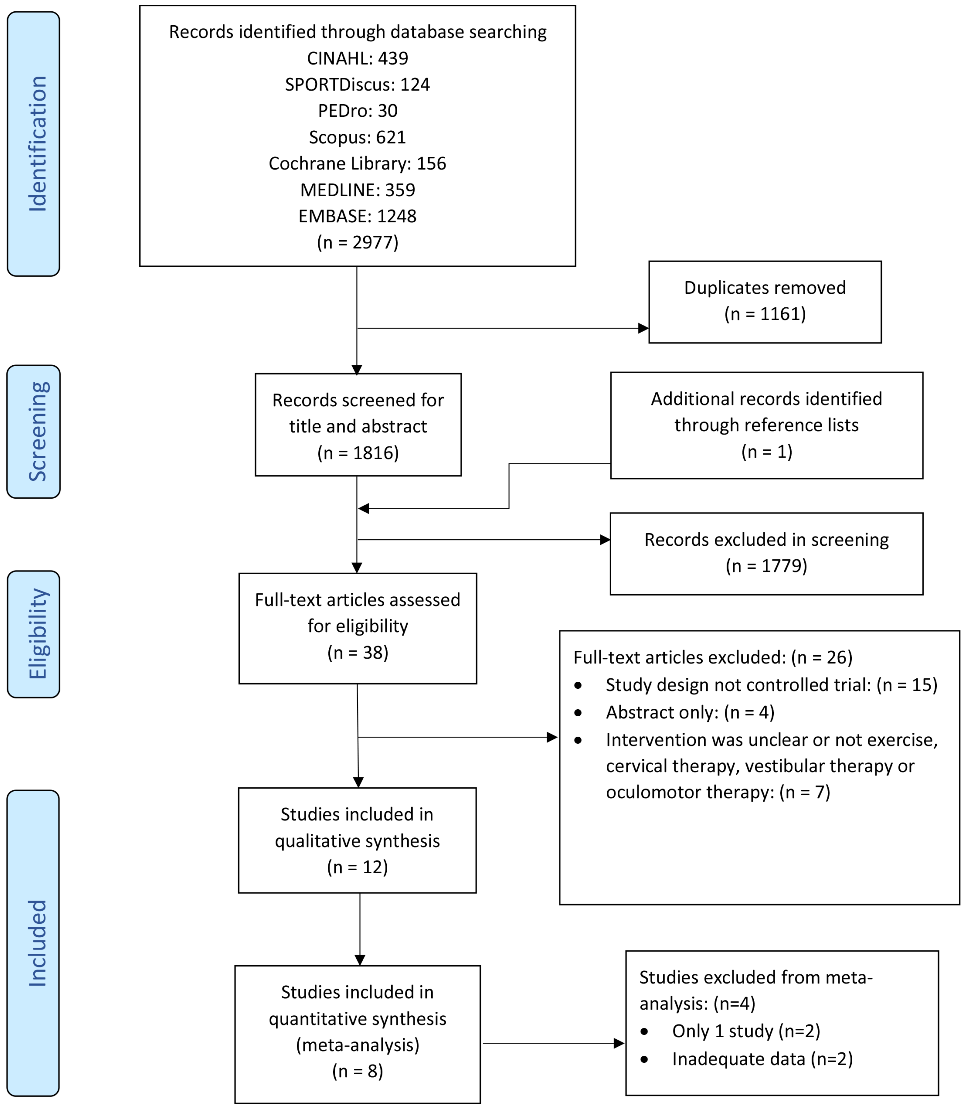

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

eligibility criteria (92%), had similar groups at baseline (75%) and blinded assessors (67%). Most trials did not make use of intention-to-treat analysis (only 33%) or conceal allocation to group (only 42%). None of the trials blinded subjects or therapists, as this was not possible for the intervention.

Meta-analysis

Not all information was readily available in the studies. The numerical data or extra information were requested from and supplied by three author groups (Micay *et al*,[19] Leddy *et al*[18] and Reneker *et al*[20]). The studies by Relander *et al*[29] and Maerlender *et al*[24] did not provide sufficient data to be included in the meta-analysis. Meta-analysis could not be performed for cervical and vestibular interventions, as there was only one study assessing each intervention. A random-effects model was used for all outcomes, as in most instances the measurement tool was different or there was high heterogeneity >50%.

Effect of subthreshold aerobic exercise

Effect of subthreshold exercise on days to symptom recovery/return to activity

Two trials[18 19] evaluating the effect of subthreshold aerobic exercise on days to symptom recovery/return to activity could be grouped for meta-analysis (figure 2). Both trials assessed participants with acute (≤2 weeks) concussion presentations. The results of our meta-analysis indicate there was no evidence of a difference in days to symptom recovery between those receiving exercise and controls (SMD=0.19, 95% CI −0.54 to 0.93, p=0.61, I^2=52%). An SMD was used as the trials differed in their definition of days to recovery: Leddy *et al*[18] evaluated recovery time using the number of days from the time of injury to the third consecutive day in which the individual's Post-Concussion Symptoms Scale (PCSS) fell below 7. Micay *et al*[19] determined recovery time by reviewing each participant's medical record for their return to play status (in days). Although Maerlender *et al*'s[24] study of acutely concussed individuals was not included in the meta-analysis, their results also showed no significant effect of subthreshold aerobic exercise on days to symptom recovery, with individuals performing 20 min/day on a stationary bicycle having a mean recovery time of 15 days, compared with those performing normal activities recovering in 13 days. However, Relander *et al*[29] studied acutely concussed individuals who received additional physical training twice a week required a mean of 17.7. days off work while the controls had 32.2 days off.

Table 1 Quality assessment of trials using the PEDro scale for methodological quality

PEdro item	1	2	3	4	5	6	7	8	9	10	11	PEDro score
Chan *et al*[16]	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	7/10
Chrisman *et al*[17]	Y	Y	N	N	N	N	Y	N	N	Y	N	5/10
Jensen *et al*[28]	Y	Y	N	Y	N	N	Y	N	N	Y	Y	5/10
Kleffelgaard *et al*[22]	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8/10
Kurowski *et al*[23]	Y	Y	N	Y	N	N	Y	Y	N	Y	Y	6/10
Leddy *et al*[18]	Y	Y	N	Y	N	N	N	Y	N	Y	Y	5/10
Maerlender *et al*[24]	N	Y	N	N	N	N	N	N	N	Y	Y	3/10
Micay *et al*[19]	Y	Y	N	Y	N	N	Y	Y	N	Y	Y	6/10
Relander *et al*[29]	Y	Y	N	Y	N	N	N	N	N	Y	Y	4/10
Reneker *et al*[20]	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	7/10
Rytter *et al*[21]	Y	Y	Y	N	N	N	Y	N	Y	Y	Y	6/10
Schneider *et al*[30]	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8/10

Pedro scale item: (1) eligibility criteria specified, (2) random allocation, (3) concealed allocation, (4) group characteristics similar at baseline, (5) blinding of subjects, (6) blinding of therapists, (7) blinding of assessors, (8) less than 15% dropouts, (9) intention-to-treat analysis, (10) between-group statistical comparisons and (11) point measures and variability data. PEDro scores of 0–4 are considered 'poor', 4–5 'fair', 6–8 'good' and 9–10 'excellent'.

Effect of subthreshold aerobic exercise on symptoms scores

Five trials[17–19 21 23] included in the meta-analysis reported on the effect of subthreshold aerobic exercise on symptom scores. Symptom outcome measures employed in these trials (figure 3) included the PCSS (0=best to 126=worst), the Post-Concussion Symptom Inventory (0=best to 72=worst), the Rivermead Post-concussion Symptoms Questionnaire (RPSQ: 0=best to 64=worst) and the Health Behaviour Inventory (0=best to 60=worst). Reassessments were conducted by Leddy *et al*[18] and Micay *et al*[19] at 4 weeks, Chrisman *et al*[17] at 6 weeks, Kurowski *et al*[23] at 7 weeks and Rytter *et al*[21] at 24 weeks. On meta-analysis, the results favoured exercise with an SMD of 0.43 (95% CI 0.18 to 0.67, p=0.001, I^2=0%) (figure 3). Separating these trials into acute (≤2 weeks)[18 19] and persistent (>2 weeks)[17 21 23] presentations also favoured exercise, with a moderate effect for acute presentations (SMD=0.38, 95% CI 0.01 to 0.74, p=0.04, I^2=0%) and a small to medium effect for persistent SMD of 0.46 (95% CI 0.13 to 0.80, p=0.006, I^2=0%) (online supplemental figures 1 and 2).

Effect of cervical, vestibular and/or oculomotor therapies

Cervical therapy

Jensen *et al*[28] assessed the effect of cervical therapy alone on individuals with persistent symptoms post-concussion that included headache. Treatment was based on findings from their cervical manual examination. The trial was of fair methodological quality. They found a significant difference after 6 weeks on the Visual Analogue Scale (VAS: 0=best to 100=worst) with a decrease in pain of 3.2 (SD=14.5) for the manual therapy group but an increase of 1.9 (SD=13.2) for those receiving cold packs. However, a change of 3.2 on a 100-point scale was not considered to be clinically significant.

Vestibular therapy

Kleffelgaard *et al*[22] evaluated the effectiveness of vestibular therapy alone on symptom scores in individuals with persistent symptoms. These included dizziness or balance concerns and targeted concussed patients with positive vestibular findings. Therapy included group and individually tailored exercises. The authors found a significant difference favouring vestibular therapy over no intervention for the Dizziness Handicap Inventory (DHI: 0=best to 100=worst) (−8.7; 95% CI −16.6 to −0.9; p=0.03), but not for the Vertigo Symptom Scale–Short Form (0=best to 60=worst) (−2.1; 95% CI −4.5 to −0.2; p=0.08) or the RPSQ (0=best to 64=worst) (−0.5; 95% CI −1.8 to −0.7; p=0.41). This high-quality study used the Balance Error Scoring System (BESS) (0=best to 60=worst) and found the mean difference of −3.7 (95% CI −7.8 to −0.5, p=0.09) between those receiving group-based vestibular rehabilitation to no treatment.

No identified trials investigated the effect of oculomotor therapy alone.

Effect of individually tailored multimodal therapy on return to sport

Two[20 30] high-quality trials of participants with persistent symptoms were grouped for meta-analysis evaluating the effect of presentation-specific, individually tailored multimodal interventions on clearance to return to sport. The interventions included cervical, vestibular and/or oculomotor therapies. Reneker *et al*[20] reported that 18/22 (82%) in the intervention group and 11/19 (58%) had medical clearance to return to sport after a 35-day intervention programme that was commenced 10 days post injury. Those in the intervention group recovered from their symptoms 1.99 (95% CI 0.95 to 4.15) times faster and were medically cleared for return to sport 2.91 (95% CI 1.01 to 8.43) times faster than the control group that received a range of subtherapeutic treatments. Schneider *et al*[30] found that those in the intervention group were 3.91 (95% CI 1.34 to 11.34) times more likely to be medically cleared for return to sport in 8 weeks than those in the control group (figure 4). Meta-analysis of these two studies found the risk ratio for return to sport by 8 weeks was 3.29 (95% CI 0.30 to 35.69, I^2=83%) (figure 4).

Effect of individually tailored multimodal therapy on symptom scores

Three studies of concussed individuals with persistent symptoms measured the effect of individually tailored multimodal interventions that included cervical, vestibular and/or oculomotor therapies on symptom scores.[16 20 30] Symptom outcome measures included the PCSS, DHI and VAS for neck pain, headache and dizziness. Two of these trials could be used for meta-analysis[16 20] showing a significant moderate effect (SMD=0.63, 95% CI 0.11 to 1.15, p=0.02, I^2=0%) (figure 5). The study by Schneider *et*

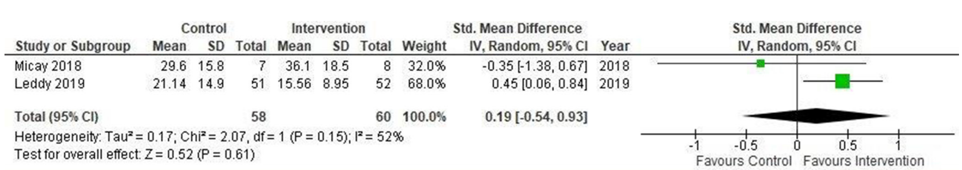

Figure 2 Effect of exercise vs control on days to symptom recovery/return to activity.

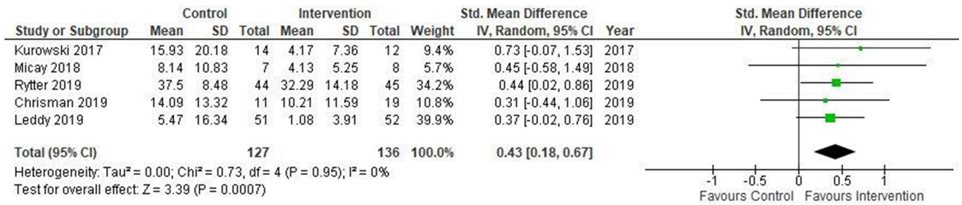

Figure 3 Effect of exercise vs control on symptom scores.

al[30] showed participants receiving the active intervention who were cleared to return to sport in 8 weeks (n=11) had a reduction in symptoms (out of 22) of −12 (−22, 0), while those not cleared to return to sport (n=4) had a change of −5.5 (−11,–2). Those individuals receiving the control intervention who were cleared to return to sport (n=1) had a change score of −15, while those not cleared (n=13) had a change score of −8.5 (−22, 3).

Two RCTs[16 30] assessed balance using the BESS and the Activities-specific Balance Confidence Scale. Schneider *et al*[30] compared multimodal interventions to sham treatments and found greater improvements in balance in the intervention group. However, as the data were presented with subgrouping, it could not be incorporated into meta-analysis. Chan *et al*[16] reported improvements in balance in both intervention and control groups. Statistical between-group analysis was not performed, and they used the data for exploratory and descriptive purposes only.

Schneider *et al*'s study[30] was the only identified study to assess gait. Using the Functional Gait Assessment, no difference in gait occurred between groups.

None of the identified trials assessed exercise capacity.

DISCUSSION

Physical interventions such as subthreshold aerobic exercise or individually tailored multimodal interventions that target deficits reduce symptoms in concussed individuals with acute and persistent symptoms. The multimodal approach leads to a faster return to sport for those with persistent symptoms. This systematic review identified 12 trials with 647 participants providing large amounts of data to guide practitioners in managing concussion in a meaningful and clinically relevant way. Seven[16 19–23 30] of the studies were of good to excellent quality, with only one[24] study being of poor quality.

Effect of subthreshold aerobic exercise

Subthreshold exercise is exercise at 80%–90% of the heart rate, where symptoms were exacerbated. Subthreshold aerobic exercise had a small to moderate effect (SMD=0.43) in reducing symptoms after a concussion; however, this estimate comes with some uncertainty. The 95% CI shows this could vary from a small effect (0.18) to a large effect (0.67). The findings show a small to moderate effect for those with both acute and persistent concussion presentations. This analysis does establish that, at worst, subthreshold aerobic exercise has only a small effect in reducing symptoms, but importantly it shows that subthreshold aerobic exercise does not make symptoms worse in both acute and persistent concussion, which to date has been somewhat unknown.

This review found no evidence of a difference in days to symptom recovery between those receiving exercise and the comparison group. Although Leddy *et al's*[18](n=103)larger trial found exercise reduced days to recovery, the smaller study by Micay *et al*[19] (n=15) found the control group (following the Berlin guidelines of graded return to sport) were cleared a few days earlier. This result was supported by Maerlender *et al*[24] (n=28) who also found those completing daily activities recovered 2 days quicker than those exercising. The intensity of exercise for the intervention group in the trial by Micay *et al*[19] (50%–70% age predicted HR max) and Maerlender *et al*[24] (mild to moderate exertion) may not have been sufficiently high as Leddy *et al*[18] used 80% of HR which was progressively increased. Also, the comparator used in the Micay *et al*'s[19] study (progressive return to activity) may have had a positive effect. Since the larger study by Leddy *et al*[18] had a positive effect, more larger studies are needed to investigate this further.

A previous systematic review with meta-analysis by Lal *et al*[7] found exercise significantly decreased PCSS (mean difference=−13.06; 95% CI −16.57 to −9.55) and symptoms as well as days off work (17.7 days vs 32.2 days), compared with control.

Effect of individually tailored multimodal intervention

Although there was limited evidence for stand-alone cervical[28] or vestibular therapy,[22] when it was incorporated into multimodal collaborative care, including cervical, oculomotor and vestibular rehabilitation that is tailored to the patient's presentation, there is evidence of a positive outcome. This multimodal treatment approach was individually prescribed for each participant based on objective findings and symptoms from assessment of the cervical spine, balance and the oculomotor and vestibular systems. All included studies of individually tailored multimodal interventions had participants with persistent symptoms.

We provide evidence from two trials[20 30] that individually tailored multimodal interventions incorporating cervical, vestibular and/or oculomotor therapies offer individuals a greater chance of earlier return to activity. The study by Reneker *et al*[20] (n=41) showed that the intervention group recovered twice as fast from their symptoms and were cleared to return to sport

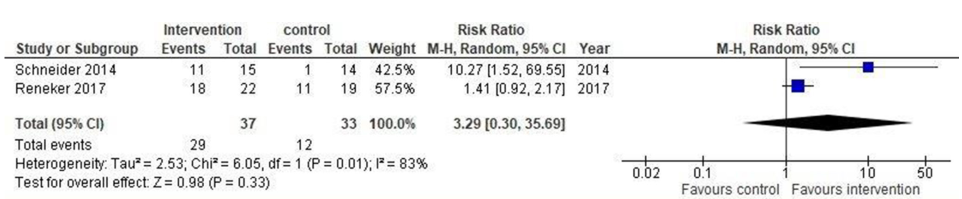

Figure 4 Effect of individually tailored, presentation-specific multimodal management vs control on days to symptom recovery/return to activity.

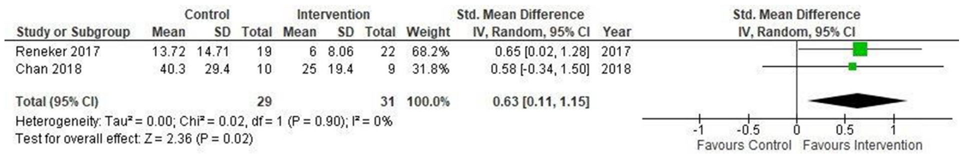

Figure 5 Effect of individually tailored, presentation-specific multimodal management vs control on symptom scores.

three times faster than the controls, but this also ranged from no different to eight times faster. This study is backed up by the very promising RCT by Schneider *et al*[30] where individuals who received the multimodal intervention were four times more likely to be cleared to return to sport in 8 weeks compared with the control group. The weakest estimate was 34% more likely to return to sport while the greatest effect was very worthwhile, being 11 times more likely. Combining this in our meta-analysis found concussed players to be three times more likely to have returned to sport by 8 weeks with this intervention. However, due to the high heterogeneity across the two studies (I^2=83%) in their definitions of recovery, the meta-analysis results are not significant.

In summary, our review adds to the existing body of evidence and is in agreement with the findings of the systematic review by Schneider *et al*,[14] which supports multifaceted collaborative care, including light subthreshold aerobic exercise, cervical and vestibular rehabilitation.

Strengths and limitations

Since the previous systematic reviews, there are six new RCTs of fair to excellent quality adding support to the evidence for physical interventions improving outcomes following concussion. Four of these add evidence for the benefits of subthreshold aerobic exercise[17–19 21 23] and two[5 15 20 28 29] for individually tailored multimodal care. By performing a meta-analysis, we were able to combine primary studies, which increased the sample size, and in turn, the power to study the effect of these interventions by combining similar primary studies and providing a precise estimate of the effects. The low I^2 values and the absence of heterogeneity for some of the analysis give credibility to our data.

The interventions that were found to be effective could easily be incorporated into clinical practice. Subthreshold aerobic exercise is feasible and affordable for participants. The multimodal approach may require some training of therapists to assess and identify cervical, vestibular and oculomotor deficits.

A limitation of the review was the small number of studies for certain interventions and the inclusion of trials with small sample sizes. With small sample sizes, resulting sampling error may lead to bias in pooled estimates of SMD and risk ratio.[31] There is a possibility that data may be skewed and thus results should be interpreted with caution. There is a need for larger sample sizes of future studies to remove potential issues resulting from this. A limitation of individual studies was that some risk ratio and interval estimates in some studies such as Schneider *et al*[30] suggest the possibility of sparse data bias and further highlights the need for studies with larger sample sizes to be undertaken.[32] If change scores were available rather than post scores, it would have provided more compelling evidence of the effect of the interventions. A limitation of this study is that no assessment of heterogeneity or publication bias was performed due to small number of studies. However, we performed a thorough search of different databases and a hand search of articles to find any studies we may have missed.

Further research is needed to evaluate these physical therapies and determine the optimal duration and timing of treatment, as well as combinations of therapies that are most effective. Future high-quality trials need to be large to reduce sampling bias and should ensure similar baseline characteristics, such as time, since onset. This may also allow for further subgroup analyses to be conducted between acute versus persistent presentations, as well as sex and age as factors influencing the outcomes of the interventions.

CONCLUSION

This clinically relevant research provides level one evidence, which could direct the optimal management of individuals following concussion. Subthreshold aerobic exercise shows a moderate effect in lowering symptom scores, however, that estimate comes with some uncertainty. Importantly, subthreshold aerobic exercise (at 80%–90% of the heart rate, where symptoms were exacerbated) does not make symptoms worse in those presenting both acutely and with persistent symptoms. Individually tailored multimodal intervention has a worthwhile effect in providing a faster return to sport and decreasing symptoms in those with persistent symptoms.

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Contributors All authors contributed to the development of the search strategy, writing and critical review of the manuscript. JF and SM undertook the process of inclusion/exclusion and independently assessed methodological quality. JF extracted all data from the included studies, SM and SAR confirmed the accuracy of this.

What is already known

- Rest for 24–48 hours followed by a graded return to activity is currently recommended.
- There is some evidence supporting physical interventions in the management of concussion, including subthreshold aerobic exercise and multimodal care involving light exercise, cervical therapy, vestibular and/or oculomotor rehabilitation.

What are the new findings

- Subthreshold aerobic exercise has a small to moderate effect on lowering symptom scores in acutely concussed individuals and those with persistent symptoms.
- Subthreshold aerobic exercise (at 80%–90% of the heart rate where symptoms were exacerbated) does not increase symptom scores when used to treat people with acute or persistent concussion.
- Concussed individuals with persistent symptoms (>2 weeks) who receive individually tailored multimodal interventions (cervical, vestibular and oculomotor) have a reduction in symptoms and are 3 times more likely to have returned to sport by 8 weeks.

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On line supplementary material

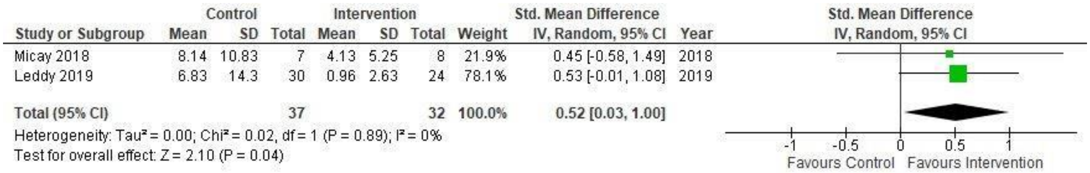
Search Strategy

Appendix 1. Databases and search terms

Database	Search terms
MEDLINE	The following 2 searches were combined with AND: • (MeSH terms: brain concussion OR postconcussion syndrome) OR (Key terms in title OR abstract: concuss* or "mild traumatic brain injury" or mTBI or post#concuss*) • (MeSH terms: Physical Therapy Modalities OR Rehabilitation OR Exercise OR Exercise Therapy OR Musculoskeletal Manipulations) OR (key terms in title OR abstract: physiotherap* OR ((therap* or rehab* or intervention) and (cervical or manual or vestibul* or oculomotor or exercise)))
CINAHL	The following 2 searches were combined with AND: • (MeSH terms: brain concussion OR postconcussion syndrome) OR (Key terms in title OR abstract: concuss* or "mild traumatic brain injury" or mTBI or post#concuss*) • (MeSH terms: Physical Therapy OR Physical Therapy Practice, Research-Based OR Research, Physical Therapy OR Physical Therapy Practice, Evidence-Based OR Physical Therapy Practice OR Rehabilitation OR Early Intervention OR Intervention Trials OR Experimental Studies OR Exercise OR Therapeutic Exercise OR Manual Therapy) OR (key terms in title OR abstract: physiotherap* OR ((therap* or rehab* or intervention) and (cervical or manual or vestibul* or oculomotor or exercise)))
SPORTDiscus	The following 2 searches were combined with AND: • (MeSH terms: brain concussion OR postconcussion syndrome) OR (Key terms in title OR abstract: concuss* or "mild traumatic brain injury" or mTBI or post#concuss*) • (MeSH terms: Physical Therapy OR Physical Therapy Practice, Research-Based OR Research, Physical Therapy OR Physical Therapy Practice, Evidence-Based OR Physical Therapy Practice OR Rehabilitation OR Early Intervention OR Intervention Trials OR Experimental Studies OR Exercise OR Therapeutic Exercise OR Manual Therapy) OR (key terms in title OR abstract: physiotherap* OR ((therap* or rehab* or intervention) and (cervical or manual or vestibul* or oculomotor or exercise)))
PEDro	concussion
Cochrane Library	The following 2 searches were combined with AND: • (MeSH terms: brain concussion OR postconcussion syndrome) OR (Key terms in title OR abstract: concuss* or "mild traumatic brain injury" or mTBI or post#concuss*) • (MeSH terms: Physical Therapy OR Physical Therapy Practice, Research-Based OR Research, Physical Therapy OR Physical Therapy Practice, Evidence-Based OR Physical Therapy Practice OR Rehabilitation OR Early Intervention OR Intervention Trials OR

	Experimental Studies OR Exercise OR Therapeutic Exercise OR Manual Therapy) OR (key terms in title OR abstract: physiotherap* OR ((therap* or rehab* or intervention) and (cervical or manual or vestibul* or oculomotor or exercise)))
EMBASE	The following 2 searches were combined with AND: • (Map terms: concussion OR brain concussion OR postconcussion syndrome) OR (Key terms in title OR abstract: concuss* or "mild traumatic brain injury" or mTBI or post#concuss*) • (Map terms: physiotherapy OR physiotherapy practice OR rehabilitation OR early intervention OR intervention study OR exercise OR aerobic exercise OR manipulative medicine) OR (key terms in title OR abstract: physiotherap* OR ((therap* or rehab* or intervention) and (cervical or manual or vestibul* or oculomotor or exercise)))
Scopus	The following 2 searches were combined with AND: • Title-abstract-keyword: concuss* or "mild traumatic brain injury" or mTBI or post#concuss* • Title-abstract-keyword: physiotherap* OR ((therap* or rehab* or intervention) and (cervical or manual or vestibul* or oculomotor or exercise))

Supplementary Figure 6. Effect of exercise vs. control on symptom scores in acute presentations (≤ 2 weeks)



Supplementary Figure 7. Effect of exercise vs. control on symptom scores in persistent presentation (> 2 weeks)

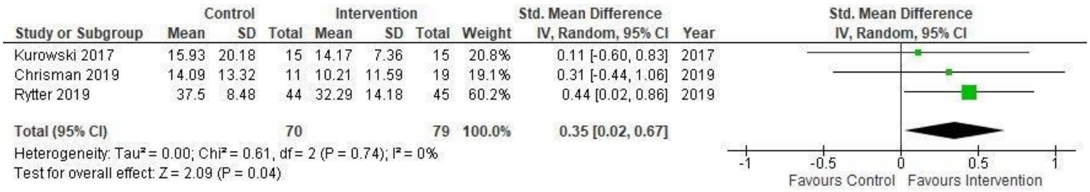


Table 1 Characteristics of included trials

Study	Participants	Intervention	Control	Relevant Outcome measures	Results
Exercise					
Chrisman et al.[17]	n = I = 19, C = 11 Sex: 12M:18F Age: (mean±SD) 15.5±1.6 Presentation: persistent	Sub-threshold aerobic exercise (exercise bike, treadmill, fast walking up an incline/stairs, or calisthenics): 5-10mins per day, increased weekly by 5-10mins per day, goal of 60min/day. Intensity: 80% of symptomatic HR. 6 weeks.	Stretching: 5-10mins daily. 6 weeks.	HBI	HBI: mean±SD I: pre = 31.21±14.10, post = 10.21±11.59 C: pre = 28±10.02, post = 14.09±13.32 Change in HBI baseline to 6 weeks: mean±SD: I:-21±15.8 C: 13.9±12.1
Kurowski et al. [23]	n = I = 12, C = 14 Sex: 13M:17F Age (mean±SD): I = 15.22±1.37, C = 15.50±1.80 Presentation: persistent	Subsymptom aerobic training: Cycling HEP for 6 weeks. 5-6 days/week. 80% of duration that exacerbated symptoms Progressed according to weekly visits.	Full body stretching HEP for 6 weeks. 5-6 days/week. Upper + lower extremities + trunk Program rotated every 2 weeks. Reviewed at weekly visits.	PCSI (self and parent assessment)	Self-PCSI: mean±SD I: pre= 37.40±25.01, post= 4.17±7.36 C: pre= 40.27±27.25, post= 15.93±20.18 Parent-PCSI: mean±SD I: pre= 38.93±15.13, post= 9.50±19.11 C: pre= 46.93±25.22, post= 10.79±13.33
Leddy et al.[20]	n = I = 52, C = 51 Sex: 55M:48F Age (mean±SD): I = 15.3±1.6, C = 15.4±1.7 Presentation: acute	Aerobic exercise: -stationary bike or treadmill (or jog/walk) -20 minutes daily -80% of HR that exacerbates symptoms on BCTT -progressed each week based on BCTT retest -30 days	Full body stretching: -20 minutes daily -progressed each week based on BCTT retest	Days to recovery since date of injury. PCSS	Days to recovery: mean±SD I: 15.56±8.95 C: 21.14±14.90 PCSS: mean±SD I: pre = 30.79±16.46, post = 1.08±3.91, change = 29.71±15.04 C: pre = 33.33±19.74, post = 5.47±16.34, change = 27.86±17.93
Maerlender et al. [21]	n = I = 13, C = 15 Sex: 8M:20F Age: NR Presentation: acute	Exertion protocol: -Schwinn Airdyne stationary bicycle with mild to moderate (0-6 RPE) exertion -20 minutes daily	Standard protocol: -instructed not to engage in systematic exertion beyond normal activities required for school (walking to class, studying, etc.)	Days to symptom recovery	Days to symptom recovery: median (range) I: 15 (5-61) C: 13 (6-56)

Micay et al.[29]	n = I = 8, C = 7 Sex: 15M Age (mean±SD): I = 15.8±1.2, C = 15.6±1.0 Presentation: acute	Aerobic exercise: -8 sessions: exercise on 2 consecutive days followed by 1 rest day for a total of 11 days -Stationary cycle ergometer -1st session: 10 mins at 50% age-predicted HR max -2nd session: 20 mins at 50% age-predicted HR max -then progressed by 5% increases of age-predicted HR max up to 70% and then maintained -5min warm-up and cool-down	Standard concussion management protocol as per Berlin 2016 guidelines.	Days to medical clearance. PCSS	Days to medical clearance: mean±SD I: 36.1±18.5 C: 29.6±15.8 Change in PCSS: Mean±SD I: 18.8±4.9 C: 10.0±6.1 Baseline: Mean ± SD I: 32.0 ±13.0 C: 24.4 ±18.7 Post scores are: I: 4.13 ± 5.25 C: 8.14 ± 10.83
Relander et al.[28]	N = I = 82, C = 96 Sex: NR Age: 23% < 21, 57% 21-50, 11% 51-65, 9% >65 Presentation: acute	Active management: -encouraged to mobilise as early as possible -physiotherapy: physical training 2/week until end of treatment → d/c from hospital -encouraged to attend follow-up clinics with same doctor after treatment completion	Routine treatment: -allowed to mobilise but not encouraged -provided with information about their injury when they asked for it. -no arrangement to see same doctor at follow-up clinics	Days in hospital. Days off work (return to activity).	Days in hospital: mean I: 6.6 C: 7.6 Days off work: mean I: 17.7 C: 32.2
Rytter et al.[23]	n = I = 45, c = 44 Sex: 30M:59F Age: I: -18-29: 12 -30-43: 21 -44+: 12 C: -18-29: 12 -30-43: 24 -44+: 8 Presentation: persistent	**S-REHAB** Module 1: 12 weeks - 12–14 individual sessions (1–2 hr/week) with a neuropsychologist -24 hr group therapy (2hr/week) combining psychoeducation, small exercises and conversations -33 hr (2–3 hr/week) of individual exercise training and coaching by a physiotherapist. Followed by Module 2: 10 weeks -10 individual consultation sessions (1 hr/week) with a neuropsychologist -16 hr of group work (1.5 h/week) combining group exercises and conversations	Standard Care: -May have received no or very limited treatment	RPSQ	RPSQ: mean±SD I: post = 32.29±14.18 C: post = 37.50±8.48 Change in RPSQ at 6 months (mean ±SD): I: 29.69 ± 12.92 C: 35.30 ± 7.57

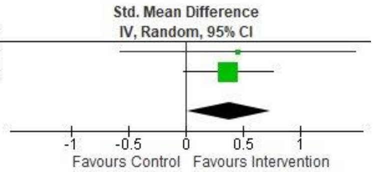
		-10.5 hr (1 hr/week) of individual exercise training with a physiotherapist -1 meeting with a case manager -2 meetings with existing or potential employer			
Cervical therapy					
Jensen et al. [27]	n = I = 10, C = 9 Sex: 7M:12F Age (mean, range): I = 32.3 (19-48), C = 30.8 (21-45) Presentation: persistent	Manual therapy: Specific mobilisation +/- muscle energy technique on 2-3 cervical spine segments. 15-20 min. Once per week for 2 weeks.	Cold pack: -14°C placed under the neck and shoulders. -15-20 minutes -Once per week for 2 weeks.	Pain index	Pain index: mean±SD I: pre19.07 (0.5-35.8), post (6 wks) 15.9 ±16.7, Change: -3.2 ±14.5 C: pre 27.8 (9.7-68.8), post 29.7 ±23.1 change:1.9±13.2
Vestibular therapy					
Kleffelgaard et al.[18]	n = I = 33, C = 32 Sex: 19M:45F Age (mean±SD): I = 37.6±12.3, C = 41.2±13.6 Presentation: persistent	Seen by physiatrist. Advice to return to normal activities and work Plus Group-based vestibular rehabilitation: -2/week for 8 weeks - Brandt-Daroff, habituation, adaptation/gaze stability,substitution,, and balance. -HEP including 2-5 individualised vestibular exercises and general physical activity.	Seen by physiatrist and multidisciplinary outpatient rehabilitation giving advice to return to normal activities and work.	DHI VSSv RPSQ BESS	DHI: mean±SD (95% CI) I: pre=47.9±16.6, post= 32.9±21.3 C: pre= 41.4±19.2, post= 36.4±22.7 Mean difference between groups: −8.7 (−16.6, −0.9) VSSv: mean±SD (95% CI) I: pre= 10.9±6.0, post= 6.7±6.0 C: pre= 10.2±6.6, post= 8.4±6.6 Mean difference between groups: −2.1 (−4.5, −0.2) RPQ3: mean±SD (95% CI) I: pre= 6.6±2.8, post= 4.9±3.3 C: pre= 5.5±2.4, post, 4.7±2.7 Mean difference between groups: −0.5 (−1.8, −0.7) BESS: mean±SD (95% CI) I: pre= 29.7±11.6, post= 19.1±10.6 n = 31 C: pre= 29.0±9.6, post= 23±9.1 *n* = 26 Mean difference between groups: −3.7 (−7.8, −0.5)
Individually tailored multimodal management					
Chan et al.[16]	n = I = 9, C = 10 Sex: 15M:14F Age (mean±SD): 15.5±1.47	Active rehab: submaximal AE; coordination & sport specific exc.; visualisation of sport; a home exercise program. Cervical manual	Treatment as usual: graded return to sport and school, physiatrist consultation	PCSS BESS	PCSS: mean±SD I: pre= 51.5±27.8, post= 25.0±19.4, change= -24.7±19.1 C: pre= 56.9±31.0, post= 40.3±29.4, change= -15.8±12.5

	Presentation: persistent	therapy vestibular rehab as needed plus 'treatment as usual' (graded return to sport and school, Education, school consultation, physiatrist consultation 6 weeks.			BESS: mean±SD I: pre= 16.0±8.1, post= 10.3±3.2 C: pre= 16.3±15.7, post= 11.4±7.4
Reneker et al.[22]	n = I = 22, C = 19 Sex: 25M:16F Age (mean±SD): I = 16.5±2.9, C = 15.9±2.9 Presentation: persistent	Progressive treatment: Eight 30-60mins sessions, 2/week. Multimodal tailored interventions depending on symptom presentation: -manual therapy (soft tissue release, mobilisations and/or thrust manipulations. -vestibular rehabilitation (habituation, adaptation, gaze stabilisation). -oculomotor training (smooth pursuit tracking, convergence, saccades). -balance exercises. Dosage and progression determined by treating physical therapist to be maximally therapeutic (i.e. challenging) within symptom-limited parameters. Also received Individualised HEP + exercise education.	Sham, subtherapeutic and non-progressed interventions.: Eight 30-60mins, 2/week. Received any of the following: -Ultrasound. -vestibulo-ocular reflex (VOR) cancellation. -Laser eye follow. -Reading Snellen eye chart. -Grade I central/unilateral PA mobilisations. -Cx ROM isometric exercises. -TENS. -predetermined progression plan. Also received standardised HEP: Cx isometric, gentle Cx ROM and VOR cancellation exercises.	Days to symptom recovery. Days to medical clearance for RTS. PCSS	Medical clearance for RTS: I: 18/22 (82%) C: 11/19 (58%) Days to symptom recovery: median I: 13.5 C: 17 Adjusted HR (95% CI): 1.99 (0.95, 4.15) Days to medical clearance for RTS: median I: 15.5 C: 26 Adjusted HR (95% CI): 2.91 (1.01, 8.43) PCSS: mean±SD I: pre = 36.9±13.4, post = 6±8.06 C: pre = 39.2±13.5, post = 13.72±14.71
Schneider et al.[30]	n = I = 15, C = 16 Sex: 18M:13F Age (median, range): I = 15 (12–27), C = 15 (13–30) Presentation: persistent	Intervention group: -1/week for 8 weeks or until medical clearance for RTS Multimodal tailored interventions depending on symptom presentation: Same as control group plus a combination of: -cervical/upper thoracic manual therapy -cervical neuromotor retraining -sensorimotor retraining -vestibular rehabilitation	Control group: -non-provocative ROM exercises -stretching -postural education -rest until symptom free followed by graded exertion	Medical clearance for RTS. Pain (0-10) ABC DHI	Medical clearance for RTS: I: 11/15 (73.3%) C: 1/14 (7.1%) Proportion medically cleared for RTS compared to control (95% CI): 66.2% (40, 92.3) Likelihood of medical clearance for RTS compared to control: Hazard ratio (95% CI) = 10.27 (1.51, 69.56) Likelihood of medical clearance for RTS compared to control with intention-to-treat analysis: Hazard ratio (95% CI) = 3.91 (1.34, 11.34)

Abbreviations: ABC (activities-specific balance confidence scale), BCTT (Buffalo Concussion Treadmill Test), BESS (balance error scoring system), C (control), Cx (cervical), DHI (dizziness handicap inventory), F (female), HBI (health behaviour inventory), HEP (home exercise program), HR (heart rate), hr (hour), I (intervention), IQR (interquartile range), M (male), NR (not reported),PCSI (post-concussion symptom inventory), PCSS (post-concussion symptoms scale), ROM (range of motion), RPE (rate of perceived exertion), RPQ3 (physiological subscale in the Rivermead post-concussion symptoms questionnaire), RTS (return to sport), S-Rehab (specialized, interdisciplinary rehabilitation), SD (standard deviation), VSSv (Vertigo Symptom Scale–Short Form, vertigo balance symptoms). Presentation acute ≤ 2 weeks; persistent >2 weeks

	Control			Intervention				Std. Mean Difference	
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**	**Year**
Micay 2018	8.14	10.83	7	4.13	5.25	8	12.5%	0.45 [-0.58, 1.49]	2018
Leddy 2019	5.47	16.34	51	1.08	3.91	52	87.5%	0.37 [-0.02, 0.76]	2019
Total (95% CI)			**58**			**60**	**100.0%**	**0.38 [0.01, 0.74]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0%
Test for overall effect: Z = 2.04 (P = 0.04)



	Control			Interventiion				Std. Mean Difference	
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**	**Year**
Kurowski 2017	15.93	20.18	14	4.17	7.36	12	17.3%	0.73 [-0.07, 1.53]	2017
Chrisman 2019	14.09	13.32	11	10.21	11.59	19	19.9%	0.31 [-0.44, 1.06]	2019
Rytter 2019	37.5	8.48	44	32.29	14.18	45	62.8%	0.44 [0.02, 0.86]	2019
Total (95% CI)			**69**			**76**	**100.0%**	**0.46 [0.13, 0.80]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.59, df = 2 (P = 0.74); I² = 0%
Test for overall effect: Z = 2.73 (P = 0.006)