

Effects of Exercise on Muscle Strength and VO₂ Peak in Patients with Pulmonary Hypertension: A Systematic Review and Meta-Analysis

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Abstract: Exercise programs are one of the treatments used to extend the life expectancy of individuals with pulmonary hypertension; however, there is conflicting evidence regarding how well exercise increases muscle strength and VO₂ peak. Six databases and one other source were used in a comprehensive search conducted from June to August 2024 to find relevant research published in English between 2006 and 2022. The standard mean difference, mean difference, and risk difference with a 95% confidence interval were used to determine the effect of exercise. Biased publications were presented with a risk of bias summary/graph. Employing the Critical Appraisal Skills Program, all reviewers independently assessed the methodological quality of the included studies and extracted data.

The results showed 13 randomized control trial studies with 421 respondents, consisting of 204 and 217 in the intervention and control groups, respectively. Exercise had significant effects on improving muscle strength, VO₂ peak (primary outcomes), oxygen saturation, cardiac output, six-minute walk test, and several aspects of health-related quality of life as assessed by the SF-36 questionnaire (secondary outcomes), and there were no serious adverse events linked to exercise. However, exercise did not significantly alter VE/CO₂ slope, cardiac index, role physical, vitality, mental health, physical component summary, or mental component summary between the intervention than control groups among people with pulmonary hypertension. In conclusion, an exercise program of supervised may improve VO₂ peak and muscle strength and does not result in an increased risk of serious adverse events. Nonetheless, individuals with severe conditions of pulmonary hypertension should be carefully considered when doing exercise programs.

Keywords: Exercise, Meta-analysis, Muscle strength, Pulmonary hypertension, Systematic review, VO₂ peak

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Introduction

Pulmonary hypertension (PH) is a serious public health problem causing death^{1,2} and high disability rates with poor prognosis.³ Previous reviews have also reported that the one-year survival rate of patients with PH ranges from 67% to 99%.⁴ This is because PH is progressive, characterized by a gradual increase in pulmonary vascular resistance, which leads to an increase in the right heart load and failure.^{2,5,6} Additionally, symptoms such as shortness of breath (SOB), dyspnea, and fatigue can reduce exercise capacity (EC), including oxygen consumption (VO₂) peak, 6-minute walking distance (6MWD), the minute ventilation/carbon dioxide production (VE/VCO₂) slope, saturation oxygen (SaO₂), cardiac output (CO), and cardiac index (CI). These conditions disrupt the tissue perfusion process and affect histological abnormalities in the skeletal muscle of PH patients.^{7,8} Therefore, there is a need to explore other strategies different from pharmacotherapy and lifestyle changes,⁵ to deal with problems caused by PH.

Muscle strength (MS) and VO₂ peak are important components for patients with PH in independently performing daily activities.^{9,10} Similarly, increasing MS and VO₂ peaks has reduced morbidity and mortality rates and improved health-related quality of life (HRQOL).^{11,12} However, symptoms of PH are still a major problem in efforts to improve MS and VO₂ peak,¹³ particularly for those with a high New York Heart Association (NYHA) Classification.¹⁴ According to previous research, patients with PH have impaired muscular and cardiopulmonary function. These alterations correlate to the VO₂ peak consumption brought on by symptoms.^{15,16} Therefore, several efforts have been made to address this problem, including therapy, medicine, and exercise rehabilitation programs.

Literature review

Exercise has been recommended for both healthy and sick young and older people. Besides that, there is compelling evidence that exercise training enhances functional ability, HRQOL, and even

long-term survival in people with other chronic heart and lung diseases.⁵ Generally, routine exercise can increase oxygen transport, CO, CI, and stroke volume (SV) due to central adaptations and cardiac remodeling mediated by volume overload, leading to increased cardiac function at rest or during exercise.^{17,18} Additionally, such exercise can boost the oxidative capacity of skeletal muscle linked to elevated enzymes in cellular respiration, particularly in oxidative phosphorylation and the citric acid cycle (also known as the Krebs cycle);^{19,20} Due to these central and peripheral adaptations, the exercising myofibril receives more oxygen and has a greater ability to metabolize oxygen for the synthesis of adenosine triphosphate. Thus, trained individuals experience increased cross-sectional area of slow twitch (Type I) and Type IIa fibers.²¹

In people with PH, developments in therapy tailored to conditions of PH have increased survival and slowed the course of the illness. Rehabilitative exercise programs are among the suggestions. A supervised exercise program under medical therapy is recommended for individuals with PH (Class of recommendation: 1, level of evidence A).²² Likewise, the European Respiratory Society recommends that routine exercise can improve EC, muscle function, HRQOL, and possibly right ventricular function.²³ Contrary to the previous study, they have found that active exercise was not recommended for individuals with PH due to concerns that it might exacerbate symptoms and negatively impact heart function.^{24,25} Moreover, several studies support the benefits of exercise in increasing MS and VO₂ peak for patients with PH, although significant results were not reported.²⁶⁻²⁸ Therefore, evidence-based research on the benefits of exercise programs such as walking, bicycling, aerobics, yoga, endurance/resistance training, and inspiratory muscle training on MS and VO₂ peak of people with PH is needed. Similarly, this study was to compile the available data on exercise programs and assess the intervention's efficacy and safety in light of the growing global acceptance of exercise programs in people with PH, although based on limited evidence.

Study Aims

This review aimed to investigate the effectiveness of exercise on increasing MS and VO2 peak (primary outcome). It also determined the benefits of exercise on EC (6MWT, VE/VCO2 slope, SaO2, CI, and CO), HRQOL, and serious adverse events (secondary outcome) for patients with PH.

Methods

Data sources and methodical review of literature

This study was registered with PROSPERO (CRD42024512031). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were guidelines used to write up this review, as shown in **Figure 1**. The PICO format was used, where Population (P): Patient with PH, Intervention (I): Exercise, Compare (C): usual care, education, healthy nutrition, physical therapy, Outcome (O): muscle strength (MS), and VO2

peak (primary outcome), health-related quality of life (HRQOL), and 6-minute walk test (6MWT) (secondary outcome). A thorough search was conducted from June to August of 2024 using six databases, including Embase, CINAHL, Medline, Cochrane, PubMed, Web of Science, and one additional source, namely the Library of Congress. Keywords and Emtree/MESH terms used for the search were essential PH, familial primary PH, PH, hypertensive pulmonary vascular disease, idiopathic pulmonary arterial hypertension, pulmonary arterial hypertension, pulmonary artery hypertension, primary PH, pulmonary fixed hypertension, pulmonary hypertensive disease, and pulmonary hypertensive disorder. Additionally, EC, exercise performance, exercise training, fitness training, fitness workout, and physical exercise (related to exercise) were used. Other keywords included dynamic strength muscle, dynamic strength muscular, muscle dynamic strength, muscle force, muscle force-velocity relationship, muscle power, muscular, dynamic strength, muscular force, muscular power, and muscular strength muscle strength (related to muscle strength).

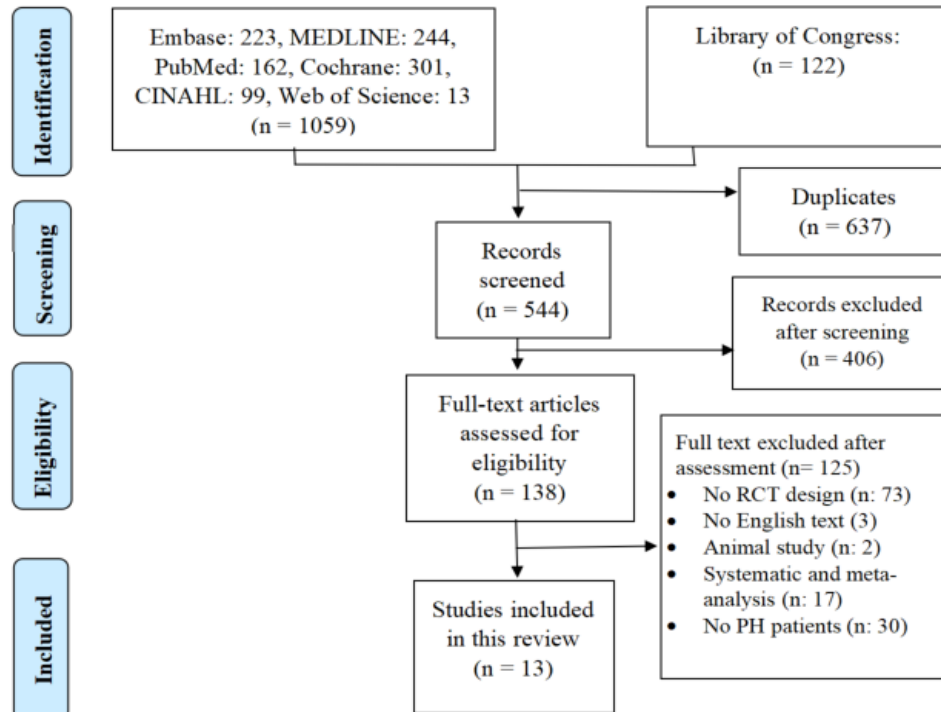


Figure 1. Studies selection process

Studies from 2006 to 2022 of the randomized control trial (RCT) design were included in this study. After identifying pertinent research using the PICO method, these studies were further scrutinized to eliminate duplicates. Screening of titles and abstracts was conducted to obtain studies that evaluated the effect of exercise on MS and VO₂ peak in patients with PH. After that, several studies that fulfilled the inclusion and exclusion criteria were selected. People with PH, English-language articles, and the RCT study design with intervention and control groups were all required for inclusion, whereas animal studies, systematic reviews, and meta-analyses were excluded. The search procedure was closed after all reviewers had looked through the full-text publications' reference lists and found no more research that satisfied the study's inclusion requirements.

Data extraction and quality assessment

Data extraction was performed independently to obtain information on eligible studies such as design, age, NYHA Class, component of intervention (type of exercise, frequency of exercise, and duration of exercise), and outcomes (MS, VO₂ peak, HRQOL, and EC). Meanwhile, quality assessment was performed independently, and differences of opinion were resolved through consensus among the reviewers. The internal validity of the studies was evaluated using the Critical Appraisal Skills Programme (CASP) methodological quality evaluation, which consists of 11 items with three possible answers: "yes, no, and can't tell."

Data synthesis and statistical analysis

Review Manager (RevMan5.3) software was used for statistical analysis. The heterogeneity of the study analysis data results was tested using the Chi-square test. When $I^2 < 50\%$, there was no statistically significant heterogeneity among the results of the studies, and the fixed-effect model was used for analysis. However, when $I^2 > 50\%$, statistical heterogeneity and a random-effect model were used for analysis. The outcomes were expressed as a change from the baseline to the follow-up. The results obtained were presented by the standardized mean difference (SMD) for MS, mean difference (MD)

for VO₂ peak, 6MWD, VE/VCO₂ slope, SaO₂, CI, CO, and HRQOL, and risk difference (RD) for serious adverse events with a significance level of 0.05 and confidence interval (CI) of 95%.

Risk of bias assessment

The Cochrane Handbook for Systematic Review of Interventions' criteria and the RoB 2 tool were used to evaluate each study's risk of bias from reviewers independently, and any discrepancies were settled by discussion. The potential of each bias source was assessed as high, low, or unclear, providing a report with a justification for the assessment in the form of a risk of bias summary and risk of bias graph (Appendix 17).

Results

Description of selected studies

A total of 1181 studies were collected from five databases (Embase: 223, Medline: 244, Cochrane: 301, Pubmed: 162, PEDro: 17, CINAHL: 99, Web of Science: 13) and one additional source (Library of Congress: 122). Meanwhile, 637 studies were removed based on duplication, and 494 were excluded due to title and abstract screening. After the full-text screening, 13 studies were included for analysis. At the same time, 125 were excluded for five reasons, namely lack of RCT study design (n: 73), no English text (n: 3), animal studies (n: 2), systematic and meta-analysis (n: 17), and absence of patients with PH (n: 30) (Figure 1).

Characteristics of the studies

A total of 13 studies with RCT design were included from 2006 to 2022, comprising 421 male and female respondents with PH. These respondents, whose mean age ranged from 35±13.68 to 57±3.7 years, were split into 204 in the intervention group and 217 in the control group. Additionally, as indicated in Table 1, the study's quality was evaluated using the CASP, with a score ranging from 7 to 11 of the total score.

Studies' methodological quality and potential for bias

The methodological quality of the studies is presented in **Table 1**, with the range of scores being seven to eleven with the total score being eleven. The risk of bias is summarized in **Appendix 17**, where seven studies provided information on how the randomization sequence was generated.^{25,26,29-33} This study assessed the studies as having a low risk of bias. Based on the results, five studies were unclear about random sequence generation (unclear risk of bias),^{27,28,34,35} and only one had a high risk.⁷ Additionally, four studies provided details about how allocation was concealed,^{27,28,31,36} eight studies had unclear risk of bias,^{25,26,29,30,32-35} and one study showed a high risk.⁷ Due to the nature of the intervention (exercise), respondents showed a tendency not to be blinded to the intervention. Nine studies had a high risk for blinding of respondents,^{7,25,26,29,30,32-35} one study was unclear,³¹ while three reported blinding.^{27,28,36} Meanwhile, nine studies were unclear in their blinding of outcome assessment.^{7,26-28,30,31,34-36} A total of eight studies reported low attrition bias per study, and each

study reported minimal dropouts.^{7,25,27-29,33,34,36} It was also discovered that four studies reported high risk,^{26,30,32,35} and one was unclear in incomplete outcome data.³¹ There were five studies with low potential for responding bias,^{25,28,29,33,34} five were unclear,^{7,27,31,32,36} and three had high potential for selective reporting bias.^{26,30,35} Finally, six studies were low in other bias,^{25,26,29,32,31,34} two did not report in detail how many respondents were screened based on inclusion/exclusion criteria (high risk),^{33,35} and five were unclear in other bias.^{7,27,28,30,36}

Effect of exercise on MS and VO2 Peak in patients with PH (Primary outcome)

Effect of exercise on MS

Figure 2 and **Table 2** show that exercise had a significant effect on increasing MS (upper limb) in the intervention group (n: 65) compared to the control group (n: 71) (SMD: 1.06, 95% CI: 0.17 to 1.96, I^2 : 82%). Similar results were shown in MS (lower limb), where there was a significant increase in the effect of exercise in the intervention group (n: 55) compared to the control (n: 52) (SMD: 1.01, 95% CI: 0.60 to 1.42, I^2 : 82%) (**Figure 3** and **Table 2**).

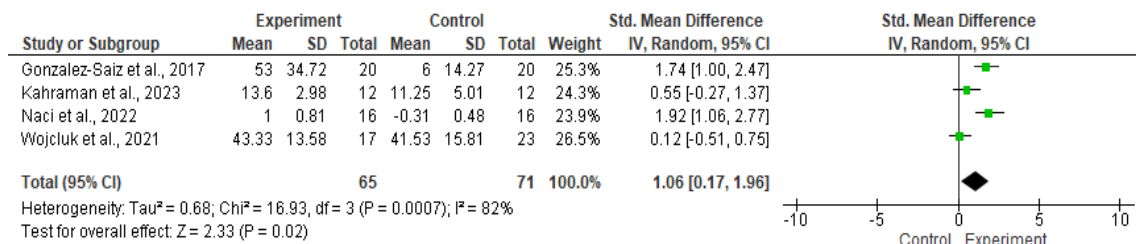


Figure 2. Effect of exercise on MS (upper limbs)

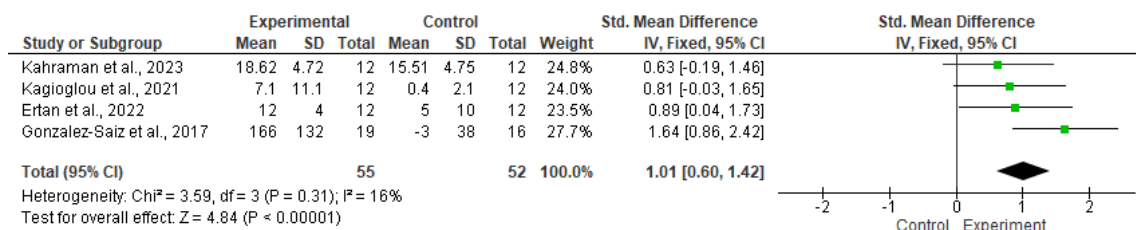


Figure 3. Effect of exercise on MS (lower limbs)

Table 1. Characteristics of the studies

No	Author	Age (Mean±SD)	E/C	NYHA Class	Component of intervention			Control	Outcome	CASP score
					Type of exercise	FE (Time/week)	DE (week)			
1	Chan et al., 2013	55.5±8.5	10/13	I-IV	Treadmill, walking, 30-45 min	2-3	10	Education	VO2 peak, 6MWD, HRQOL	9/11
2	Ehikien et al., 2016	55±15	38/38	II-IV	10-25 min: cycle ergometer, 60 min: walking, 30 min: RT, 30 min: respiratory training	5-7	12	Usual care	VO2 peak, 6MWD, HRQOL	7/11
3	Ertan et al., 2022	49.6±9.9	12/12	I-IV	Walking 30 to 45 min	≥3	8	Usual care	Muscle strength, 6MWD	8/11
4	Fukui et al., 2015	70±7	17/17	II, III	Walking, bicycle ergometer, and low-intensity RT	3	12	Usual care	Muscle strength, VO2 peak, 6MWD	8/11
5	Fox et al., 2011	57±3.7	11/11							9/11
6	Ganderton et al., 2011	53	15/20	I-IV	Endurance exercise (walking, cycling)	3	12	Usual care	VO2 peak, 6MWD, HRQOL	10/11
7	González-Saiz et al., 2017	46±11	19/19	I-IV	Aerobic, RT, inspiratory training	3-5	8	Usual care	Muscle strength, VO2 peak, 6MWD, HRQOL	11/11
8	Kagioglou et al., 2021	54.7±15.6	12/10	I-IV	Aerobic, walking, cycling, treadmill, RT	3	24	Usual care	Muscle strength, VO2 peak, 6MWD, HRQOL	9/11
9	Kahraman et al., 2023	49.16±17.09	12/12	II, III	Inspiratory muscle training 40 to 60% MIP	7	8	Usual care	Muscle strength, 6MWD	10/11
10	Mereles et al., 2006	53±14	15/15	II-IV	RT, bicycle ergometer, walking, respiratory training	3	12	Healthy nutrition, physical therapy, usual care	VO2 peak, 6MWD, HRQOL	10/11
11	Naci et al., 2022	50.38±9.02	16/16	I-III	Osteopathic manipulative treatment combines with yoga	2	8	Usual care	Muscle strength, 6MWD, VO2 peak, 6MWD, HRQOL	9/11
12	Yilmaz et al., 2020	35±13.68	11/11	I-III	Aerobic, ergometer 50 to 80% MHR	3	6	Alternative exercise	VO2 peak, 6MWD, HRQOL	8/11
13	Wojciuk et al., 2021	48.88±18.25	16/23	II, III	RT, inspiratory muscle training	6	24	Usual care	Muscle strength, HRQOL	10/11

Note. CASP = Critical Appraisal Skills Programme, FE = Frequency of exercise, DE = Duration of exercise, 6MWD = 6-minute walk distance, HRQOL = Health-related quality of life, RT = Resistance training, MHR = Maximal heart rate, MIP = Maximal inspiratory pressure

Table 2. Summarized experimental versus control

Outcome	No. of studies	No. of participants	Statistical method	Effect size	Test for overall effect Z (p-value)
Muscle strength					
Upper limb	4	136	SMD (IV, R, 95% CI)	1.06 (0.17, 1.96)	2.33 (0.02)
Lower limb	4	107	SMD (IV, F, 95% CI)	1.01 (0.60, 1.42)	4.84 (0.00001)
VO2 peak	8	265	MD (IV, F, 95% CI)	2.50 (1.79, 3.20)	6.94 (0.00001)
Exercise capacity					
6MWD	13	418	MD (IV, R, 95% CI)	30.09 (23.84, 36.33)	9.44 (0.00001)
VE/VCO2 slope	5	133	MD (IV, F, 95% CI)	0.40 (-2.62, 3.41)	0.26 (0.80)
SaO2	4	225	MD (IV, F, 95% CI)	2.19 (1.48, 2.91)	6.00 (0.00001)
Cardiac index	2	110	MD (IV, F, 95% CI)	0.69 (-0.38, 1.76)	1.26 (0.21)
Cardiac output	2	102	MD (IV, F, 95% CI)	1.19 (0.70, 1.67)	4.81 (0.00001)
Health-related quality of life (SF-36)					
Physical functioning	7	219	MD (IV, F, 95% CI)	4.94 (-1.20, 31.01)	1.58 (0.11)
Role physical	7	218	MD (IV, F, 95% CI)	16.50 (10.08, 22.92)	5.04 (0.00001)
Bodily pain	6	190	MD (IV, F, 95% CI)	5.19 (-2.03, 12.40)	1.41 (0.16)
General health	5	176	MD (IV, F, 95% CI)	5.13 (-0.40, 10.65)	1.82 (0.07)
Vitality	7	217	MD (IV, F, 95% CI)	11.08 (5.93, 16.24)	4.22 (0.00001)
Social functioning	7	220	MD (IV, F, 95% CI)	12.47 (8.48, 16.46)	6.13 (0.00001)
Role emotional	6	189	MD (IV, F, 95% CI)	3.35 (-4.64, 11.33)	0.82 (0.41)
Mental health	6	189	MD (IV, F, 95% CI)	6.11 (1.76, 10.46)	2.75 (0.006)
Physical component summary	7	248	MD (IV, F, 95% CI)	3.40 (1.48, 5.33)	3.46 (0.0005)
Mental component summary	7	247	MD (IV, F, 95% CI)	3.14 (0.93, 5.35)	2.79 (0.005)
Serious adverse events	14	472	RD (MH, F, 95% CI)	0.02 (-0.02, 0.06)	0.79 (0.43)

Note: SMD = Standardized mean difference, MD = Mean difference, RD = Risk difference, CI = Confidence interval, IV = Inverse variance,

MH = Mantel Haenszel, F = Fixed, R = Random

Effect of exercise on VO₂ peak

Nine studies, consisting of 185 and 196 respondents in the intervention and control groups, respectively, were included in the analysis. The results

showed that exercise had a significant effect on increasing the VO₂ peak for **PH patients** in the intervention groups (MD: 1.87, 95% CI: 1.32 to 2.42, I^2 : 45%) compared to the control, as presented in **Figure 4** and **Table 2**.

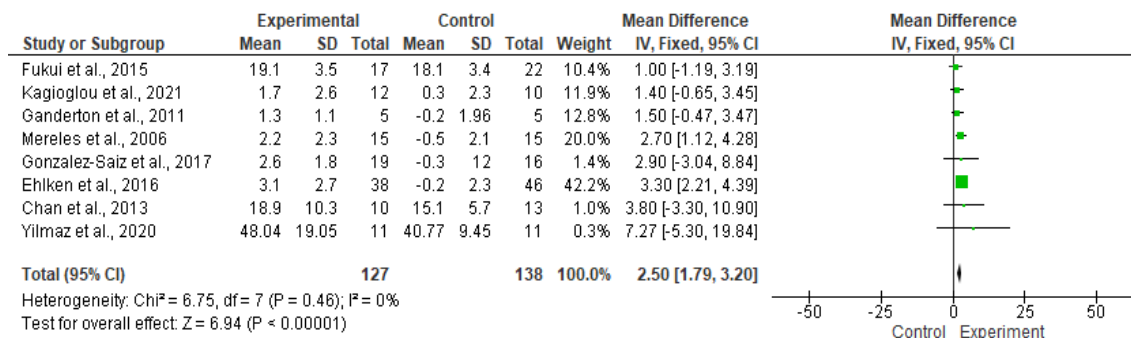


Figure 4. Effect of exercise on VO₂ peak

Effect of exercise on EC, HRQOL, and serious adverse events in patients with PH (Secondary outcome)

Effect of exercise on EC

Appendix 1 and **Table 2** show that the effect of exercise was proven to increase 6MWD in those in the intervention group significantly (n: 205) (MD: 30.09, 95% CI: 23.84 to 36.33, I^2 : 48%) compared to the control group (n: 213). Furthermore, there was a significant rise in SaO₂ in the intervention group (n: 111) (MD: 2.19, 95% CI: 1.48 to 2.91, I^2 : 0%) compared to the control group (n: 114) (**Appendix 3** and **Table 2**). A significant increase was also observed in CO in the intervention group (n: 48) (MD: 1.19, 95% CI: 0.70 to 1.67, I^2 : 0%) compared to the control (n: 54) (**Appendix 5** and **Table 2**).

The results shown in **Appendices 2** and **4** and **Table 2** show that effect of exercise did not significantly decrease the VE/VCO₂ slope in the intervention group (n: 133) (MD: -0.14, 95% CI: -2.76 to 2.47, I^2 : 14%) compared to the control group (n: 69). Additionally, there was no significant increase in CI of **PH patients** in the intervention group (n: 69) (MD: 0.69, 95% CI: -0.38 to 1.76, I^2 : 0%) compared to the control group (n: 41).

Effect of exercise on HRQOL

The results presented in **Appendices 7, 10, 11, and 13–15** and **Table 2** show that the effect of exercise could significantly improve HRQOL using the 36-item Short Form Health Survey questionnaire (SF-36) in the intervention group compared to the control group. These included physical role (MD: 16.50, 95% CI: 10.08 to 22.92, I^2 : 48%, n: 218), vitality (MD: 11.08, 95% CI: 5.93 to 16.24, I^2 : 0%, n: 217), social functioning (MD: 12.47, 95% CI: 8.48 to 16.46, I^2 : 38%, n: 220), mental health (MD: 6.11, 95% CI: 1.76 to 10.46, I^2 : 38%, n: 189), physical component summary (MD: 3.40, 95% CI: 1.48 to 5.33, I^2 : 32%, n: 248), and mental component summary (MD: 3.14, 95% CI: 0.93 to 5.35, I^2 : 0%, n: 247). **Appendices 6, 8, 9, and 12**, and **Table 2** show that the effect of exercise did not significantly improve HRQOL using SF-36 in the intervention group compared to the control group in physical functioning (MD: 4.94, 95% CI: -1.20 to 11.09, I^2 : 14%, n: 220), bodily pain (MD: 5.19, 95% CI: -2.03 to 12.40, I^2 : 0%, n: 2190), general health (MD: 5.13, 95% CI: -0.40 to 10.65, I^2 : 0%, n: 176), and role emotion (MD: 3.35, 95% CI: -4.64 to 11.33, I^2 : 0%, n: 189).

Effect of exercise on serious adverse events

This study showed the effect of exercise among 448 PH patients, consisting of 211 and 237 in the intervention and control groups, respectively. Based on the results, exercise did not affect serious adverse events in the intervention group compared to the control group (RD: 0.02, 95% CI: -0.03 to 0.06, I²: 1%), as shown in **Appendix 16** and **Table 2**.

Discussion

This study compared the effect of exercise on MS (upper and lower limbs) and VO2 peak in PH patients in the intervention and control groups (primary outcome). The comparison was carried out to address the issues related to the effectiveness of exercise in improving MS and VO2 peak commonly observed in adult populations. Additionally, analyses were carried out to determine whether there were differences in the effect of exercise on HRQOL, EC, and serious adverse events in both groups of PH patients (secondary outcome). The quality of evidence from the studies included was categorized as moderate quality, as shown in Table 1.

Effect of exercise on MS and VO2 Peak in PH Patients (Primary outcome)

Patients with PH often experience fatigue, SOB, and decreased exercise tolerance, particularly those with a higher NYHA Class,¹⁴ which has an impact on decreasing MS and VO2 peak.^{15,16} Previous studies have supported this notion; however, they recommended strict supervision for patients with PH engaging in exercise to prevent exacerbation of disease symptoms.⁵ Moreover, proper exercise can provide many benefits, such as increased pulmonary function and cardiovascular efficiency, where the heart works more effectively in increasing aerobic capacity.³⁶⁻³⁸ Routine exercise is also capable of increasing oxygen in the body, which plays a significant role in the metabolic process and improves blood flow to the muscle.^{19,25} This is supported by the current review that exercise

significantly increases MS (upper and lower limbs) in the intervention group compared to the control group.^{26,27,29,30,32,36}

Previous studies, which included 14 RCT study designs, showed that routine exercise can significantly reduce mean pulmonary artery pressure (mPAP), which impacts increasing EC.³⁷ Moreover, the benefits of exercise using walking, bicycle, endurance/resistance training, inspiratory muscle training, aerobics, and yoga have been proven to stimulate the release of the vascular endothelial growth factor (VEGF) functioning to repair and form new blood vessels as well as increase blood flow and tissue oxygenation.^{7,27,36,38} This process can increase the aerobic capacity and VO2 peak of patients with PH.^{38,39} Additionally, regular exercise significantly raises plasma levels of interleukin 6 (IL-6), IL-10, and tumor necrosis factor- α , which can strengthen the immune system and repair tissue damage.^{38,40} These two cytokines work together to reduce inflammation and improve vascular health for PH patients, and they also influence muscle growth, repair, and metabolism.^{39,40}

Effect of exercise on EC, HRQOL, and serious adverse events in patients with PH (secondary outcome)

Several previous studies found benefits of exercise in improving cardiopulmonary functioning.^{31,36} Exercise can increase energy metabolism in the body due to increased blood flow to the tissues thereby oxygenation is sufficient, causing a rise in 6MWD, SaO₂, and CO in PH patients.^{31,34-36} This study supported the results, where routine exercise 2 to 7 times/week for 6 to 24 weeks showed a good effect on EC, including a significant increase in 6MWD, SaO₂, and CO. However, the effect of exercise was not significant on the increase in CI and the decrease in the VE/VCO₂ slope. This could be attributed to the decrease in pulmonary capacity of PH patients capable of affecting exercise on a low VE/VCO₂ slope.^{7,41} In addition, the underlying pathophysiological changes in the pulmonary vasculature and cardiac function are associated with changes in VE/VCO₂ slope and CI

of people living with PH.^{37,41} On the other side, the type of PH, such as chronic thromboembolic pulmonary hypertension (CTEPH), NYHA Class, age, or procedures that had not been performed by patients, such as balloon pulmonary angioplasty (BPA) limit the effectiveness of exercise.^{7,27,35,42} However, exercise was identified as a good and safe recommendation for patients with PH.

Efforts to improve HRQOL in PH patients could be performed with routine exercise as supported by Chan et al.³⁴ Moreover, exercise demonstrated a good effect on improving the HRQOL of patients with PH, proving to be safe without serious adverse events.^{30,34} However, the severity of PH disease, such as high NYHA Class and patient age, negatively influenced the effect of exercise and HRQOL.^{9,10,14,25,42} This was observed when there was an increase but insignificant in the dimensions of physical functioning, general health, and emotional role decrease in the dimension of bodily pain (SF-36) between the intervention and control groups of PH patients. It is important to note that exercise is not completely risk-free for patients with PH,³⁷ and according to current international guidelines, exercise rehabilitation should only be carried out by facilities that have experience caring for patients with PH and rehabilitating compromised patients.^{5,24}

Studies' methodological quality and potential for bias

The methodological quality assessment using CASP scores is presented in **Table 1**. The methodological quality of these studies was moderate, and each reviewer evaluated the risk of bias separately. To report different outcome measures, we could pull data from 13 studies, all published articles. However, there were still some biased sources. The overall risk of reporting bias across all studies was low regarding blinding of random sequence generation and incomplete outcome data. Only three studies reported this clearly regarding the blinding of participants and personnel, while three did not report on selective reporting and other biases. Some studies were unclear in reporting the blinding of outcome assessment (**Figure 17**).

Review Limitations

Some limitations were observed. First, the inability to avoid publication bias from several studies included, as shown in **Appendix 17**. However, with reviewers working independently, using six databases and one additional source, and good analysis methods, publication bias could be overcome. Second, this analysis only included papers in English. The evaluation of clinical trial quality and some effect estimates would have been impacted if the review had included more publications, including those published in non-English. Therefore, it is advised that future studies consider incorporating larger and more thorough investigations. Third, several conditions of patients with PH that were not examined could affect the results. Therefore, further studies were recommended to conduct sub-group analysis on PH type, age, and NYHA Classification to strengthen the evidence for the effect of exercise on patients with PH.

Conclusion and Implications for Nursing Practice

In conclusion, this study found that exercise had benefits for patients with PH. Routine exercise, either walking, cycling, or in combination with aerobic, resistance training, yoga, and inspiratory muscle training, effectively improved primary outcomes (MS and VO2 peak). Generally, routine exercise is a safe recommendation without causing serious adverse events, and it is one of the recommended strategies for cardiac rehabilitation in patients with PH. However, further studies are recommended to conduct sub-group analysis on PH type, NYHA Class differences, and age differences to provide evidence-based exercise benefits for patients with PH.

Regarding implications for nursing practice, this study showed that routine exercise had an effect on increasing MS (upper and lower limbs) and VO2 peak in the intervention group compared to the control

group. Additionally, exercise was useful in increasing 6MWD, SaO₂, and CO in EC, as well as physical role, vitality, social functioning, mental health, physical component summary, and mental component summary in the HRQOL dimension of patients with PH. However, these patients require supervision from nurses and others, especially those with more severe conditions. This study provides evidence-based data for patients, families, and healthcare providers concerning the benefits of routine exercise in enhancing the health status of patients with PH.

Conflicts of Interest

No conflict of interest is reported by the authors.

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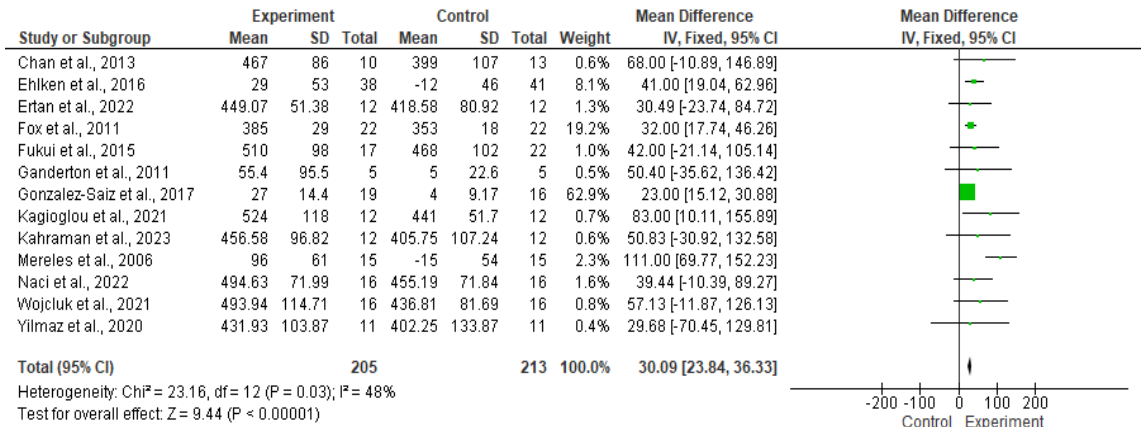
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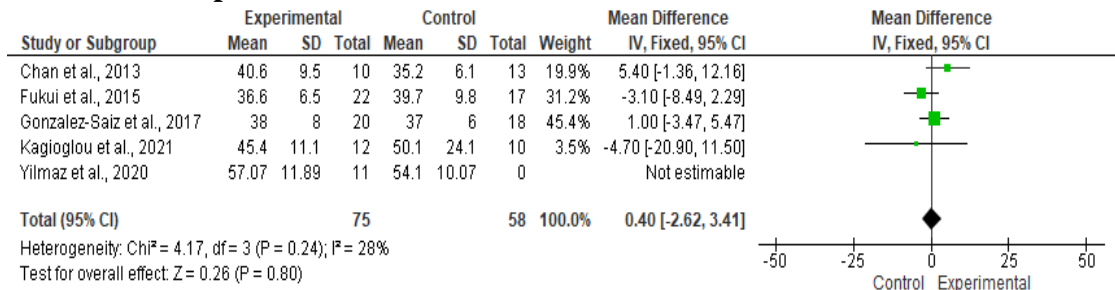
Appendix

Effect of exercise on EC (6MWD, VE/VCO₂ slope, SaO₂, CI, CO), HRQOL, and serious adverse events (secondary outcome)

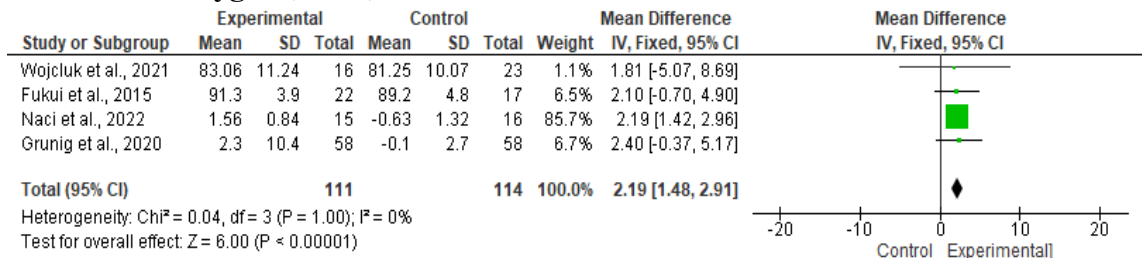
1. 6MWD



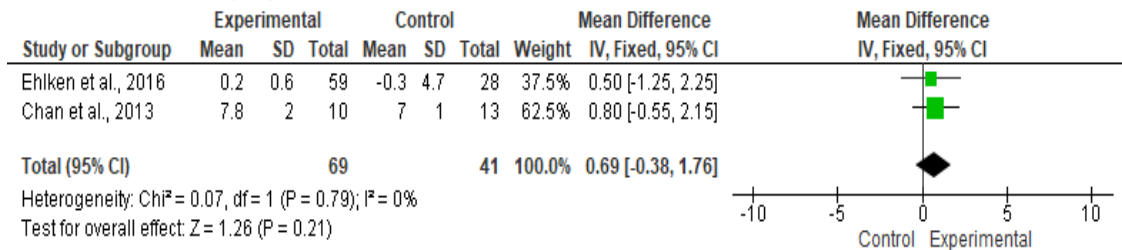
2. VE/VCO₂ slope



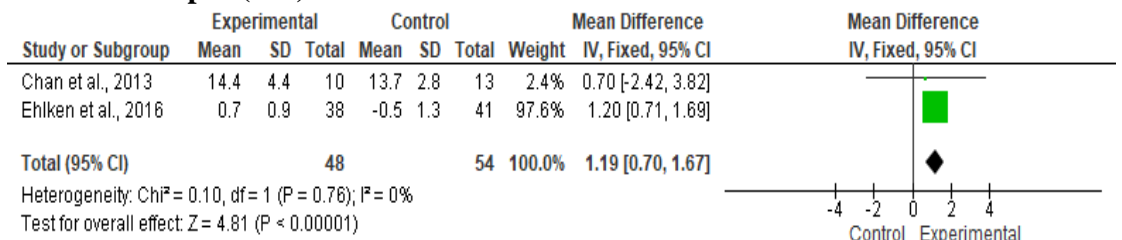
3. Saturation oxygen (SaO₂)



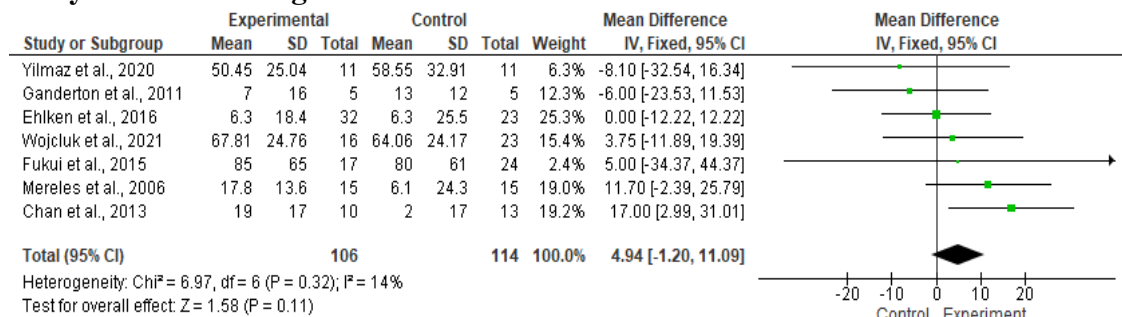
4. Cardiac index (CI)



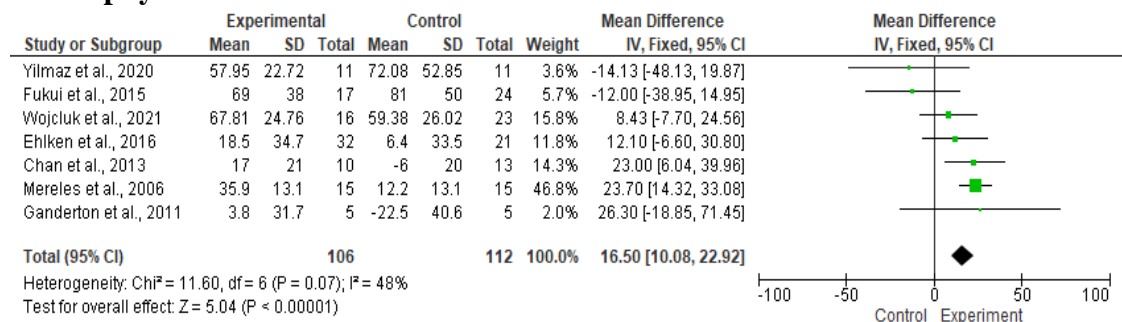
5. Cardiac output (CO)



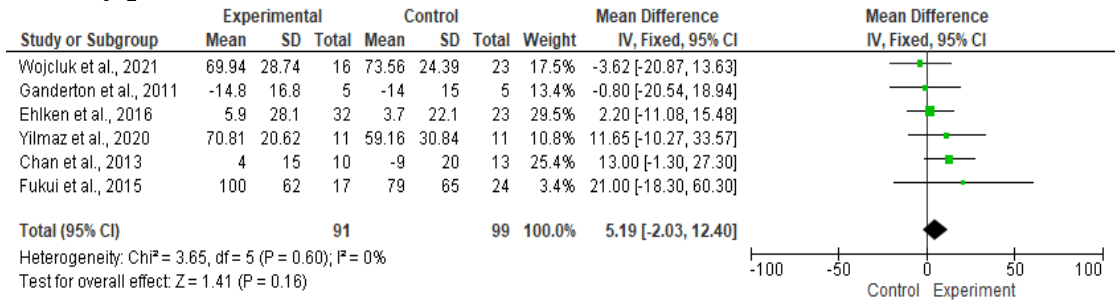
6. Physical functioning



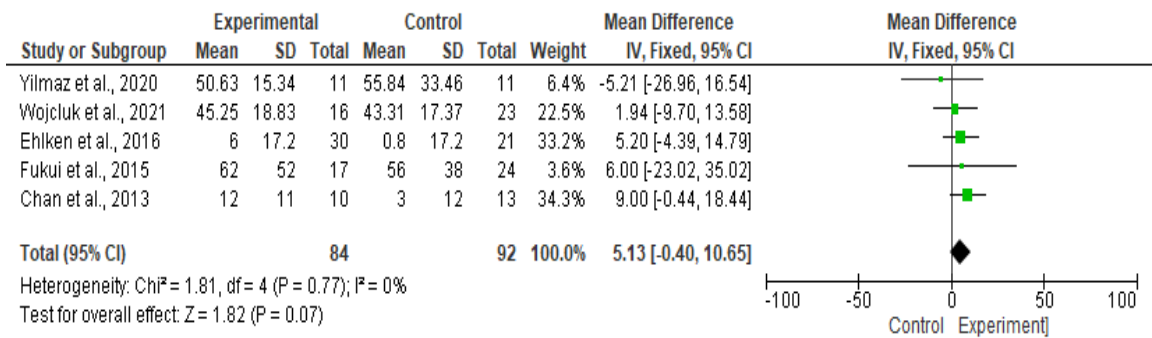
7. Role physical



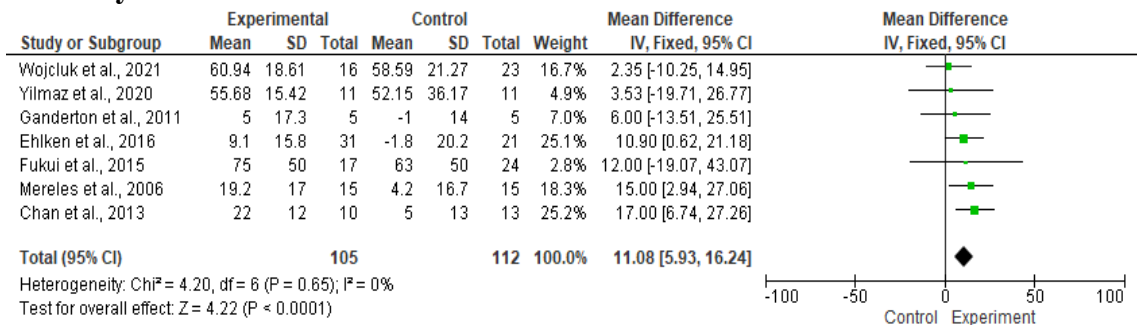
8. Bodily pain



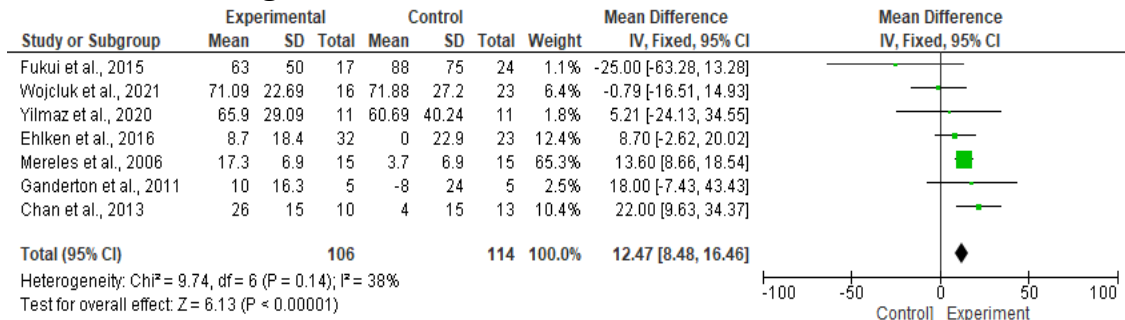
9. General health



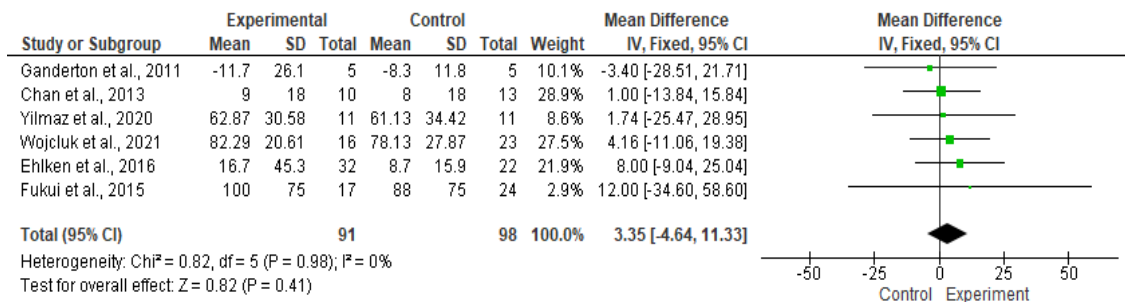
10. Vitality



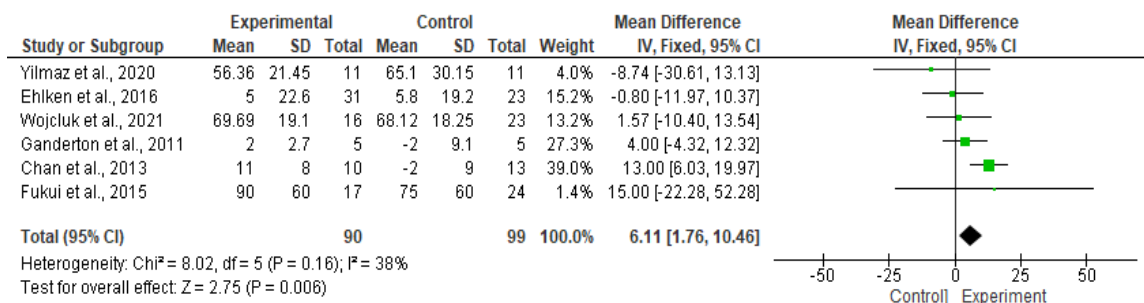
11. Social functioning



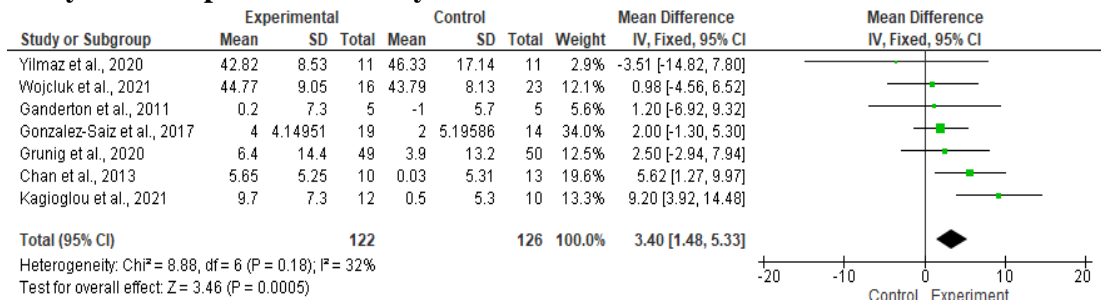
12. Role emotional



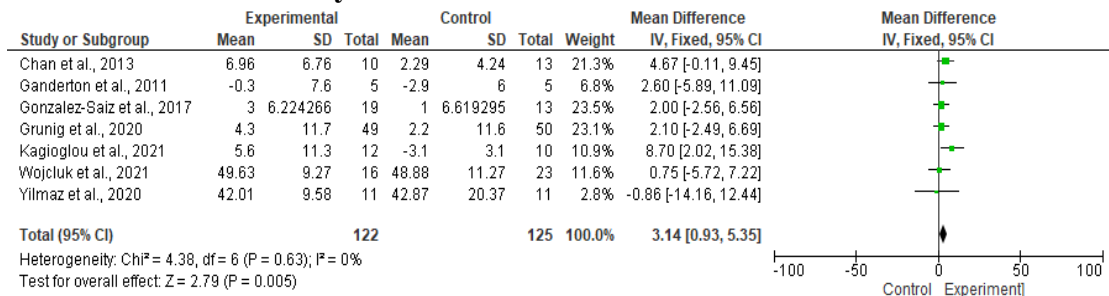
13. Mental health



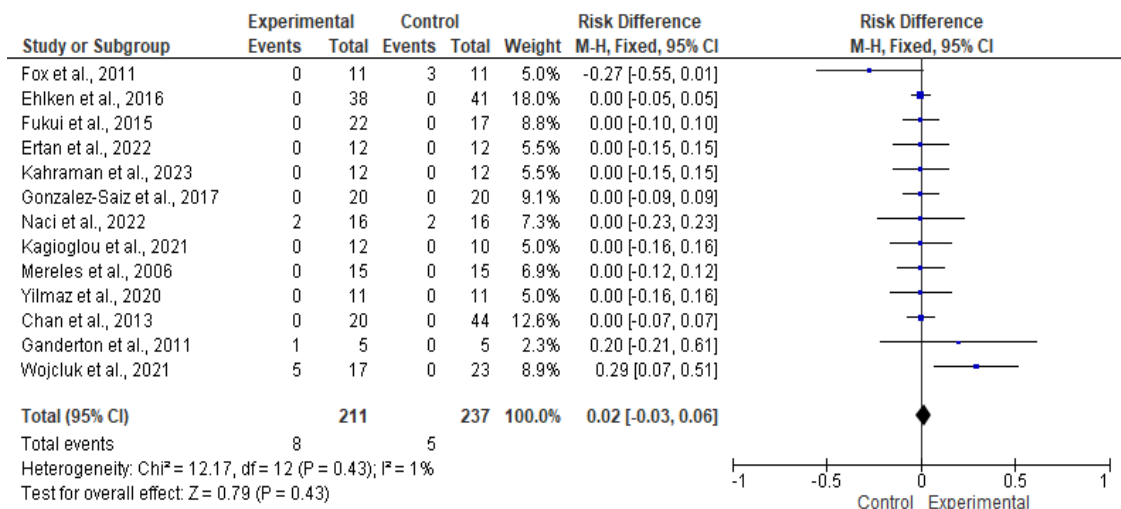
14. Physical component summary



15. Mental health summary



16. Serious adverse events

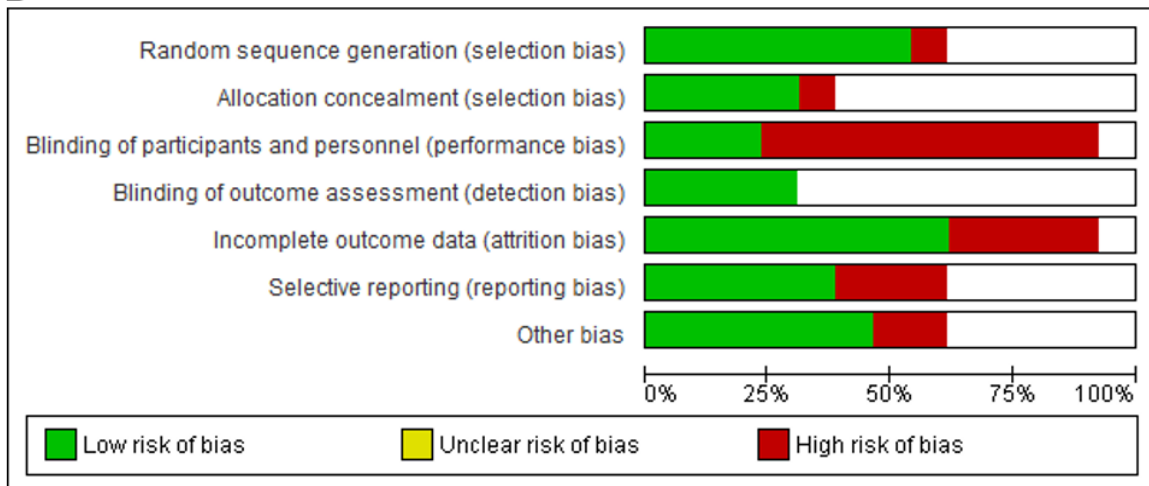


17. Risk of bias

A

Author	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Chan et al., 2013							
Ehken et al., 2016							
Ertan et al., 2022							
Fox et al., 2011							
Fukui et al., 2015							
Ganderton et al., 2011							
Gonzalez-Saiz et al., 2017							
Kagioglou et al., 2021							
Kahraman et al., 2023							
Mereles et al., 2006							
Naci et al., 2022							
Wojcik et al., 2021							
Yilmaz et al., 2020							

B



Note: (A) Risk of bias summary; (B) Risk of bias graph

ผลของการออกกำลังกายต่อความแข็งแรงของกล้ามเนื้อและค่าการใช้ ออกซิเจนสูงสุดในผู้ป่วยที่มีภาวะความดันโลหิตเลือดปอดสูง : การทบทวน วรรณกรรมอย่างเป็นระบบและการวิเคราะห์อภิมาน

Andreas Rantepadang, Angelia Friska Tendean, Ellen Padaunan, I Gede Purnawinadi, Silvia Dewi Mayasari Riu, Denny Maurits Ruku*

บทคัดย่อ: โปรแกรมการออกกำลังกายเป็นการรักษาอย่างหนึ่งซึ่งช่วยให้อายุขัยเฉลี่ยยืนยาวขึ้นในผู้ป่วยที่มีภาวะความดันโลหิตเลือดปอดสูง อย่างไรก็ตาม มีหลักฐานที่ขัดแย้งกันในประเด็นที่ว่า การออกกำลังกายช่วยเพิ่มความแข็งแรงของกล้ามเนื้อและค่าการใช้ออกซิเจนสูงสุด (VO₂ peak) ได้ดีเพียงใด ผู้ศึกษาค้นคว้างานวิจัยจาก 6 ฐานข้อมูลและแหล่งข้อมูลอื่นอีกหนึ่งแหล่งโดยดำเนินการตั้งแต่เดือนมิถุนายน ถึง สิงหาคม พ.ศ. 2567 เพื่อค้นหาการวิจัยที่เกี่ยวข้องและตีพิมพ์เป็นภาษาอังกฤษระหว่างปี พ.ศ. 2549 ถึง 2565 ผู้ศึกษาใช้ค่าความแตกต่างของค่าเฉลี่ยมาตรฐาน ค่าความแตกต่างของค่าเฉลี่ย และค่าความแตกต่างของความเลี้ยว ช่วงความเชื่อมั่น 95% ในการวิเคราะห์ผลของการออกกำลังกาย มีการนำเสนอ งานวิจัยที่มีอคติพร้อมกับการสรุป/กราฟความเสี่ยงของอคติ โดยใช้โปรแกรมทักษะการประเมินเชิงวิพากษ์ (the Critical Appraisal Skills Program) ผู้ตรวจสอบทั้งหมดประเมินคุณภาพเชิงวิธีการของงานวิจัยที่ใช้ศึกษา และดึงข้อมูลออกมาอย่างเป็นอิสระ ผลการศึกษาพบงานวิจัยเชิงทดลองแบบสุ่มและมีกลุ่มควบคุม 13 ฉบับ โดยมีผู้ตอบแบบสอบถาม 421 ราย ซึ่งประกอบด้วยกลุ่มที่ได้รับโปรแกรมการออกกำลังกาย 204 ราย และกลุ่มควบคุม 217 ราย ตามลำดับ พบว่าการออกกำลังกายมีผลอย่างมีนัยสำคัญต่อการสร้างเสริม ความแข็งแรงของกล้ามเนื้อ ค่าการใช้ออกซิเจนสูงสุด (ผลลัพธ์หลัก) ค่าความอิ่มตัวของออกซิเจนในเลือด ปริมาณเลือดที่ออกทางหัวใจ การทดสอบเดิน 6 นาที และคุณภาพชีวิตที่เกี่ยวข้องกับสุขภาพหลายประการ ซึ่งประเมินโดยแบบสอบถาม SF-36 (ผลลัพธ์รอง) และไม่พบเหตุการณ์ไม่พึงประสงค์ร้ายแรงที่เชื่อมโยง กับการออกกำลังกาย อย่างไรก็ตาม การออกกำลังกายไม่ได้เปลี่ยนแปลงความลาดชันของการระบายอากาศ ต่อนาที/การผลิตคาร์บอนไดออกไซด์ (VE/VCO₂) ดัชนีการเต้นของหัวใจ บทบาททางกายภาพ ความ มีชีวิตชีวา สุขภาพจิต องค์ประกอบทางกายภาพโดยรวม หรือองค์ประกอบทางจิตโดยรวมอย่างมีนัยสำคัญ ระหว่างกลุ่มที่ได้รับโปรแกรมเมื่อเทียบกับกลุ่มควบคุมในผู้ที่มีความดันโลหิตเลือดปอดสูง สรุปได้ว่า โปรแกรมการออกกำลังกายได้การดูแลอาจช่วยให้ค่าการใช้ออกซิเจนสูงสุด และความแข็งแรงของ กล้ามเนื้อดีขึ้นได้ และไม่ส่งผลกระทบให้มีความเสี่ยงต่อเหตุการณ์ไม่พึงประสงค์ร้ายแรงเพิ่มขึ้น อย่างไรก็ตาม สำหรับผู้ที่มีความดันโลหิตเลือดปอดสูงแบบรุนแรง ควรมีการพิจารณาอย่างรอบคอบในการ ออกกำลังกาย

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คำสำคัญ: การออกกำลังกาย ความแข็งแรงของกล้ามเนื้อ การวิเคราะห์อภิมาน ภาวะความดัน
โลหิตเลือดปอดสูง การทบทวนอย่างเป็นระบบ ค่าการใช้ออกซิเจนสูงสุด

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