Effects of Exercise Training in Postoperative Patients With Congenital Heart Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Background—The purpose of this meta-analysis is to assess the effects of exercise training on quality of life, specific biomarkers, exercise capacity, and vascular function in congenital heart disease (CHD) subjects after surgery.

Methods and Results—We searched the Cochrane Central Register of Controlled Trials, MEDLINE, and EMBASE from the date of the inception of the database through April 2019. Altogether, 1161 records were identified in the literature search. Studies evaluating outcomes before and after exercise training among postoperative patients with congenital heart disease were included. The assessed outcomes were exercise capacity, vascular function, serum NT-proBNP (N-terminal pro-B-type natriuretic peptide) levels and quality of life. We analyzed heterogeneity by using the I² statistic and evaluated the evidence quality according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines. Nine randomized controlled trials were included. The evidence indicated that exercise interventions increased the one of the quality of life questionnaire score (mean difference=3.19 [95% CI, 0.23, 6.16]; P=0.03; I²=39%) from the score before the interventions. However, no alterations in exercise capacity, vascular function, NT-proBNP or quality of life were observed after exercise training. The results of the subgroup analysis showed that NT-proBNP levels were lower in the group with exercise training than in the group without exercise training over the same duration of follow-up. The evidence quality was generally assessed to be low.

Conclusions—in conclusion, there is insufficient evidence to suggest that physical exercise improves long-term follow-up outcomes of congenital heart disease, although it has some minor effects on quality of life. (J Am Heart Assoc. 2020;9:e013516. DOI: 10.1161/JAHA.119.013516.)

Key Words: congenital heart disease • exercise training • meta-analysis

Congenital heart disease (CHD) is one of the most common birth defects in the world.¹ Reportedly, the total CHD birth prevalence worldwide is 8.0% to 9.1%,²,³ and ≈1.35 million infants are born with CHD every year.³ From 2000 to 2010, the CHD prevalence rates increased by 11% and 57% among children and adults, respectively.⁴ With the improvement of CHD medical care, catheter interventions, and surgical procedures over the past 2 decades, increasing numbers of CHD patients can be treated, which improves survival for these patients.⁵–⁷ However, research on cardiac surgery in patients with CHD has shown cognitive dysfunc-

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**Clinical Perspective**

**What Is New?**

- This study is a systematic review of the literature on the effects of exercise training in patients with congenital heart disease (CHD).
- The findings suggest that CHD-TNO/AZL Adult Quality of Life (CHD-TAAQOL) questionnaire (impact) scale scores increase after exercise training.

**What Are the Clinical Implications?**

- The current meta-analysis provides weight to the increasing evidence supporting exercise training as a postoperative strategy to improve the prognosis of CHD patients.
- Compared with the usual interventions, exercise interventions have been shown to improve quality of life among patients with CHD.

The recruitment of participants in different age groups in different trials may weaken the generalizability of previous results to the broader population of CHD patients. Previously, a similar meta-analysis focused on aerobic capacity and pulmonary function, although few randomized clinical trials were included, which may result in increased bias. To our knowledge, no systematic reviews and meta-analyses of randomized clinical trials have addressed exercise training in postoperative CHD patients thus far. The goal of this study was to estimate the effects of exercise training on exercise capacity, vascular function, disease-specific biomarkers, and quality of life in postoperative CHD patients.

**Method**

The authors declare that all supporting data are available within the article (and its supplementary files).

**Search Strategy**

Two independent authors (C.X. and X.S.) searched all scientific publications reporting follow-up outcomes of an exercise training program in patients with CHD who had undergone cardiac surgery. PubMed, Embase, and Web of Science were searched from inception to April 1, 2019. The search strategy combined 3 concepts: the disease of interest (CHD), method of intervention (exercise training program), and outcome of interest (follow-up). We applied Medical Subject Headings to ensure precise keyword terms. The keyword terms are listed in Table S1. The search strategy was in accord with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. No language or other restrictions were applied. This study is registered with PROSPERO (CRD42019128366).

**Study Selection**

After integrating all searched articles to EndNote software, duplicate studies were removed (n=56). The remaining studies were reviewed by 2 independent investigators (C.X. and X.S.) to determine eligibility according to inclusion and exclusion criteria. If ambiguity arose, the third author (S.Y.M.) made a final decision. The flow chart is presented in Figure 1.

**Data Analysis and Statistics**

The Newcastle–Ottawa Quality Assessment Scale for Cohort Studies was analyzed to assess the quality and risk of bias of included studies.

The exercise capacity (peak oxygen uptake [VO2]), vascular function (systolic blood pressure [SBP], heart rate [HR]), disease-specific biomarkers (serum NT-proBNP [N-terminal pro-B-type natriuretic peptide] levels), and quality of life (Short Form 36 item [SF-36] health survey and CHD-TNO/AZL Adult Quality of Life [CHD-TAAQOL] questionnaire) were selected as evaluated outcomes of our concern. The SBP and HR values contain the resting and max conditions. SF-36 scores were combined into 2 higher-ordered clusters: the physical component summary and the mental component summary. CHD-TAAQOL contains 3 subscales: symptoms, worries, and impacts of the medical examinations.

Because the outcomes of several studies were reported as medians and interquartile ranges only, we replaced means with medians and replaced standard deviations with interquartile ranges divided by 1.35 in the case of data with a normal distribution according to the Cochrane Handbook for Systematic Reviews of Interventions guidelines (Cochrane Handbook for Systematic Reviews of Interventions).

Review Manager software version 5.3 (The Cochrane Collaboration) and Stata version 12.0 (StataCorp, College Station, TX) were used in the present study. The I² statistic was used to assess the heterogeneity of the results. A random-effects model was used when moderate or high heterogeneity was detected, and a fixed-effects model was used when no or low heterogeneity was observed. The results are presented as the standardized mean differences and 95% CIs as well as forest plots. Sensitivity analysis, which involved computing the meta-analysis estimate after omitting 1 study at a time, was calculated to evaluate the contribution of each study. We conducted a meta-regression analysis with changes in NT-proBNP level or SBP or the CHD-TAAQOL worries scale as the dependent variable and the following characteristic variables as independent variables: sample size, age, percentage of patients with New York Heart Association (NYHA)
class I and male patients, and β-blocker use. Follow-up time was extracted from every included study.

We performed Egger's test to assess the risk of publication bias for each outcome. The risk of bias of every included study was assessed according to the recommendation by the Cochrane Collaboration. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used to evaluate the quality of the evidence for each outcome.

Result

Study, Patient, and Intervention Characteristics

Eight of 9 studies were published after 2012 and were performed in Europe (Table). The median follow-up was 12 weeks, with 6 studies reporting at least 12 weeks of follow-up and 1 reporting a follow-up of 3 years. Although some included studies were multicenter studies (5 participating centers of pediatric cardiology, 4 centers), a total of 167 samples were included (median n=20; range 9 to 24). In all, a number of 66 subjects (40% of all participants) resulted from the 3 large multicenter trials contributing. The exercise interventions in each study were not identical. Each study had its own sports training program, which differed in terms of frequency and duration. In most studies, the intervention groups engaged in aerobic exercise, and the control group members were requested to continue their habitual daily activities. The intensity of each aerobic exercise was moderate, and training exercises included brisk walking, jogging, running, or bicycling. One study's intervention was divided into 3 phases, and the duration and frequency of exercise were increased incrementally in each. Two studies focused on standardized exercise training. Other studies' interventions mostly consisted of training sessions.

All the participants included had complex CHD. The average age of the recruited participants ranged from 14.8 to 40.1 years. The subjects of 3 studies were adolescents, and those of the remaining 5 were adults. Most participants were NYHA class I (median n=75%; range 54.2% to 100%), and fewer people used β-blocker drugs (median n=16.7%; range 11.1% to 33.3%).

Outcome Results

NT-proBNP

Three studies (n=87) reported the effect of exercise training intervention on serum NT-proBNP among postoperative CHD subjects (Figure S1A), and no statistically significant change in serum NT-proBNP was found with exercise training intervention (mean difference=−17.53 [95% CI, −80.48, 45.42]; P=0.59; I²=99%). After excluding the population with
### Table. Characteristics of the Included Studies

| Author, Y | % of Male | Location | Age (Y) | Sample Size | CHD Subtype | NYHA Class I (%) | β-Blocker Used (%) | Intervention | Outcome Assessment | Follow-Up Time |
|-----------|-----------|----------|---------|-------------|--------------|-----------------|-------------------|--------------|-------------------|----------------|
| Winter, 2012 | 38% | Netherlands and Italy | 31±10 | 24 | TGA | 75 | 20.8 | Exercise training protocol of 10 consecutive weeks | NT-proBNP; peak VO₂; SF-36; CHD-TAAQOL; Hemodynamics | 10 wk |
| Westhoff-Bleck, 2013 | 54% | Germany | 29.9±3.1 | 19 | D-TGA | 54.2 | 16.7 | 6-month aerobic exercise training | Peak VO₂ | 24 wk |
| Dulfer, 2014 | 72.2% | Netherlands | 15.2 | 20 | ToF | NP | NP | Three training sessions of 1 h per week, over a 3-month period | SF-36; CHD-TAAQOL | 12 wk |
| Duppen, 2015a | 74.5% | Netherlands | 16.1±2.6 | 24 | ToF | 78.7 | NP | A 12-wk standardized aerobic dynamic exercise training program | NT-proBNP | 12 wk |
| Duppen, 2015b | 72.1% | Netherlands | 14.8±3.7 | 23 | Fontan* | 72.1 | NP | A 12-wk standardized aerobic dynamic exercise training program | NT-proBNP | 12 wk |
| van der Bom, 2015 | 59% | Netherlands and Italy | 31±11 | 22 | TGA | 72.7 | 13.6 | Exercise training protocol of 10 consecutive wks | NT-proBNP; peak VO₂; SF-36; CHD-TAAQOL; Hemodynamics | 3 y |
| Novakovic, 2018a | 22% | Slovenia | 36.2±6.8 | 9 | TOF | 100 | 11.1 | Interval training | Hemodynamics; NT-proBNP; peak VO₂; SF-36 | 12 wk |
| Novakovic, 2018b | 44% | Slovenia | 40.1±10.4 | 9 | TOF | 100 | 33.3 | Continuous training | Hemodynamics; NT-proBNP; peak VO₂; SF-36 | 12 wk |
| Therrien, 2003 | 58.8% | Canada | NP | 17 | ToF | NP | NP | Structured exercise program | Peak VO₂, heart rate max | 12 wk |

Age, mean±SD. CHD-TAAQOL indicates CHD-TNO/AZL Adult Quality of Life; NP, not reported; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SF-36, Short Form 36 item; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; VO₂, oxygen uptake.

*Fontan circulation.
biventricular CHD, the result suggested that exercise training intervention does not reduce serum NT-proBNP levels among postoperative CHD subjects (mean difference = -25.68 [95% CI, -101.25, 49.89]; P = 0.51; I² = 99%) (Figure S1B).

Quality of life
Participants demonstrated a slight but significant increase in the CHD-TAAQOL impact scales after exercise training (3 studies: mean difference = 3.19 [95% CI, 0.23, 6.16]; P = 0.03; I² = 39%), as shown in Figure 2. However, no significant differences in SF-36 (physical and mental health) and CHD-TAAQOL (symptoms and worries) scores were found between the exercise training intervention and control groups (Figure S2).

Hemodynamics
A total of 3 studies focused on hemodynamic outcomes, ie, SBP (resting), SBP (max), HR (resting), and HR (max); 1 research study focused on the HR (max) outcome. After meta-analysis, there were still no significant differences in hemodynamic outcomes between CHD patients with exercise training intervention and controls (Figure S3; SBP resting: mean difference = -2.14 [95% CI, -4.79, 9.07]; P = 0.55, I² = 64%; SBP max: mean difference = -2.30 [95% CI, -10.67, 6.07], P = 0.59, I² = 0%; HR resting: mean difference = -1.28 [95% CI, -3.22, 5.77], P = 0.58, I² = 0%; HR max: mean difference = -2.33 [95% CI, -10.23, 5.57], P = 0.56, I² = 0%).

Peak VO2
CHD patients who received exercise training intervention had similar postoperative physical fitness, measured by peak VO2, as patients who did not receive exercise training (mean difference = -1.63 [95% CI, -3.63, 0.36]; P = 0.11; I² = 0%, Figure S4).

Sensitivity Analysis
Meta-analyses of the changes in serum NT-proBNP levels and SBP rest levels (the 2 outcomes with high heterogeneity) after exercise training intervention were conducted after both including and excluding each study. After performing the sensitivity analysis, the results of the SBP rest levels were not changed, while the results of the serum NT-proBNP levels were changed (Figure S5). Therefore, we retained studies with the same follow-up times in a subgroup analysis and found that after exercise intervention, NT-proBNP levels were significantly reduced (Figure S6), suggesting that follow-up time had a substantial impact on NT-proBNP levels, which should be noted in future meta-analyses.

Meta-Regression Analysis
For serum NT-proBNP levels, we found that the follow-up time of the population was the only significant predictor of NT-proBNP changes (β = 0.17; P = 0.003) in a meta-regression analysis, as illustrated in Figure S7. Other variables, such as the percentage of male patients (P = 0.88), mean age (P = 0.77), sample size (P = 0.62), and percentage of NYHA class I patients (P = 0.45), were not correlated with the standardized mean differences of the change in NT-proBNP levels.

For resting SBP levels, we observed no significant correlations between the percentage of male patients (P = 0.32), mean age (P = 0.16), sample size (P = 0.12), percentage of NYHA class I patients (P = 0.12), percentage of β-blockers used (P = 0.96), follow-up time (P = 0.50), and resting SBP levels.

Publication Bias
We performed Egger’s test and graphed it with funnel plots (Figure S8). No evidence of publication bias (P = 0.351) for the CHD-TAAQOL impact scale was observed in the present study.

Risk of Bias
Overall, a low or unclear risk of bias existed in the included studies (Figure S9). Although all included studies were randomized clinical trial studies, 1 study had a high risk of bias because of nonblinded allocation. In addition,

Figure 2. Forest plot for the role of exercise training in CHD postoperative patients with CHD-TAAQOL impact score. CHD indicates congenital heart disease; CHD-TAAQOL, CHD-TNO/AZL Adult Quality of Life.

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performance and detection biases were unclear because of insufficient information regarding whether participants and personnel were blinded and insufficient information regarding whether investigators were blinded and, if so, who was blinded, to all clinical conditions of the participants. No other overt bias was presented in the reports of all included studies.

Quality of Evidence Assessment

According to the GRADE guidelines, the quality of evidence of each outcome is presented in Tables S2 through S5. We evaluated the inconsistency by comparing the results of the included studies. Because the existing selection, performance, and detection biases were in the included articles, all the outcomes were downgraded for risk of bias. In summary, the quality of evidence for the effects of exercise training on exercise capacity, vascular function, disease-specific biomarkers, and quality of life in postoperative CHD patients was assessed as low and unclear.

Discussion

This study is the first to systematically review and meta-analyze exercise interventions for patients with CHD after surgery. Our results showed that CHD-TAAQOL (impact) scale scores were increased after exercise training. However, exercise training did not increase exercise capacity, and most quality of life questionnaire scales as well as serum NT-proBNP, peak VO₂, and hemodynamics parameters were stable. The NT-proBNP results of the sensitivity analysis suggested that heterogeneity still existed. After removing the study with the different follow-up duration, we observed that NT-proBNP levels were significantly decreased in the exercise training intervention group. Additionally, no publication bias was found in our study, and the risk of bias and the quality of evidence presented in the study was low or unclear.

SF-36 and CHD-TAAQOL were 2 of the most common scales for assessing quality of life among CHD subjects. Three studies reported both SF-36 and CHD-TAAQOL scores. Our findings indicated an increase in CHD-TAAQOL (impact) scores after exercise training, which was consistent with a previous report. We speculated that a significant result existed in only 1 included study. The reason may be that the original purpose of the CHD-TAAQOL questionnaire design is for patients with CHD aged 17 to 32 years, while the mean age of subjects from the other 2 studies was over 31 years old. The CHD-TAAQOL (impact) questionnaire principally contains routine cardiac testing and medical follow-up questions, and the significant increase in the CHD-TAAQOL impact scales after exercise training suggested that exercise may improve cardiac function and reduce drug use in patients after CHD surgery. However, the specific impact needs to be determined by more specific questionnaire and laboratory tests. Although our study found that the SF-36 scale scores were negative before and after the intervention, Novakovic et al reported that SF-36 mental scores were increased in the continuous training group but not in the interval training group. It appears that continuous training may have positive effects on postoperative patients with CHD, although the molecular mechanisms need further study. The remaining included studies showed no differences in SF-36 or CHD-TAAQOL quality of life scores after exercise training.

Regarding hemodynamics, no differences among SBP (resting), SBP (max), HR (resting), and HR (max) were found between baseline and follow-up in the present meta-analyses. However, Winter et al found that exercise interventions can reduce resting SBP. Neither our meta-analyses nor the meta-regression results were able to address the positive findings, and the small sample size may be 1 of the reasons.

We found that the peak VO₂ was unchanged after exercise training. Four of the included studies found that exercise contributed to peak VO₂ elevation. The rest of the included articles showed no significant difference, and we speculate that the reason for this finding is that exercise is not helpful in improving peak VO₂, which may have been because of a long follow-up period of up to 3 years, suggesting that exercise may not be effective for long-term cardiopulmonary exercise capacity. Moreover, peak VO₂ is affected by many factors, such as muscle oxygenation, endothelial function, and muscle mass. In addition, our results are negative because the sample size is not large enough; furthermore, because of individual differences, the standard deviation of the peak VO₂ measurement results is large.

In our meta-analysis, serum NT-proBNP levels were similar at baseline and follow-up. Notably, interval training could decrease serum NT-proBNP. NT-proBNP plays a role in predicting prognosis in patients with heart failure, as it is mainly secreted by cardiomyocytes. Low NT-proBNP levels may predict good clinical outcomes and prognoses. The increased serum NT-proBNP concentrations were considered to be associated with impaired long-term prognosis of CHD. We speculated that interval training may have caused depressed NT-proBNP because interval training weakens the elevating effect of exercise treatment; furthermore, exercise itself possibly helps prevent heart failure. Moreover, we observed high heterogeneity in this outcome. Sensitivity analysis and meta-regression both indicated that the time of follow-up may be the reason for the high heterogeneity. This suggests that age may interfere with the effect of exercise training on NT-proBNP levels. However, studies have shown
that NT-proBNP levels are not associated with age\textsuperscript{42} or that NT-proBNP levels are positively correlated with age, although only among those older than 60 years.\textsuperscript{43} Although we excluded 1 study in our analysis in which the follow-up time was 3 years,\textsuperscript{18} the result showed that exercise training can significantly reduce the serum NT-proBNP concentration, although this could also be because of other biasing factors that we did not consider and the small sample size. Thus, more studies are needed to explain the effects of exercise training intervention and aging on serum NT-proBNP among postoperative patients with CHD.

The strengths of this meta-analysis were that all the included publications were randomized controlled studies, which helped to reduce bias. In the present study, we were able to evaluate the effects of exercise training on NT-proBNP, peak VO$_2$, hemodynamics, and quality of life simultaneously in a larger study sample through a meta-analysis of different studies and the attempt to adjust several confounding factors. Indeed, we used a meta-regression method and found that follow-up time was a potential predictor of exercise training results, as indicated by changes in serum NT-proBNP levels.

Several potential limitations exist in the present meta-analysis. First, the age span is large, and postoperative times were different in our included studies, which may dilute the positive effects of exercise intervention. A larger sample size and stratified analysis can help solve this problem. Second, the follow-up times ranged from 10 weeks to 3 years; however, if the follow-up time was too long, other factors, such as an individual’s different exercise habits, may have interfered with the potential positive effects of exercise intervention. Third, other factors such as arrhythmia might have affected the outcome indicators we observed. However, some articles did not include arrhythmia information, and some articles regarded arrhythmia as an exclusion criterion,\textsuperscript{16,20} so we were unable to conduct a subgroup analysis. Studies have reported that arrhythmia is associated with the NT-proBNP level.\textsuperscript{44} Fourth, although the intervention groups were all exercise interventions, the specific intervention measures in each study were not exactly the same. Thus, the different effects of intervention measures could not be explained, and the possible effects could not be ruled out. Fifth, the standard deviations of some parameters were converted by quartiles. The handbook for systematic reviews of interventions suggested that the means and standard deviations could be replaced with medians and $r$ interquartile ranges divided by 1.35; however, a possible bias should not be excluded (Cochrane Handbook for Systematic Reviews of Interventions). Sixth, appropriate multiple comparison methods will be required in the future. Finally, all included patients had complex CHD and were NYHA class I/II; the effect of exercise may not be applicable to simple CHD patients or NYHA class III/IV.

Conclusions

Our meta-analysis suggests that there is currently little evidence from randomized studies supporting the idea that physical training improves the long-term follow-up prognosis of congenital heart defects, with the exception of some small effects on quality of life. Further explorations, including larger samples and well-designed prospective studies, are warranted to address these issues.

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Author contributions: C.X. and X.M. contributed to the design of this study. S.M. and Y.L.H. conducted eligible study selection, data extraction, and risk of bias assessment. Y.S. and Y.Z. performed the data analysis. C.X. drafted the manuscript. X.M. and C.X. edited and reviewed the manuscript.

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Disclosures

None.

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Supplemental Material
Table S1. Search strategy details.

Heart Defects, Congenital

- Congenital Heart Defect
- Defect, Congenital Heart
- Heart, Malformation Of
- Defects, Congenital Heart
- Heart Abnormalities
- Heart Defect, Congenital
- Abnormality, Heart
- Abnormalities, Heart
- Heart Abnormality
- Congenital Heart Defects

Pubmed: "Heart Defects, Congenital"[Mesh] OR (((((((((((Heart Defects, Congenital[Title/Abstract]) OR Congenital heart defect[Title/Abstract OR Congenital Heart Defect[Title/Abstract]) OR Defect, Congenital Heart[Title/Abstract]) OR Heart, Malformation Of[Title/Abstract]) OR Defects, Congenital Heart[Title/Abstract]) OR Heart Abnormalities[Title/Abstract]) OR Heart Defect, Congenital[Title/Abstract]) OR Abnormality, Heart[Title/Abstract]) OR Abnormalities, Heart[Title/Abstract]) OR Heart Abnormality[Title/Abstract]) OR Congenital Heart Defects[Title/Abstract]) OR Congenital heart defect[Title/Abstract]

Embase: 'congenital heart malformation'/exp ' OR congenital heart malformation' OR 'congenital heart defects':ti,ab OR 'heart abnormality':ti,ab OR 'abnormalities, heart':ti,ab OR 'abnormality, heart':ti,ab OR 'heart defect, congenital':ti,ab OR 'heart abnormalities':ti,ab OR 'defects, congenital heart':ti,ab OR 'heart, malformation of':ti,ab OR 'defect, congenital heart':ti,ab OR 'congenital heart defect':ti,ab OR 'heart defects, congenital':ti,ab

Cochrane: Heart Defects, Congenital:ti,ab,kw OR Congenital heart defect:ti,ab,kw OR Congenital Heart Defect:ti,ab,kw OR Defect, Congenital Heart:ti,ab,kw OR Heart, Malformation Of:ti,ab,kw OR Heart Abnormalities:ti,ab,kw OR Heart Defect, Congenital:ti,ab,kw OR Abnormality, Heart:ti,ab,kw OR Abnormalities, Heart:ti,ab,kw OR Heart Abnormality:ti,ab,kw OR Congenital Heart Defects:ti,ab,kw

Exercise

- Exercises
- Physical Activity
Activities, Physical
Activity, Physical
Physical Activities
Exercise, Physical
Exercises, Physical
Physical Exercise
Physical Exercises
Acute Exercise
Acute Exercises
Exercise, Acute
Exercises, Acute
Exercise, Isometric
Exercises, Isometric
Isometric Exercises
Isometric Exercise
Exercise, Aerobic
Aerobic Exercise
Aerobic Exercises
Exercises, Aerobic
Exercise Training
Exercise Trainings
Training, Exercise
Trainings, Exercise

Pubmed: "Exercise"[Mesh] OR (((((((((((Exercises [Title/Abstract]) OR Physical Activity[Title/Abstract OR Activities, Physical[Title/Abstract]) OR Activity, Physical[Title/Abstract]) OR Physical Activities[Title/Abstract]) OR Exercise, Physical [Title/Abstract]) OR Exercises, Physical[Title/Abstract]) OR Physical Exercise[Title/Abstract]) OR Physical Exercises[Title/Abstract]) OR Acute Exercise[Title/Abstract]) OR Acute Exercises[Title/Abstract]) OR Exercise, Acute[Title/Abstract]) OR Exercises, Acute[Title/Abstract]) OR Exercise, Isometric[Title/Abstract OR Exercises, Isometric[Title/Abstract]) OR Isometric Exercises[Title/Abstract]) OR Isometric Exercise[Title/Abstract]) OR Exercise, Aerobic[Title/Abstract]) OR Aerobic Exercises[Title/Abstract]) OR Aerobic Exercises[Title/Abstract]) OR Exercises, Aerobic[Title/Abstract]) OR Exercise Training[Title/Abstract]) OR Exercise Trainings[Title/Abstract]) OR Training, Exercise[Title/Abstract]) OR Trainings, Exercise[Title/Abstract])

Embase: 'Exercise'/exp ' OR Exercises' OR 'Physical Activity':ti,ab OR 'Activities, Physica':ti,ab OR 'Activity, Physical':ti,ab OR 'Physical Activities':ti,ab OR 'Exercise, Physical':ti,ab OR 'Exercises, Physical':ti,ab OR 'Physical Exercise':ti,ab OR 'Physical Exercises':ti,ab OR 'Acute Exercise':ti,ab OR 'Acute Exercises':ti,ab OR 'Acute Exercises':ti,ab' Exercise, Acute':ti,ab OR 'Exercises, Acute':ti,ab OR 'Exercise,
Isometric:ti,ab OR 'Exercises, Isometric':ti,ab OR 'Isometric Exercises':ti,ab OR 'Isometric Exercise':ti,ab OR 'Exercise, Aerobic':ti,ab OR 'Aerobic Exercise':ti,ab OR 'Aerobic Exercises':ti,ab OR 'Exercises, Aerobic':ti,ab OR 'Exercise Trainings':ti,ab OR 'Exercise Training':ti,ab OR 'Training, Exercise':ti,ab OR 'Trainings, Exercise':ti,ab

Cochrane: Exercise:ti,ab,kw OR Exercises:ti,ab,kw OR Physical Activity:ti,ab,kw OR Activities:ti,ab,kw OR Physical Activity:ti,ab,kw OR Physical Exercise:ti,ab,kw OR Acute Exercise:ti,ab,kw OR Acute Exercises:ti,ab,kw OR Exercise:ti,ab,kw OR Isometric:ti,ab,kw OR Isometric Exercises:ti,ab,kw OR Isometric Exercise:ti,ab,kw OR Aerobic:ti,ab,kw OR Aerobic Exercise:ti,ab,kw OR Aerobic Exercises:ti,ab,kw OR Exercise Training:ti,ab,kw OR Exercise Trainings:ti,ab,kw OR Training, Exercise:ti,ab,kw OR Trainings, Exercise:ti,ab,kw

**Randomized controlled trial**

PUBMED: randomized controlled trial[Publication Type] OR Controlled clinical trial[Publication Type] OR randomized[Title/Abstract] OR Controlled[Title/Abstract] OR trial[Title/Abstract] OR random[Title/Abstract] OR placebo[Title/Abstract] OR groups[Title/Abstract]

EMBASE: 'randomized controlled trial':ti,ab OR 'controlled clinical trial':ti,ab OR 'randomized':ti,ab OR 'controlled':ti,ab OR 'trial':ti,ab OR 'random':ti,ab OR 'placebo':ti,ab OR 'groups':ti,ab OR 'double-blind':ti,ab
Table S2. Quality of evidence was assessed for each outcome using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines.

after exercise training compared to before exercise training for postoperative patients with congenital heart disease

| Patient or population: | postoperative patients with congenital heart disease |
|------------------------|-----------------------------------------------------|
| Settings:              | hospital                                            |
| Intervention:          | after exercise training                             |
| Comparison:            | before exercise training                            |

| Outcomes | Illustrative comparative risks* (95% CI) | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|----------|----------------------------------------|--------------------------|-----------------------------|-------------------------------|----------|
|          | Assumed risk                           | Corresponding risk       |                             |                               |          |
|          | Before exercise training               | After exercise training  |                             |                               |          |
| SBP, rest| The mean sbp, rest in the intervention groups was | 2.14 higher (4.79 lower to 9.07 higher) | 128 (4 studies) | ⊕⊕ ⊝ ⊝ low*<sup>a</sup> |          |
|          | Follow-up: 10/12/156 weeks              |                          |                             |                               |          |
| SBP, max | The mean sbp, max in the intervention groups was | 2.3 lower (10.67 lower to 6.07 higher) | 128 (4 studies) | ⊕⊕⊕ ⊝ moderate<sup>a</sup> |          |
|          | Follow-up: 10/12/156 weeks              |                          |                             |                               |          |
| HR, rest | The mean hr, rest in the intervention groups was | 1.28 higher (3.22 lower to 5.77 higher) | 128 (4 studies) | ⊕⊕⊕ ⊝ moderate<sup>a</sup> |          |
|          | Follow-up: 10/12/156 weeks              |                          |                             |                               |          |
| HR, max  | The mean hr, max in the intervention groups was | 2.33 lower (10.23 to 5.57 higher) | 146 (5 studies) | ⊕⊕⊕ ⊝ moderate<sup>a</sup> |          |
|          | Follow-up: 10/12/156 weeks              |                          |                             |                               |          |

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval;

GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

* due to high selection bias, and unclear selection bias, and unclear performance bias, and unclear detection bias

^ No explanation was provided
Table S3. Quality of evidence was assessed for each outcome using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines.

after exercise training compared to before exercise training for postoperative patients with congenital heart disease

| Outcomes                  | Illustrative comparative risks* (95% CI)                                                                 | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|---------------------------|-------------------------------------------------------------------------------------------------------------|--------------------------|------------------------------|---------------------------------|----------|
|                           | Assumed risk                                                                                               | Corresponding risk       |                             |                                 |          |
| Before exercise training  | After exercise training                                                                                   |                          |                              |                                 |          |
| CHD-TAAQOL(impact)        | The mean chd-taaqol(impact) in the intervention groups was                                                  | 3.19 higher (0.23 to 6.16 higher) | 132 (3 studies)              | ⊕⊕⊕⊕                            | moderate* |
| Follow-up: 10/12/156 weeks|                                                                                                             |                          |                              |                                 |          |
| CHD-TAAQOL(Worries)       | The mean chd-taaqol(worries) in the intervention groups was                                                 | 2.91 lower (9.88 lower to 4.07 higher) | 132 (3 studies)              | ⊕⊕⊕⊕                            | moderate* |
| Follow-up: 10/12/156 weeks|                                                                                                             |                          |                              |                                 |          |
| CHD-TAAQOL(Symptoms)      | The mean chd-taaqol(symptoms) in the intervention groups was                                                | 0.68 lower (4.23 lower to 2.87 higher) | 132 (3 studies)              | ⊕⊕⊕⊕                            | moderate* |
| Follow-up: 10/12/156 weeks|                                                                                                             |                          |                              |                                 |          |
| SF-36 (Mental health component) | The mean sf-36 (mental health component) in the intervention groups was                                    |                          | 120 (4 studies)              | ⊕⊕⊕⊕                            | moderate* |
| Follow-up: 10/12/156 weeks|                                                                                                             |                          |                              |                                 |          |
| SF-36 (Physical health component) | The mean sf-36 (physical health component) in the intervention groups was | 120 | ⊕⊕⊕⊕ | moderate* |
|----------------------------------|-------------------------------------------------------------------------|-----|------|----------|
| Follow-up: 10/12/156 weeks       | 0.37 higher (4.56 lower to 5.29 higher)                                 |     |      |          |

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

* due to high selection bias, and unclear selection bias, and unclear performance bias, and unclear detection bias
Table S4. Quality of evidence was assessed for each outcome using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines.

after exercise training compared to before exercise training for postoperative patients with congenital heart disease

Patient or population: postoperative patients with congenital heart disease

Settings: hospital

Intervention: after exercise training

Comparison: before exercise training

| Outcomes | Illustrative comparative risks* (95% CI) | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|----------|----------------------------------------|--------------------------|-----------------------------|---------------------------------|----------|
|          | Assumed risk                           | Corresponding risk       |                             |                                 |          |
|          | Before exercise training               | After exercise training  |                             |                                 |          |
| peak VO2 | Follow-up: 10/12/24/156 weeks          |                          |                             |                                 |          |
|          | The mean peak vo2 in the intervention  | 1.63 lower               | 184                         | ☞⊕⊕⊕                            |          |
|          | groups was                             |                          | (6 studies)                 |                                 |          |
|          | (3.63 lower to 0.36 higher)            |                          |                             |                                 |          |

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

* due to high selection bias, and unclear selection bias, and unclear performance bias, and unclear detection bias
Table S5. Quality of evidence was assessed for each outcome using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines.

exercise training for postoperative patients with congenital heart disease

| Outcomes | Illustrative comparative risks* (95% CI) | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|----------|-------------------------------------------|--------------------------|-----------------------------|---------------------------------|----------|
|          | Assumed risk | Corresponding risk |                               |                                  |          |
| NT-proBNP | Before exercise training                  | After exercise training  |                               |                                  |          |
| Follow-up: 10/12/156 weeks | The mean nt-proBNP in the intervention groups was | 174 | (5 studies) | ⊗⊗⊗⊗ | low*6 |
|          | 17.53 lower | (80.48 lower to 45.42 higher) |                               |                                  |          |

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

* due to high selection bias, and unclear selection bias, and unclear performance bias, and unclear detection bias

6 due to very serious inconsistency (I²=99%) with differing directions of effect

Patient or population: postoperative patients with congenital heart disease

Settings: hospital

Intervention: after exercise training

Comparison: before exercise training
Figure S1. Forest plot of the role of exercise training in CHD postoperative patients with serum NT-proBNP.

A. Overall population. B. Biventricular population.
Figure S2. Forest plot of the role of exercise training in CHD postoperative patients with quality of life.

A. SF-36 physical component summary. B. SF-36 mental component summary. C. CHD-TAAQOL worries score. D. CHD-TAAQOL symptoms score. CHD, congenital heart disease; SF-36, Short Form-36 item; CHD-TAAQOL, CHD-TNO/AZL Adult Quality of Life.
Figure S3. Forest plot of the role of exercise training in CHD postoperative patients with vascular function.

A. Resting SBP. B. SBP max. C. Resting HR. D. HR max. SBP, systolic blood pressure; HR, heart rate.
Figure S4. Forest plot of the role of exercise training in CHD postoperative patients with peak oxygen uptake (VO₂).

| Study or Subgroup        | Baseline Mean | Baseline SD | Baseline Total | Follow up Mean | Follow up SD | Follow up Total | Weight | Mean Difference IV, Fixed, 95% CI |
|--------------------------|---------------|-------------|----------------|----------------|--------------|----------------|--------|-----------------------------------|
| Novakovic 2018a          | 21.8          | 6.9         | 9              | 23.6           | 5.3          | 9              | 12.3%  | -1.80 [-7.48, 3.88]                |
| Novakovic 2018b          | 21.2          | 9.8         | 9              | 22.9           | 10.6         | 9              | 4.6%   | -1.70 [-11.04, 7.04]               |
| Therssen 2003            | 22.1          | 5.6         | 9              | 24.3           | 8.2          | 9              | 9.5%   | -2.20 [-8.69, 4.29]                |
| van der Born 2015        | 26.8          | 6.8         | 22             | 26.9           | 9.7          | 22             | 16.6%  | -0.10 [-5.00, 4.80]                |
| Washoff-Bleck 2013       | 24            | 5           | 19             | 25.9           | 6.1          | 19             | 31.7%  | -1.90 [-5.45, 1.65]                |
| Winter 2012              | 27            | 7           | 24             | 29             | 7           | 24             | 25.4%  | -2.00 [-5.96, 1.96]                |

Total (95% CI) 92 92 100.0% -1.63 [-3.63, 0.36]

Heterogeneity: Chi² = 4.56, df = 5 (P = 0.39); I² = 0%
Test for overall effect: Z = 1.60 (P = 0.11)
Figure S5. Sensitivity analysis for each outcome with high heterogeneity ($I^2>$50%).

A. The serum NT-proBNP. B. The SBP rest.
Figure S6. Subgroup analysis for serum NT-proBNP.

| Study or Subgroup | Baseline Mean | SD | Total | Follow up Mean | SD | Total | Mean Difference | IV, Fixed, 95% CI | Mean Difference | IV, Fixed, 95% CI |
|-------------------|---------------|----|-------|----------------|----|-------|-----------------|-------------------|-----------------|-------------------|
| Duppen 2015a      | 72.3          | 19.9 | 24    | 61.6          | 17 | 24    | 10.70 (0.23, 21.17) |                   |                 |                   |
| Duppen 2015b      | 128.7         | 16.6 | 23    | 122.9         | 20 | 23    | 5.89 (-4.51, 16.11) |                   |                 |                   |
| Novakovic 2018a   | 83            | 145.2 | 9 | 94 | 151.9 | 9 | 0.3% | -11.00 (-148.29, 126.29) |                   |                 |                   |
| Novakovic 2018b   | 202           | 170.4 | 9 | 199 | 220.7 | 9 | 0.2% | 12.00 (-170.16, 194.16) |                   |                 |                   |
| Total (95% CI)    | 65            |    |       | 65            |    | 100.6% | 8.16 (0.83, 15.48) |                   |                 |                   |

Heterogeneity: Chi² = 0.50, df = 3 (P = 0.92); I² = 0%
Test for overall effect: Z = 2.18 (P = 0.03)
Figure S7. Meta-regression analysis of SMD in serum NT-proBNP levels after exercise training in postoperative patients with CHD correlated with the mean follow-up time of participants.

Circles represent each study, and the size of each circle represents the weight of the study in the meta-analysis. SMD, standardized mean difference.
Figure S8. Funnel plots with pseudo 95% CIs for evaluating the publication bias of the included studies.

MD was plotted against SE for the CHD-TAAQOL impact score. No evidence of publication bias was present in the dataset.

CIs, confidence intervals; MD, mean difference; SE, standard error; CHD-TAAQOL, CHD-TNO/AZL Adult Quality of Life.
Figure S9. The risk of bias was presented according to the Cochrane Collaboration.

A. Risk of bias graph, based on assessment for each item. B. Risk of bias summary. Yellow, unclear risk of bias; red, high risk of bias; green, low risk of bias.
Supplemental References:

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