Table E.1.4.d.4: Effects of physical activity on fitness and functional capacity among people living with HIV

Questions: What is the association between physical activity, functional capacity and fitness? Is there a dose response association (volume, duration, frequency, intensity)? Does the association vary by type or domain of PA?
Population: People living with HIV
Exposure: Greater volume, duration, frequency, or intensity of physical activity
Comparison: No physical activity or lesser volume, duration, frequency, or intensity of physical activity
Outcome: Measures of fitness and functional capacity (VO_2max, Exercise time, strength)

Exercise modality	Study	No. of Studies No. of participants	AMSTAR 2 Score	GRADE CRITERIA					Summary of findings	CERTAINTY
				Risk of Bias	Inconsistency	Imprecision	Indirectness	Publication Bias		
Aerobic Exercise	O'Brien, 2016 *(67)*	24 RCTs, N=936	high	**VO_2max**					The mean age of participants in this study ranged from 30-49 years with 73 % males. Duration of exercise ranged from 6 – 52 weeks, 3 times a week for 20 – 120 min. Six meta-analyses were performed for $\dot{V}O_{2max}$, five of which were significant favouring exercise compared with non-exercise. Meta-analyses showed a significant improvement in $\dot{V}O_{2max}$ of 2.63 mL/kg/min for participants in the aerobic exercise intervention group compared with the non-exercising control group; significant improvement occurred in $\dot{V}O_{2max}$ of 2.40 ml/kg/min for participants in the constant aerobic exercise group compared with the non-exercising control group; significant improvement occurred in $\dot{V}O_{2max}$ of 3.71 ml/kg/min for participants in the combined aerobic and PRE group compared with the non-exercising control group; significant improvement occurred in $\dot{V}O_{2max}$ of 2.87 ml/kg/min for participants in the aerobic or combined aerobic and PRE group compared with non-exercising control group and a trend towards an improvement in $\dot{V}O_{2max}$ of 4.30 mL/kg/min for participants in the heavy-intensity exercise group compared with the moderate-intensity exercise group. No significant difference in $\dot{V}O_{2max}$ was found for participants in the combined aerobic exercise and diet or nutrition counselling group compared with the diet or nutrition	VERY LOW (+ve effect)
				No Serious risk of bias	No serious inconsistency	No serious imprecision	Serious indirectness	No serious publication bias		

									counselling group. All point estimates were greater than 2 mL/kg/min, which suggested a potentially clinically important improvement in $\dot{V}O_{2max}$ among exercisers, and a greater improvement with heavy- versus moderate-intensity exercise.	
				Maximum Heart Rate (HRmax)					Duration of exercise ranged from 12 – 16 weeks, 3 times a week for 45 – 135 min. Three meta-analyses showed a non-significant trend towards a decrease in HR_{max} of −9.81 beats/min, 7.33 beats/min and 4.91 beats/min for participants in the aerobic exercise intervention group compared with the non-exercising control group; aerobic or combined aerobic and PRE group compared with the non-exercising control; and combined aerobic and PRE compared with non-exercising control, respectively.	MODERATE (no effect)
				Serious risk of bias	No serious inconsistency	No serious imprecision	No serious indirectness	No serious publication bias		
				Exercise time					Duration of exercise ranged between 20-120-min three times per week for 12-52 weeks. Two meta-analyses showed significant increases in exercise time of 3.29 min for participants in the combined aerobic and PRE group compared with the non-exercising control group; and 2.66 min for participants in the aerobic or combined aerobic and PRE group compared with the non-exercising control group. Point estimates did not reach the 5 min threshold for clinical importance.	HIGH (+ve effect)
				Serious risk of bias	No serious inconsistency	No serious imprecision	No serious indirectness	No serious publication bias		
				Strength					Duration of exercise ranged between 20-120 min three times per week for 12-52 weeks	LOW (+ve effect)

				Serious risk of bias	No serious inconsistency	No serious imprecision	No serious indirectness	No serious publication bias	Meta-analyses showed significant improvements in upper and lower body strength as measured by increases in 1-repetition maximum for chest press, and knee flexion; and a non-significant improvement in 1-RM for leg press and knee extension for participants in the combined aerobic and PRE group versus the non-exercising control group. There were significantly greater increases in strength among participants in the PRE group compared with to the aerobic exercise only group for upper and lower body muscle groups. All six-point estimates for upper and lower extremity strength were greater than 2 kg and 5 kg, respectively, indicating a clinically important increase in strength for resistive exercise compared with aerobic exercise.	
	O'Brien, 2010 *(69)*	14 RCTs, N=454	high	**VO_2max**					The age of the participants ranged from 18-58 years and ~70% were males. Participants exercised 30-90 min three times per week for 12-24 weeks Three meta-analyses showed a significant improvement in $\dot{V}O_{2max}$ of 2.63 mL/kg/min for participants in the aerobic exercise intervention group compared with the non-exercising control group (95% CI: 1.19, 4.07, n=276, p=0.0003) (Perna, 1999; Smith, 2001; Stringer, 1998; Baigis, 2002; Mutimura, 2008a); significant improvement occurred in $\dot{V}O_{2max}$ of 2.40 ml/kg/min for participants in the constant aerobic exercise group compared with the non-exercising control group (95% CI: 0.82, 3.99, n=248, p=0.003) (Stringer, 1998; Smith, 2001; Baigis, 2002; Mutimura, 2008a); and a trend towards an improvement in $\dot{V}O_{2max}$ of 4.30 mL/kg/min for participants in the heavy-intensity exercise group compared with the moderate-intensity exercise group (95% CI: 0.61,7.98, n=24, p=0.02). All point estimates were greater than 2 mL/kg/min, which suggested a potentially clinically important improvement in $\dot{V}O_{2max}$ among exercisers, and a greater improvement with heavy- versus moderate-intensity exercise.	HIGH (+ve effect)
				Serious Risk of bias	No serious inconsistency	No serious imprecision	No serious indirectness	No serious publication bias		
				Maximum Heart Rate (HRmax)					Participants exercised 45 min three times per week for 12 weeks One meta-analysis showed a non-significant decrease in HR_{max} of -9.81 beats/min (95% CI: -26.28, 6.67, n=49, p=0.24) for participants in the aerobic exercise intervention group compared with the non-exercising control group (Lox, 1995; Perna, 1999).	HIGH (+ve effect)
				No serious risk of bias	No serious inconsistency	No serious imprecision	No serious indirectness	No serious publication bias		

				Exercise Time (minutes)					Participants exercised 60-120 min three times per week for 12-16 weeks. One meta-analysis showed a non-significant increase in exercise time of 3.92 minutes (95% CI: -0.63, 8.47, n=62, p=0.09) for participants in the combined aerobic and PRE group compared with the non-exercising control group (Rigsby, 1992; Dolan, 2006).	HIGH (+ve effect)
				No serious risk of bias	No serious inconsistency	No serious imprecision	No serious indirectness	No serious publication bias		
				Strength					Participants exercised 20-120 min three times per week for 12-16 weeks. Six of the 14 included studies assessed muscle strength (Rigsby, 1992; Lox, 1995; Perna, 1999; Grinspoon, 2000; Driscoll, 2004a; Dolan, 2006). Meta-analysis could not be performed for strength, due to differences in the types of strength outcomes assessed, types of interventions, types of comparison groups, and types of participants; however, individual studies suggested improvements in strength among exercisers compared with non-exercisers.	LOW (+ve effect)
				Serious risk of bias	No serious inconsistency	No serious imprecision	Serious indirectness	No serious publication bias		
	Nixon, 2005 *(70)*	10 RCTs, N=276	high	Serious risk of bias	No serious inconsistency	No serious imprecision	Serious indirectness	No serious publication bias	The age of the participants in this study ranged from 18-58 years and ~70% were males. Participants exercised 30-40 min three times per week for 6-15 weeks. Nine of the 10 included studies reported cardiopulmonary outcomes, six of which compared constant or interval aerobic exercise to non-exercising controls (Baigis, 2002; LaPerriere, 1990; Lox, 1995; Perna, 1999; Smith, 2001; Stringer, 1998). Meta-analysis showed a non-significant improvement in $\dot{V}O_{2max}$ of 1.8 ml/kg/min (95% CI: -0.5, 4.2, n=179, p=0.13) for participants in the aerobic exercise intervention group compared to the non-exercising control group (Baigis, 2002; Perna, 1999; Smith, 2001; Stringer, 1998). The confidence interval demonstrated a positive trend towards improvement in $\dot{V}O_{2max}$ in the exercise group.	MODERATE (+ve effect)
	O'Brien, 2004 *(73)*	10 RCTs, N=458 HIV+ only participants	high	Serious risk of bias	No serious inconsistency	No serious imprecision	Serious indirectness	Serious publication bias	The age of the participants in this study ranged from 18-58 years. Participants exercised 30-45 min three times per week for 6-15 weeks. Nine studies assessed cardiopulmonary status (Rigsby, 1992; MacArthur, 1993; Jadad, 1996; Stringer, 1998; Ledergerber, 1999; Perna, 1999; Terry, 1999; Smith, 2001; Baigis, 2002). Significant improvements were found among individual trials of aerobic exercisers when compared with non-exercising controls, but meta-analysis could only be performed using	HIGH (+ve effect)

									$\dot{V}O_{2max}$ due to varying outcomes reported. Three meta-analyses showed non-significant improvement in $\dot{V}O_{2max}$ of 1.84 $mL \cdot kg^{-1} \cdot min^{-1}$ (95% CI:-0.53, 4.20, n=179) for participants in the aerobic exercise intervention group compared with the non-exercising control group; non-significant improvement occurred in $\dot{V}O_{2max}$ of 1.56 $mL \cdot kg^{-1} \cdot min^{-1}$ (95% CI: -0.94, 4.07, n=151) for participants in the constant exercise group compared with the non-exercising control group, and statistically non-significant improvement occurred in $\dot{V}O_{2max}$ of 4.29 $mL \cdot kg^{-1} \cdot min^{-1}$ (95% CI: -1.23, 9.82, n=24) for participants in the heavy-intensity aerobic exercise group compared with participants in the moderate-intensity exercise group. This finding reached clinical importance, but not statistical significance.	
Resistance Exercise	Poton, 2017 *(78)*	13 RCTs, N=291	moderate	Serious risk of bias	No serious inconsistency	No serious imprecision	No serious indirectness	No serious publication bias	The mean age of the participants (43.1% female) in this study was 40.2 ± 4.8 years. The mean training duration was 14.6 ± 5.3 weeks with a frequency of three times a week. Improvements occurred in muscular strength with resistance exercise with an overall effect size of 1.58 (1.46–1.70; p<0.01; ~35.5%). In addition, the I^2 statistic confirmed high heterogeneity for trials that investigated muscular strength (I^2=66.28; P<0.001).	MODERATE (+ve effect)
	O'Brien, 2008 *(74)*	10 RCTs, N=332	high	Serious risk of bias	No serious inconsistency	No serious imprecision	Serious indirectness	No serious publication bias	The age of the participants in this study ranged from 18-66 years old (<30% females). Participants exercised approximately 20-25 min ranging from 1-5 sets of 4-18 repetitions three times per week for 6-16 weeks. Two studies evaluated sub-maximum heart rate (Lox, 1995; Rigsby, 1992). Meta-analysis showed a non-significant reduction in heart rate of -13.02 beats/minute (95% CI: -26.67, 0.64; p=0.06; n=46) for participants in the PRE or combined PRE and aerobic exercise group compared to the non-exercising control group. The confidence interval indicated a trend towards a clinically important improvement in sub-maximum heart rate among exercisers compared with non-exercisers (10 beats/min). This meta-analysis reported statistical significance for heterogeneity using a random effects model. Heterogeneity was likely attributed to the different exercise interventions between the studies. Two studies measured $\dot{V}O_{2max}$ (Dolan, 2006; Lox, 1995). Meta-analysis showed no difference in $\dot{V}O_{2max}$ among participants in the PRE or combined PRE and	HIGH (+ve effect)

									aerobic exercise group compared to the non-exercising control group. Two studies assessed exercise time (Dolan, 2006; Rigsby, 1992). Meta-analysis showed a non-significant increase in exercise time of 3.92 minutes (95% CI: -0.63, 8.47; p=0.09; n=62) for participants in the combined PRE and aerobic exercise group compared to the non-exercising control group. The confidence interval indicated a trend towards an improvement in exercise time among exercisers compared with non-exercisers. This meta-analysis reported statistical significance for heterogeneity using a random effects model. all studies reported on strength outcomes, but meta-analyses could not be performed due to differences in outcomes and participants; however, nine of the 10 studies suggested improvements in strength among exercisers compared to non-exercisers. Grinspoon (2000) found no significant differences in strength for participants in the combined aerobic and PRE exercise group compared with participants in the non-exercising control group.	
	O'Brien, 2017 *(72)*	20 RCTs, N=764	high	**VO_2max**					The mean age of the participants ranged from 32 to 49 years (23% were females). Participants exercised 30-120 min three times per week for 12-52 weeks. Two meta-analyses showed a significant and potentially clinically important improvement in $\dot{V}O_{2max}$ of 3.71 mL/kg/min for participants in the aerobic exercise intervention group compared with the non-exercising control group. There was no statistical significance for heterogeneity.	MODERATE (+ve effect)
				Serious risk of bias	No serious inconsistency	No serious imprecision	Serious indirectness	No serious publication bias		
				HRmax					Participants exercised 20-135 mins three times per week for 12-16 weeks. Two meta-analyses showed no significant difference in HR_{max} for participants in the PRE or combined PRE and aerobic exercise group compared with the non-exercising control; and combined PRE and aerobic exercise group compared with non-exercising control. Heterogeneity was present in both meta-analyses.	LOW (no effect)
				Serious risk of bias	No serious inconsistency	No serious imprecision	Serious indirectness	No serious publication bias		
				Exercise time					Participants exercised 20-120 min three times per week for 12-52 weeks. Two meta-	HIGH (+ve effect)

				Serious risk of bias	No serious inconsistency	No serious imprecision	Serious indirectness	No serious publication bias	analyses demonstrated a significant increase in exercise time of 3.29 min for participants in the combined PRE and aerobic exercise group compared with the non-exercising control group. The point estimate did not reach the 5 min threshold for clinical importance.	
				Strength					Participants exercised 30-120 mins three times per week for 12-52 weeks Meta-analyses showed that improvements occurred in upper and lower body strength, as determined by increases in 1-repetition maximum for chest press, and knee flexion; and a non-significant trend towards improvement in 1-RM for leg press and knee extension for participants in the combined PRE and aerobic group versus non-exercising control group. Two more meta-analyses were conducted comparing combined exercise and testosterone with testosterone alone. Results indicated a non-significant trend towards increased strength among participants in the combined exercise and testosterone group compared with participants in the testosterone alone group for knee flexion and extension. Five of the six-point estimates for upper and lower extremity strength were greater than 2 kg and 5 kg, respectively, indicating a clinically important increase with exercise compared with non-exercise. Heterogeneity was present in five meta-analyses.	LOW (inconclusive)
				Serious risk of bias	No serious inconsistency	No serious imprecision	Serious indirectness	No serious publication bias		

Multimodal Exercise	Voigt, 2018 *(77)*	15 RCTs, N=537	moderate	No serious risk of bias	No serious inconsistency	No serious imprecision	Serious indirectness	No serious publication bias	The age of the participants in this study ranged from 18-73 years old. The duration ranged between 31-120 min 2-4 times a week; intensity ranged from low to vigorous for 6-24 weeks. For aerobic exercise training, Galantino (2005) revealed significant improvements in both cardiovascular (maximum oxygen consumption) and flexibility outcomes. Two studies (Agin, 2001 and Strawford, 1999) also reported significant improvements in strength outcomes in the intervention group compared to those in the control group using progressive resistance training interventions. Seven studies which used combined aerobic and PRT interventions found significant improvement in overall strength, cardiovascular, and flexibility parameters. One study with a combined yoga and meditation, and another study with yoga alone found no changes in functional capacity. In another study that used tai chi exercise intervention revealed significant improvements in both flexibility and cardiovascular outcomes.	HIGH (+ve effect)
	Pedro 2017 *(72)*	5 RCTs, N=253	high	No serious risk of bias	No serious inconsistency	No serious imprecision	Serious indirectness	No serious publication bias	The age of the participants in this study ranged from 18-60 years old. The duration ranged between 12-24 weeks. Muscular strength increased in response to resistance and concurrent training in three studies (Lindegaard, 2008; Dolan, 2006; Mendes, 2013). Strength also increased slightly in response to aerobic training (Lindegaard, 2008). The $\dot{V}O_{2max}$ increased in response to concurrent training (Dolan, 2006; Mendes, 2013) and aerobic training (Lindegaard, 2008; Mendes, 2013; Terry, 2006), but did not increase in response to resistance training (Lindegaard, 2008).	MODERATE (+ve effect)
	Chaparro 2018 *(76)*	13 RCTs, N=NR	high	No serious risk of bias	No serious inconsistency	No serious imprecision	Serious indirectness	Serious publication bias	The mean age for the control group was 42 ± 5.7 years and for the intervention group 42.9 ± 5.3 years. The duration ranged between 60-120 min 2-3 times a week for 6-24 weeks. Two overall meta-analyses and 34 subgroup analyses showed that change in upper body strength in PLWH from baseline was 18 kg (95% CI: 11.2–24.8, p<0.001) favouring the intervention group. Lower body strength also increased by 16.8 kg (95% CI: 13–20.6, p< 0.001) favouring the intervention group. Sub-analysis revealed a significant increase in the weight lifted for each muscle group, favouring the intervention group. After long-term exercise, the intervention group showed a	HIGH (+ve effect)

									significant change in upper body strength of 13.7 kg (95% CI: 6–21.5, p<0.001), as well as lower-body strength of 16 kg (95% CI: 11.6–20.4, p<0.001).	
	Gomes Neto, 2015 *(68)*	7 RCTs, N=386	high	Serious risk of bias	No serious inconsistency	No serious imprecision	No serious indirectness	No serious publication bias	The age of the participants in this study ranged from 37-46 years old. The duration ranged between 20-85 min 2-3 times a week for 6-24 weeks. Mendes (2013) and Dolan (2006) found significant improvements in muscle strength of the knee extensors and elbow flexors of 25.06 Kg (95% CI: 10.46, 39.66, n=118) and of 4.44 Kg (95% CI: 1.22, 7.67,n=118), respectively, for participants in the concurrent resistance and aerobic exercise group compared with no exercise group. Five studies (including 318 patients) assessed $\dot{V}O_{2peak}$ as outcome. In the study by Mutimura (2008), VO_{2peak} improved from 4.7 ± 3.9 vs 0.5 ± 0.3 ml/kg per min in the intervention group compared to the control, while the study of Hand (2008), detected an improvement of 21% in $\dot{V}O_{2peak}$ estimated in the exercise group versus no improvement in the control. Similarly, Dolan (2006) observed an improvement (1.5 ± 0.8 vs -2.5 ± 1.6 $mL/kgmin^{-1}$) in VO_{2peak} in the training group compared to the control. However, Ogalha (2011) observed a non- significant improvement (0.6 ± 0.9 vs -0.2 ± 0.7 $mL/kgmin^{-1}$) VO_{2peak} in the training group compared to the control. The mean VO_{2peak} in the analysed studies was 26.8 mL kg-1 min^{-1} at baseline, and it increased to 30.7 mL $kgmin^{-1}$ at the end of the intervention. The meta-analyses showed a significant improvement in VO_{2peak} of 4.48 mL kg-1 min^{-1} (95% CI: 2.95, 6.0, n=318) for participants in the CARE group compared with no exercise group.	HIGH (+ve effect)

	Zech, *2019 (75)*	27 RCTs, N=1294	high	Serious risk of bias	No serious inconsistency	No serious imprecision	No serious indirectness	Serious publication bias	The average age was 41.46 ± 5.04 years for the intervention groups and 40.99 ± 5.93 years for the control groups. The duration ranged between 30-120 min 2-5 times a week for 6-26 weeks. Seven main meta-analyses and 45 subgroup analyses found in favour of the exercise group. Statistical heterogeneity was moderate, indicating that there was relatively moderate variation in the effect sizes across trials. For the 6-minute walk test, an overall SMD=0.59 in favour of the exercise group was found. There was a significant overall effect of exercise compared with the control group at post treatment. For maximum heart rate, an overall SMD=-0.38 in favour of the exercise group was found. There was no significant overall effect of exercise compared with the control group. For resting heart rate, an overall SMD=-0.29 was found in favour of the exercise group. There was no significant overall effect of exercise compared with the control group. For systolic blood pressure, an overall SMD=-0.27 in favour of the exercise group was found. There was no significant overall effect of exercise compared with the control group. For diastolic blood pressure, an overall SMD=0.01 in favour of the exercise group was found. There was no significant overall effect of exercise compared with the control group. For maximum power output, an overall SMD=0.80 in favour of the exercise group was found. There was a significant overall effect of exercise compared with the control group at post treatment.	MODERATE (+ve effect)
	Ibeneme, 2019a *(64)*	23 RCTs, N=1073	High	Serious risk of bias	Serious inconsistency	No serious imprecision	Serious indirectness	No serious publication bias	The age of the participants in this study ranged from 18-65 years old. The duration ranged between 20-60 min 3-5 times per week for a range of 6-16 weeks. Eight studies reported statistically significant improvement in the VO_{2max}/ VO_{2peak} in the post-training period in the intervention group, while two studies reported no significant improvement of the intervention on the stated outcomes. Two other trials reported a significant increase in the mean forced expiratory volume (FEV_1) in the intervention group compared to the control group. Farinatti (2010) observed a significant improvement in the slope/ intercept values for the rate - workload relationship. Furthermore, a total of 13 studies also reported a statistically significant improvement in the cardiopulmonary-related parameters, while two other studies reported no significant	HIGH (+ve effect)

									improvement in the study group. The results of the meta-analysis revealed a significant change in VO_{2max} between the intervention and control groups. Results demonstrated a trend towards an increase in VO_{2max} in subjects in the aerobic exercise and resistance exercise group compared normal activities in the control group that favoured the intervention. There was also a trend towards an increase in VO_{2max} in subjects in the aerobic exercise group compared to the normal activities in the control group.	

Abbreviations: PICO = population, intervention, comparator, outcome; RoB = risk of bias; RCTs = randomised controlled trials

1. O'Brien, 2016:
   - VO2max: Downgraded to VERY LOW by the authors of the review due to attrition (withdrawals of included studies >15 %), suspected publication bias, substantial heterogeneity (I2 = 67 %); and because the lower level of the confidence interval did not cross the estimated clinically important change in VO2max (despite the estimate surpassing the author's hypothesized clinically important change in VO2max of 2 ml/kg/min).
   - HRmax: Downgraded to MODERATE due to attrition and performance bias.
   - Exercise time: Downgraded to MODERATE due to attrition and performance bias (inability to blind participants to exercise interventions). This was then upgraded to high due to the evident dose-response relationship in the findings.
   - Strength: The authors of the review downgraded the outcome from HIGH to LOW due to incomplete outcome data (withdrawals of included studies were >15 %), publication bias suspected, and MODERATE to considerate heterogeneity (I2 = 46 % and 88% for chess and leg press, respectively).
2. O'Brien, 2010:
   - VO_{2max}: MODERATE due to heterogeneity in the studies included. This was later upgraded to HIGH due to the evident dose-response relationship in the findings.
   - Maximum Heart Rate (HRmax): HIGH because there is no reason to downgrade.
   - Exercise Time (minutes): HIGH because there is no reason to downgrade.
   - Strength: Downgraded to LOW due to a higher magnitude of indirectness.

3. O'Brien, 2004: Downgraded to LOW because the authors report a possibility of publication bias, there was also attrition bias (20% drop out in 6 studies and more than 50% dropout in 2 studies), the review is also based on a small number of trials and participants. Heterogeneity may have occurred due to a variety of exercise interventions being used. This low GRADE was then upgraded to HIGH due to the evident dose-response relationship in the findings.
4. O'Brien, 2008: Downgraded to LOW because of a lot of variation among individual studies in the types of interventions, participants and outcomes, which may have led to heterogeneity and Indirectness. Also, there is RoB due to attrition bias because of high withdrawal rates (>15%). There was also lack of blinding to the PRE intervention which may have resulted in the Hawthorn effect. The authors also report a possibility of performance bias due to increased levels of interaction between the investigators and participants in the exercise group resulting in more favourable outcomes for exercisers compared to non-exercisers. The review also used a small number of studies (n = 10) and there was total outcome data not available for 69 (17%) participants. This was then upgraded to HIGH because of evidence of a dose-response relationship.
5. Nixon, 2005: Downgraded to LOW due to (a) RoB due to attrition bias as a result of high withdrawal rates ranging from 4-76% (b) indirectness which may have been caused by the heterogeneity of outcome measures. This was later upgraded to HIGH due to the evident dose-response relationship in the findings.
6. O'Brien, 2017:

   - VO_{2max}: Graded MODERATE because the authors of the review were moderately confident in the effect estimate demonstrating a significant increase of 3.71 ml/kg/min for VO2max comparing PRE exercise (or combined PRE and aerobic exercise). The authors downgraded the outcome from HIGH to MODERATE GRADE quality of evidence because the lower level of the confidence interval did not cross the estimated clinically important change in VO2max (despite the estimate surpassing their hypothesized clinically important change in VO2max of 2 ml/kg/min).
   - HRmax: Downgraded to LOW because a high risk of performance bias existed across the included studies as 85% of them had a high risk of performance bias due to lack of participant blinding to the exercise intervention. Furthermore, Heterogeneity was present in both meta-analyses ($p < 0.1$) used for this outcome.

- Exercise time: Downgraded to VERY LOW because a high risk of performance bias existed across the included studies as 85% of them had a high risk of performance bias due to lack of participant blinding to the exercise intervention. Furthermore, Heterogeneity was present in both meta-analyses ($p < 0.1$) used for this outcome. This was then upgraded to HIGH due to the presence of a dose-response relationship.
- Strength: The authors of the review graded the outcome as LOW because their confidence was limited in the effect estimate of a significant increase of 11.86 kg for 1-repetition maximum for chest press comparing PRE exercise (or combined PRE and aerobic exercise) with non-exercising control. The outcome was downgraded from HIGH to LOW on the GRADE quality of evidence due to incomplete outcome data (withdrawals of included studies were >15%), publication bias suspected, and moderate heterogeneity (I^2=46%).

7. Pedro, 2017: Downgrade to MODERATE due to indirectness which might have been caused by different type of individuals in different studies, different types of exercise interventions and different types of assessment methods.
8. Chaparro, 2018: Graded LOW because there was publication bias on the systematic review and indirectness which could have been caused by the various differences among the included studies. This was then upgraded to HIGH due to the presence of a dose-response relationship.
9. Gomes Neto, 2015: Moderate due to RoB because the risk to selective reporting was uncertain and none of the studies described blinding of therapists. This was then upgraded to HIGH due to the presence of a dose-response relationship.
10. Zech, 2019: Downgraded to MODERATE because 9 of the 27 included studies showed a high risk of bias and potential publication bias.
11. Poton 2017: Downgraded to MODERATE due to RoB, inconsistency and imprecision as there is insufficient information in the review.
12. Voigt, 2018: downgraded to MODERATE due to heterogeneity as a result of the different exercise intervention and small sample size. This was then upgraded to HIGH due to the presence of a dose-response relationship.
13. Ibeneme, 2019a: Downgraded to MODERATE due to RoB, inconsistency in the outcome measure and variability in the types of intervention used in the study. This was then upgraded to HIGH due to the presence of a dose-response relationship.