Mechanisms through which exercise reduces symptom severity and/or functional impairment in posttraumatic stress disorder (PTSD)

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Results

Flow of Study Selection and Descriptives

We identified 11870 records. See Figure 1 for the PRISMA flow diagram. A total of 11 studies with data from 771 participants were eligible for inclusion.The additional texts included secondary analyses, abstracts, trial registries, and protocol papers.

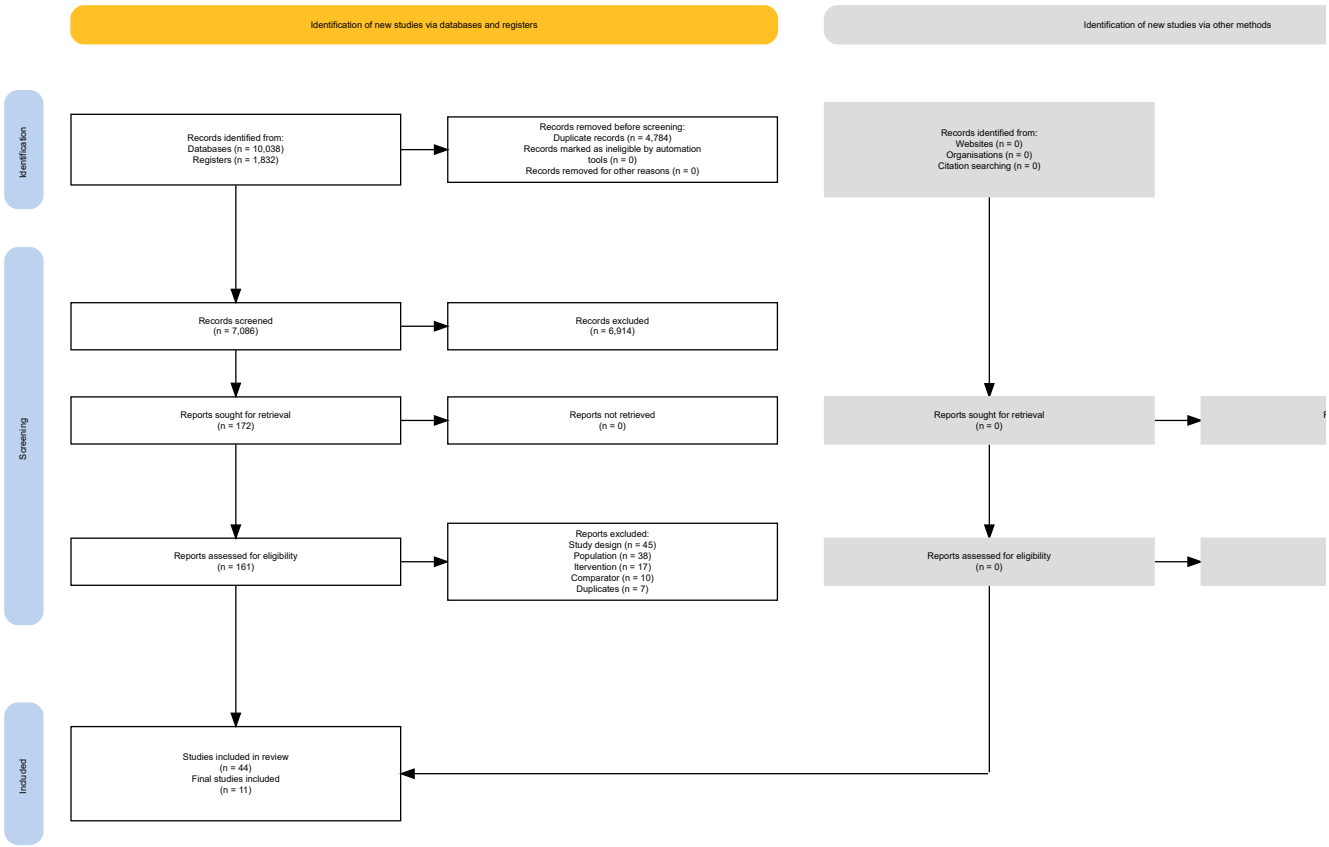

Figure 1: PRISMA flow diagram

10 of the studies were RCTs, and 1 was a crossover RCT (Greene & Petruzzello, 2022). 8 of the 11 studies were included in the meta-analyses (Bryant et al., 2023; Huseth, 2021; Nordbrandt et al., 2020; Rosenbaum et al., 2015; Voorendonk et al., 2023; Whitworth et al., 2019a; Whitworth et al., 2019b; Young-McCaughan et al., 2022). Meta-analysis was not feasible for 3 of the 11 studies (Crombie et al., 2021a; Greene & Petruzzello, 2022; Powers et al., 2015). Three of the studies provided follow-up PTSD outcome data which were insufficient for synthesis, which were synthesized descriptively without meta-analysis (Crombie et al., 2021a; Greene & Petruzzello, 2022; Powers et al., 2015). Three studies examined putative mediators which was not sufficient to carry out a meta-analysis (Crombie et al., 2021a; Powers et al., 2015; Whitworth et al., 2019a).

Study characteristics of the 8 studies included in the meta-analysis are summarized in Table 1. From these 8 studies, there were 9 eligible comparisons. One study presented findings from two independent comparisons, including a total of four distinct intervention groups (Young-McCaughan et al., 2022). One of the first authors published findings from two different but methodologically similar trials in the same year (Whitworth et al., 2019a; Whitworth et al., 2019b).

Study	Year	N	Intervention	Comparison	PTSD tool	Trial registered	Exercise type	Exercise intensity	Intervention length	FU1	FU2	Country
Bryant2023	2023	130	exercise + therapy	attention control + therapy	CAPS-IV	yes	aerobic	high	10 weeks	34 weeks	NA	Australia

Study	Year	N	Intervention	Comparison	PTSD tool	Trial registered	Exercise type	Exercise intensity	Intervention length	FU1	FU2	Country
Voorendonk2023	2023	120	exercise + therapy	attention control + therapy	PCL-5	yes	mixed	moderate	12 weeks	26 weeks	NA	Netherland
Nordbrandt2020	2020	224	exercise + TAU	TAU	HTQ	yes	mixed	moderate	20 weeks	NA	NA	Denmark
Rosenbaum2014	2014	81	exercise + TAU	TAU	PCL-4	yes	mixed	high	12 weeks	NA	NA	Australia
Young-McCaughan2022b	2022	36	exercise + therapy	therapy only	PCL-5	no	aerobic	high	8 weeks	12 weeks	32 weeks	USA
Huseth2022	2022	21	exercise only	WLC	PCL-5	no	aerobic	moderate	8 weeks	NA	NA	USA
Young-McCaughan2022a	2022	36	exercise only	TAU	PCL-5	no	aerobic	high	8 weeks	12 weeks	32 weeks	USA
Whitworth2019a	2018	30	exercise only	attention control	PDS-5	no	anerobic	high	3 weeks	NA	NA	USA
Whitworth2019b	2019	22	exercise only	attention control	PDS-5	no	anerobic	high	3 weeks	NA	NA	USA

TAU = treatment as usual; WLC = waiting list control; CAPS-IV = Clinician-Administered PTSD Scale - 4th edition; PCL-4 = PTSD Checklist - version 4; PCL-5 = PTSD Checklist - version 5; PDS-5 = Posttraumatic Diagnostic Scale – version 5; HTQ = Harvard Trauma Questionnaire; Aerobic exercise = physical performance behaviour pattern that increases heart rate and respiration while using large muscle groups repetitively and rhythmically; anaerobic exercise = physical performance behaviour pattern that is performed in short intense bursts with limited oxygen intake; mixed exercise = combination of aerobic and anaerobic exercise; USA = United States of America.

Table 1: Study characteristics of the 8 studies included in the meta-analysis.

Study characteristics of the 3 studies not included in the meta-analysis are summarized in Table 2. From these 3 studies, there were 4 eligible comparisons. One study reported two comparisons (Greene & Petruzzello, 2022).

Study	Year	N	Intervention	Comparison	Trial registered	Exercise type	Exercise intensity	Intervention length	Country
Crombie2021	2021	38	exercise + extinction learning	attention control + extinction learning	yes	aerobic	moderate	3 days	USA
Greene2022a	2022	24	exercise only	attention control	no	anaerobic	high	130 min	USA
Greene2022b	2022	NA	exercise only	attention control	no	aerobic	moderate	130 min	USA
Powers2015	2015	9	exercise + therapy	therapy alone	yes	aerobic	moderate	12 weeks	USA

Aerobic exercise = physical performance behaviour pattern that increases heart rate and respiration while using large muscle groups repetitively and rhythmically; anaerobic exercise = physical performance behaviour pattern that is performed in short intense bursts with limited oxygen intake; USA = United States of America.

Table 2: Study characteristics of the 3 studies not included in the meta-analysis.

The specific intervention and comparison groups for the 11 eligible studies (0 comparisons) are presented in Table 3.

Study	Intervention	Comparison	Exercise type	Therapy	TAU	Attention control
Bryant2023	exercise + therapy	attention control + therapy	aerobic	exposure therapy	NA	static stretching
Voorendonk2023	exercise + therapy	attention control + therapy	mixed	PE + EMDR	NA	guided (creative) tasks
Nordbrandt2020	exercise + TAU	TAU	mixed	NA	combination: medical doctor, 1 to 2 sessions with social worker / psychologist	NA
Rosenbaum2014	exercise + TAU	TAU	mixed	NA	combination: individual and group psychotherapy, pharmacotherapy	NA
Young-McCaughan2022b	exercise + therapy	therapy only	aerobic	imaginal exposure	NA	NA
Huseth2022	exercise only	WLC	aerobic	NA	NA	NA
Young-McCaughan2022a	exercise only	TAU	aerobic	NA	self-care intervention delivering educational and instructional information	NA
Whitworth2018	exercise only	attention control	anaerobic	NA	NA	videos on various educational topics (excluding exercise and mental health).

Study	Intervention	Comparison	Exercise type	Therapy	TAU	Attention control
Whitworth2019	exercise only	attention control	anaerobic	NA	NA	videos on various educational topics (excluding exercise and mental health).
Crombie2021	exercise + extinction learning	attention control + extinction learning	aerobic	extinction learning	NA	NA
Greene2022a	exercise only	attention control	mixed	NA	NA	remained sedentary in the lab
Greene2022b	exercise only	attention control	aerobic	NA	NA	remained sedentary in the lab
Powers2015	exercise + therapy	therapy alone	aerobic	prolonged exposure	NA	NA

Aerobic = physical performance behaviour pattern that increases heart rate and respiration while using large muscle groups repetitively and rhythmically; anaerobic = physical performance behaviour pattern that is performed in short intense bursts with limited oxygen intake; mixed = combination of aerobic and anaerobic exercise. TAU = treatment as usual; WLC = waiting list control.

Table 3: Specific interventions for all the included studies

Risk of bias assessment

###Risk of bias for the PTSD symptom severity outcome

The results of the risk of bias assessment per domain and study for the primary outcome, PTSD symptom severity is presented below in Figure 2 of the Extended Data. Nine studies reported PTSD outcome data post-intervention. Two studies did not report PTSD outcome data (Crombie et al., 2021a; Greene & Petruzzello, 2022). Five of the nine studies had an overall high risk of bias, three had some concerns, and only one was had low risk of bias. High risk of bias was mainly due to deviations from intended intervention (D2)(Voorendonk et al., 2023; Whitworth et al., 2019a; Whitworth et al., 2019b), missing outcome data (D3)(Rosenbaum et al., 2015; Voorendonk et al., 2023; Whitworth et al., 2019a; Whitworth et al., 2019b), and selection of reported results (D5)(Voorendonk et al., 2023; Young-McCaughan et al., 2022).

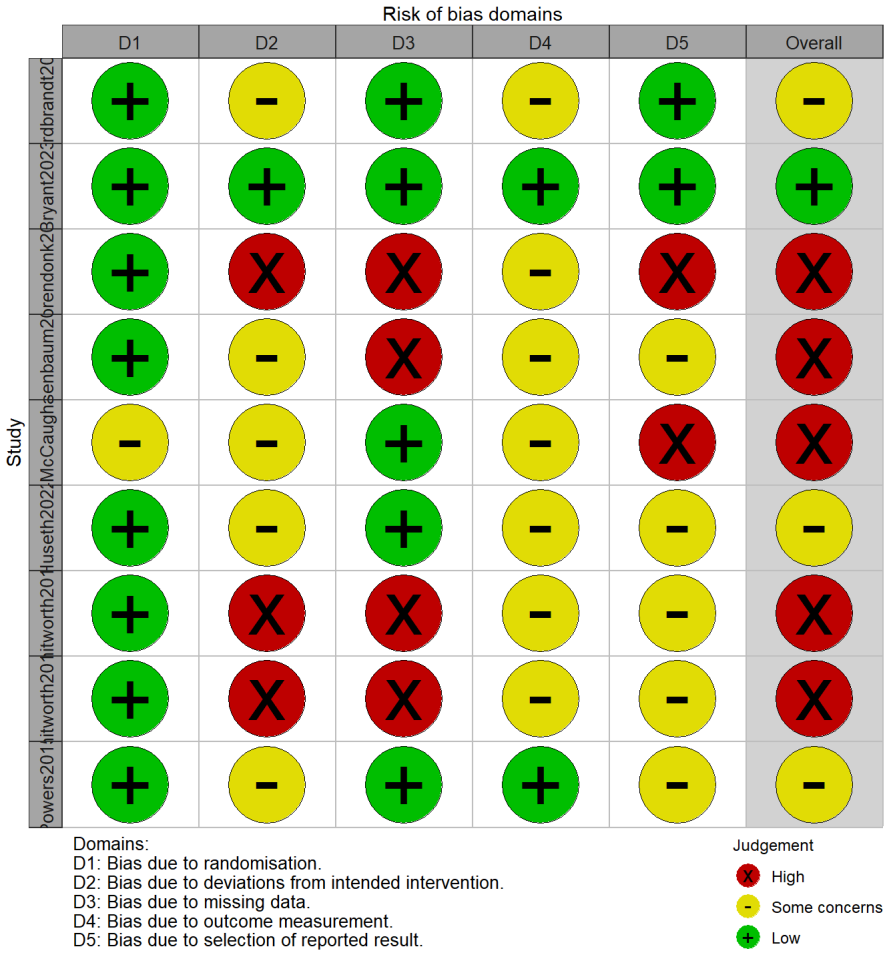

Figure 2 Results of the risk of bias assessment per domain and overall

###Risk of bias for the mediation studies *insert*

Research question I

Meta-analysis of PTSD Symptom Severity (Primary Outcome)

For the studies included in the meta-analyses, the earliest study was performed in 2014, while the most recent study was performed in 2023. The median sample size across the studies was 36 participants per study. The median of the mean participant age was 37 years (ranging from 29 to 50 years).

####Post-intervention (weeks) 8 studies provided data for PTSD symptom severity and contributed 9 effect measures to the PTSD symptom severity meta-analysis. The summary for PTSD symptom severity is shown in Figure 3.

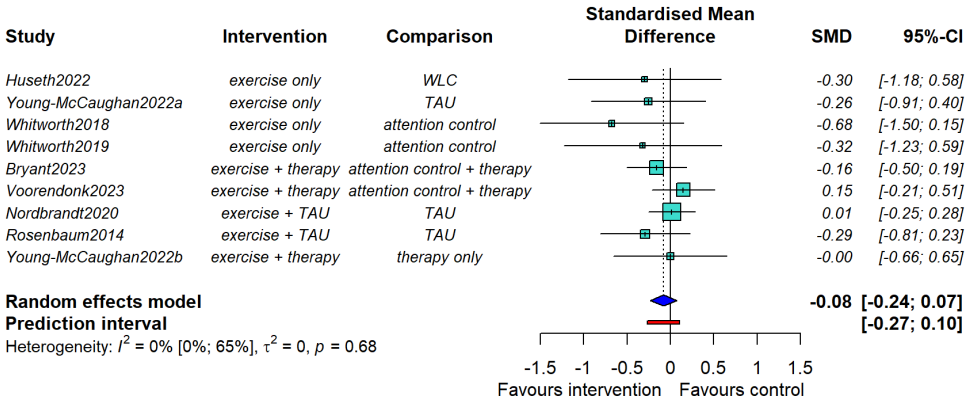

Figure 3: Meta-analysis of the effects of exercise on PTSD symptom severity.

The meta-analysis found no significant difference in PTSD symptom severity between exercise and comparison groups (SMD = -0.08 , 95% CI: -0.24 , 0.07). Low heterogeneity was found as suggested by the prediction interval which is only slightly wider than the confidence interval.

Subgroup Analyses and Meta-regressions

We explored whether heterogeneity could be potentially explained by differences in study-level characteristics using subgroup analyses and meta-regressions. The following characteristics were explored as sources of heterogeneity for the primary outcome, PTSD symptom severity:

- Exercise intensity (moderate intensity or high intensity)
- Specific exercise type (aerobic or anaerobic or mixed)
- Exercise augmented by treatment as usual (TAU)/therapy (exercise only or exercise + therapy/TAU)
- Intervention length (weeks)

Subgroup analysis by exercise intensity

There was no significant difference in PTSD symptom severity between studies with moderate intensity and those with high intensity exercise groups (see Figure 4). However, visual inspection of the forest plot suggests the effect is larger in the high intensity exercise subgroup.

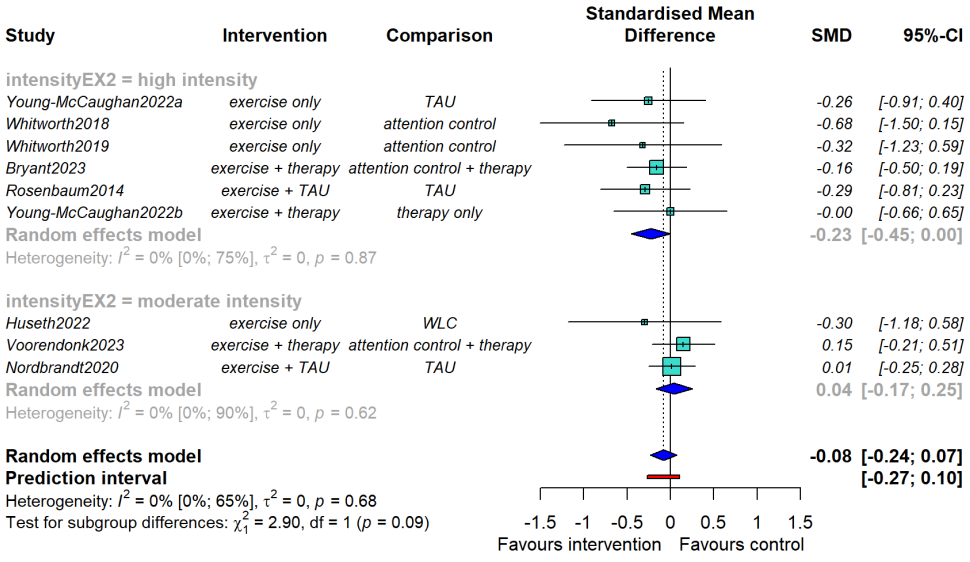

Figure 4: Sub-group analysis of the effects of exercise on PTSD symptom severity by exercise intensity

Subgroup analysis by specific exercise type

The were no significant difference in PTSD symptom severity between studies of aerobic exercise, anaerobic exercise, or mixed (see Figure 5).

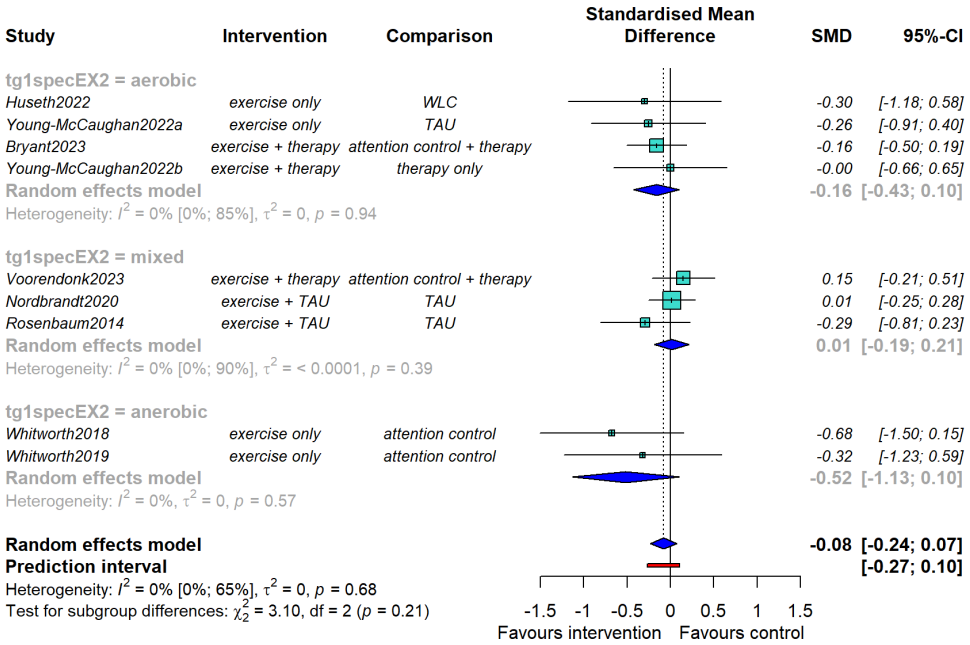

Figure 5: Sub-group analysis of the effects of exercise on PTSD symptom severity by specific exercise type

Subgroup analysis by exercise alone or tau/therapy augmented by exercise.

There was no significant difference in PTSD symptom severity outcome between studies of exercise alone and therapy/TAU augmented by exercise (see Figure 6). However, visual inspection of the forest plot suggests the effect is larger for exercise alone compared with an inactive comparison group than for the studies that augmented psychotherapy and TAU with exercise.

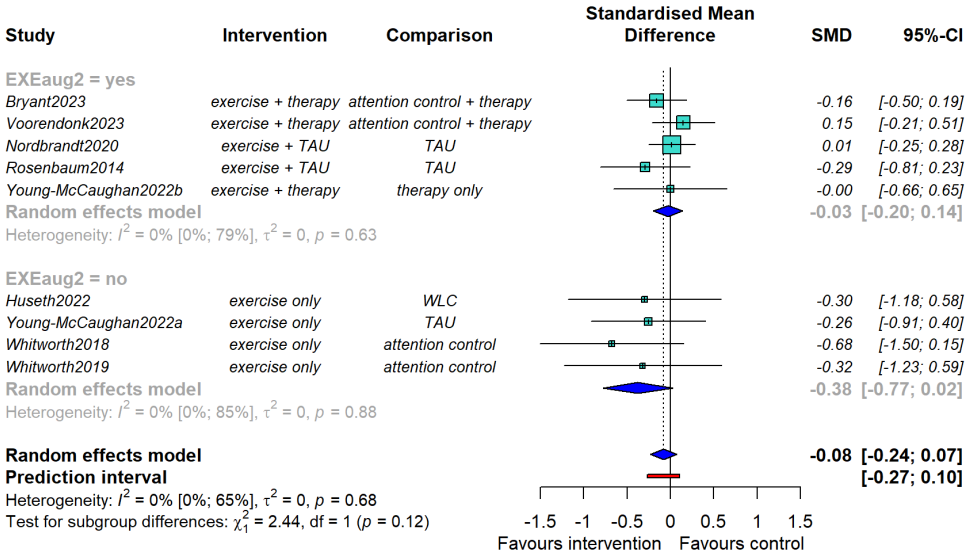

Figure 6: Sub-group analysis of the effects of exercise on PTSD symptom severity by exercise alone or TAU/therapy augmented by exercise

Meta-regression by intervention length

Overall, there is no strong evidence that the intervention length affected the treatment effect. The meta-regression analysis yielded a coefficient of 0.02 (95% CI: -0.01, 0.05).

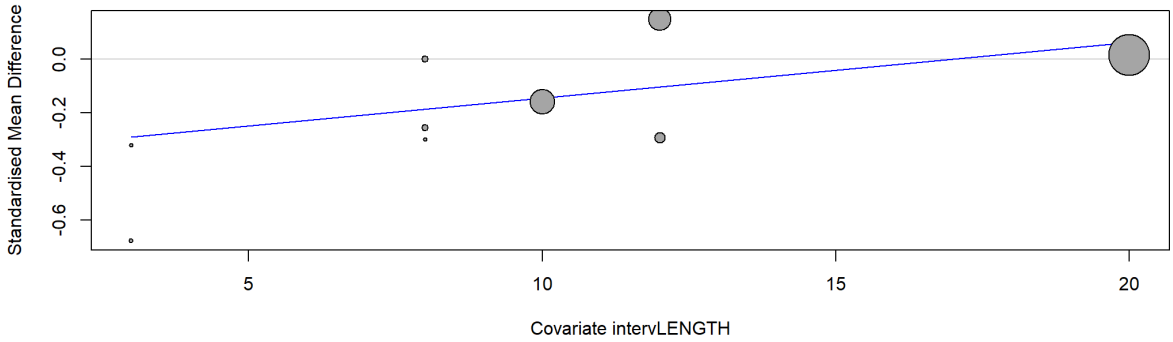

Figure 7: Meta-regression of the effects of exercise on PTSD symptom severity by intervention length

Meta-analysis of Treatment Dropout (secondary outcome)

8 studies provided data for treatment dropout, and contributed 9 effect measures to the treatment dropout meta-analysis. The forest plot for the risk of treatment dropout is shown in Figure 8.

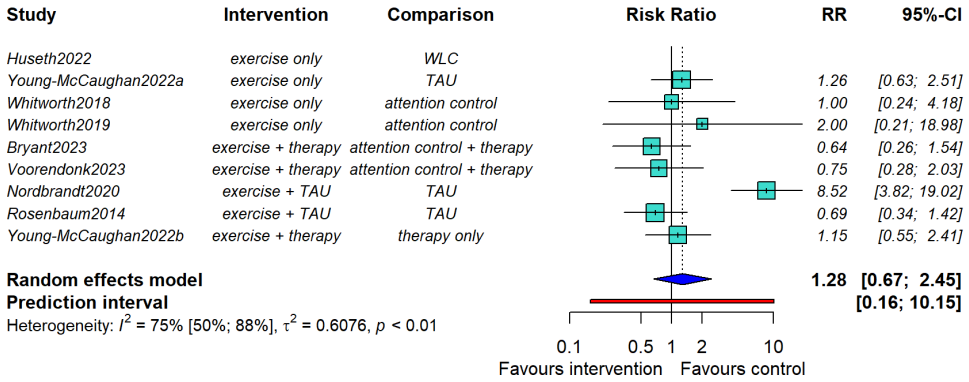

Figure 8: Meta-analysis of the dropout rates between the intervention and control groups

There is no evidence of a difference in treatment dropout between exercise and comparison groups (RR = 1.28 , 95% CI: 0.67 , 2.45) and there is large heterogeneity, as shown by the prediction interval (0.16 to 10.15).

Sensitivity Analyses

We examine the robustness of the findings for the primary outcome by excluding studies with high risk of bias. 3 studies included in the meta-analyses were rated as low or some concerns. When restricting the analysis to studies with moderate or low risk of bias, the effect of exercise on PTSD symptoms severity is SMD = -0.06 (95% CI: -0.27 , 0.14). For reference, the main effect size for the primary outcome is SMD = -0.08 (95% CI: -0.24 , 0.07), so the results do not change substantially.

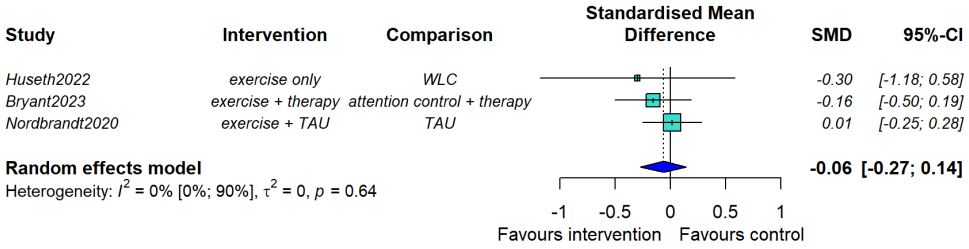

Figure 9: Meta-analysis of the effects of exercise on PTSD symptom severity when excluding studies with high risk of bias

Reporting bias

The forest plot below shows the meta-analysis results of the primary outcome ordered by the precision of the studies. It seems that smaller studies showed larger effects favouring the intervention.

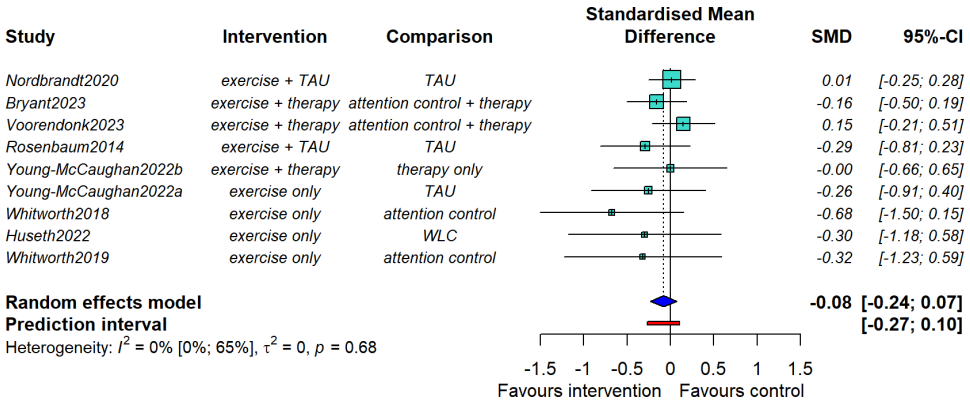

Figure 10: Forest plot of the meta-analysis results of the primary outcome ordered by the precision of the studies

Synthesis Without Meta-analysis

PTSD symptom severity

Meta-analysis could not be conducted for three studies addressing the primary outcome of PTSD symptom severity (Crombie et al., 2021a; Greene & Petruzzello, 2022; Powers et al., 2015). Two of the studies did not report outcome data for PTSD symptom severity post-intervention (Crombie et al., 2021a; Greene & Petruzzello, 2022). The third study did not provide sufficient data to include in the meta-analysis (Powers et al., 2015). Powers et al. (2015) examined the efficacy of adding moderate-intensity aerobic exercise before prolonged exposure (PE) in reducing PTSD symptoms. The participants who underwent PE plus exercise experienced a greater reduction in PTSD symptoms (d = 2.65, SE = 0.92). compared to the group that received PE only. This outcome was observed after the 12-week intervention.

PTSD symptom clusters

2 of the 11 studies examined the effects of exercise on PTSD symptom clusters, namely, avoidance, reexperiencing, hyperarousal, as well as negative cognitions and mood (Whitworth et al., 2019a; Whitworth et al., 2019b). One study reported significantly lower levels of avoidance symptoms (F(1, 20) = 8.50, p=.009, d=1.26, 95% CI [0.39, 2.14] and hyperarousal symptoms (F(1, 20) = 4.41, p = .049, d = 0.90, 95% CI [0.06, 1.74]) in the exercise group relative to the control group post-intervention (Whitworth et al., 2019a). While intrusion, F(1,20) = 2.48, p = .131, d = 0.67, 95% CI [−0.15, 1.49]; and mood and cognitive symptoms F(1, 20) = 0.65, p = .442, d = 0.34, 95% CI [−0.47, 1.14] did not differ significantly (Whitworth et al., 2019a). The other study found no significant between-group differences for intrusion (F(1, 17) < 0.01, p=0.98), avoidance (F(1, 17) = 0.63, p = 0.49), mood and cognitive symptoms (F(1, 17) = 0.02, p=0.91), and hyperarousal symptoms (F(1, 17) = 0.21, p = 0.67) between the exercise and comparison group (Whitworth et al., 2019b)

Functional impairment

Two of the examined the effects of exercise on functional impairment post-intervention indices (Nordbrandt et al., 2020; Voorendonk et al., 2023). One study reported small significant improvement over time for Quality of life evaluated (mean difference (SE) = 9.68 (2.79), p = .0005)(Topp et al., 2015), Global Assessment of Functioning for Symptom (mean difference (SE) = 4.37 (1.34), p = .0011)(Bastin et al., 2013), as well as level of functioning (mean difference (SE) =-2.54 (0.86), p = .0032)(Sheehan & Sheehan, 2008) for the exercise group (Nordbrandt et al., 2020). However, no significant difference over time was found for the Global Assessment of Functioning for Function (mean difference (SE) = 3.64 (1.31), p = .05990) (Bastin et al., 2013) in the exercise group (Nordbrandt et al., 2020). While most variables showed significant improvement in rating scores over time in both the exercise and comparison group, no significant between-group differences were found at the pre- or post-intervention assessments. The other study reported a large significant increase in quality of life (Priebe et al., 1999) in both the exercise and comparison groups, and also found no significant between group differences (Voorendonk et al., 2023).

Loss of PTSD diagnosis

Only one study reported data on loss of PTSD diagnosis post-intervention (Voorendonk et al., 2023). Loss of diagnosis was high in both the exercise and comparison groups. More specifically, 80.0% and 82.7% of the in the intervention and comparison groups respectively no longer met the diagnostic criteria for PTSD. The between-group difference was non-significant ($\chi 2[1] = 0.13$, p = 0.721).

Research question II

Three studies examined putative mediators, but the available data was insufficient to carry out a meta-analysis (Crombie et al., 2021a; Powers et al., 2015; Whitworth et al., 2019a).

###Synthesis Without Meta-analysis

In the first study, 35 participants were randomized to a 3-day protocol involving fear acquisition, extinction, and recall. They examined whether exercise-induced increases in circulating concentrations of candidate biomarkers mediated the effects of exercise on threat expectancy ratings during the extinction recall phase (Crombie et al., 2021a). Biomarkers included Brain-derived neurotrophic factor (BDNF), Anandamide (AEA), 2-arachidonoylglycerol (2-AG), and Homovanillic acid (HVA). Threat expectancy ratings evaluate an individual's anticipation levels toward encountering threatening situations. Individuals with PTSD often exhibit elevated ratings. Decreasing these anticipations may lead to a reduction in the severity of PTSD symptoms. For the total effect, the exercise group exhibited lower threat expectancy ratings following reinstatement than the comparison group (d = 0.75). Circulating concentrations of BDNF (95% CI for the indirect effect, path ab: -0.941, -0.005) and AEA (95% CI for the indirect effect, path ab: -0.623, -0.005) following exercise mediated the relationship between exercise and reduced threat expectancy ratings following reinstatement. 2-AG (95% CI for the indirect effect, path ab: -0.050, -0.210) and HVA (95% CI for the indirect effect, path ab: -0.190, -0.134) did not reach statistical significance. The second study examined BDNF levels as a potential mediator of the relationship between exercise and PTSD symptom severity (Powers et al., 2015). Post-intervention, the exercise group experienced a significant increase in circulating concentrations of BDNF (d = 1.08). in addition to greater reduction in PTSD symptoms compared to the comparison group. The third study examined whether changes in cognitive appraisal, perceived exertion, affect, arousal, and distress in a sample of 22 adults with PTSD predicted changes in PTSD symptoms (Whitworth et al., 2019a). They found changes in the perception of the resistance training sessions (cognitive appraisal; b = 7.1, SE = 2.9, p = .02) and perceived exertion (b = -3.1, SE = 1.2, p = .01) significantly mediated the relationship between exercise and PTSD symptom severity. Affect (b = 0.82, SE = 1.7, p = .63), arousal (b = 2.4, SE = 1.5, p = .12), and distress (b = 0.18, SE = .13, p = .17) did not reach statistical significance. This outcome was observed at the conclusion of the 3-week intervention.

Summary of the evidence on the primary outcome from the human studies

The primary outcome was efficacy in reducing overall PTSD symptom severity in patients with PTSD. The summary of the evidence on PTSD symptom severity outcome for PTSD is reported below.

|————|————|————|————|————|————| | **Source of evidence** | **Summary of the association** | **Bias due to study limitations** | **Bias due to reporting bias** | **Bias due to indirectedness** | **Bias due to other reasons** | | Exercise intervention vs comparison group | n = 9 , k = 700 , SMD = -0.08, 95%CI: -0.24, 0.07 | Overall, five studies were rated as high, three studies as some concerns, and one was rated as low risk of bias. High risk of bias due to to deviations from intended intervention, missing outcome data, and selection of reported results. | Two studies rated as high risk of bias | *what here* | Lack of blinding of participants and outcomes assessors. |