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

Cheng Xu, MD, PhD;* Xiaoqi Su, MM;* Siyu Ma, MM; Yaqin Shu, MD; Yuxi Zhang, MD; Yuanli Hu, MD; Xuming Mo, MD, PhD

***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 I^2 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; I^2=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 dysfunction,[8] affected hemodynamics, abnormal psychosocial development,[9] renal dysfunction, restrictive lung disease, anemia, cirrhosis, and reduced quality of life.[10] Thus, multi-aspect management is becoming progressively more important for cardiac surgery in patients with CHD.

An exercise training program is part of the multi-aspect management for postoperative patients with CHD and is recommended by the American Heart Association[11] and the European Society of Cardiology.[12] Exercise training can be considered beneficial to postoperative patients with CHD, as it enhances cardiovascular fitness, improves cardiac function, regulates renewal and regeneration capability, reduces inflammatory responses, elevates quality of life, and decreases the long-term risk of acquired heart disease.[13–15]

To date, few studies have focused on the effects of exercise training programs on cardiac surgery in patients with CHD.[16–23] Moreover, with the above studies including small samples and reaching different conclusions, the exact effects of exercise training programs remain unclear. Additionally, the

From the Department of Cardiothoracic Surgery, Children's Hospital of Nanjing Medical University, Nanjing, China

Accompanying Tables S1 through S5, Figures S1 through S9 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.013516

*Dr Xu and Dr Su contributed equally to this work and are co-first authors.

Correspondence to: Xuming Mo, MD, PhD, Department of Cardiothoracic Surgery, Children's Hospital of Nanjing Medical University, 72 Guangzhou Rd, Nanjing, 210008, China. E-mail: mohsuming15@sina.com

Received June 5, 2019; accepted November 15, 2019.

© 2020 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

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.

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,[24] 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.[25] 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.[26]

The exercise capacity (peak oxygen uptake [VO_2]), 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 I^2 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)

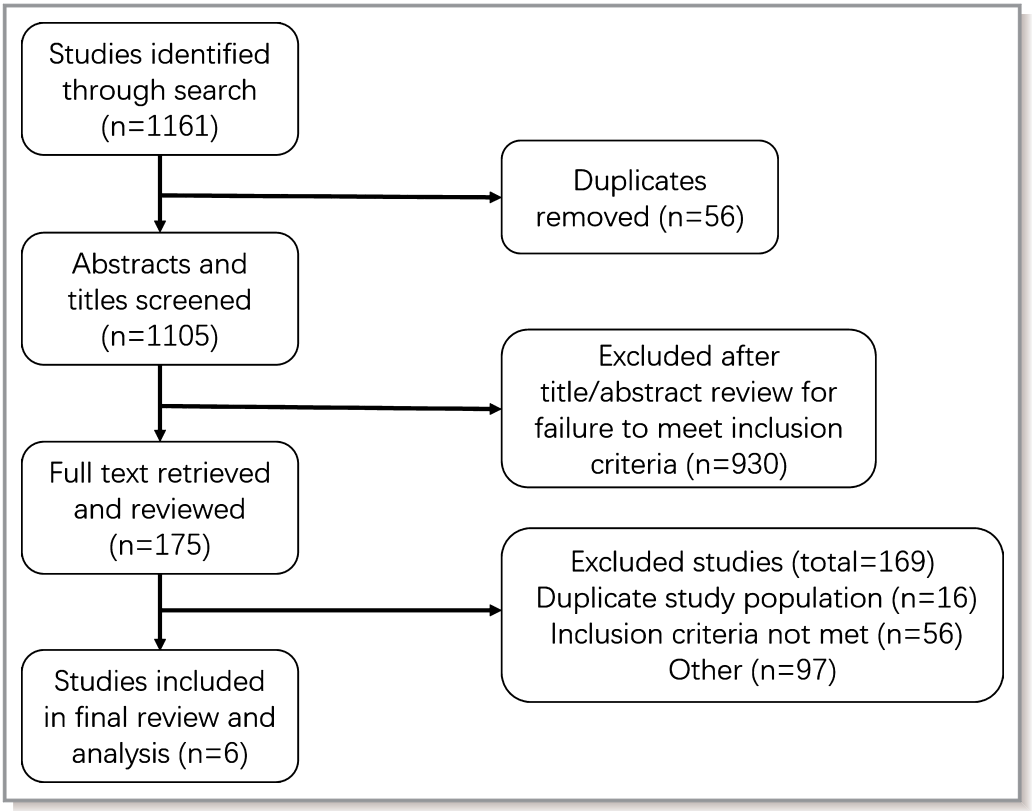


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart.

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.[27] 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;[22] 4 centers[16,18]), 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,[20] and the duration and frequency of exercise were increased incrementally in each. Two studies focused on standardized exercise training.[17,22] 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; I^2=99%). After excluding the population with

DOI: 10.1161/JAHA.119.013516

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[16]	38	Netherlands and Italy	31±10	24	TGA	75	20.8	Exercise training protocol of 10 consecutive weeks	NT-proBNP; peak VO_2; SF-36; CHD-TAAQOL; Hemodynamics	10 wk
Westhoff-Bleck, 2013[20]	54	Germany	29.9±3.1	19	D-TGA	54.2	16.7	6-month aerobic exercise training	Peak VO_2	24 wk
Dulfer, 2014[22]	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[17]	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[17]	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[18]	59	Netherlands and Italy	31±11	22	TGA	72.7	13.6	Exercise training protocol of 10 consecutive wks	NT-proBNP; peak VO_2; SF-36; CHD-TAAQOL; Hemodynamics	3 y
Novakovic, 2018a[19]	22	Slovenia	36.2±6.8	9	TOF	100	11.1	Interval training	Hemodynamics; NT-proBNP; peak VO_2; SF-36	12 wk
Novakovic, 2018b[19]	44	Slovenia	40.1±10.4	9	TOF	100	33.3	Continuous training	Hemodynamics; NT-proBNP; peak VO_2; SF-36	12 wk
Therrien, 2003[23]	58.8	Canada	NP	17	ToF	NP	NP	Structured exercise program	Peak VO_2, 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; VO_2, 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; I^2=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; I^2=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, I^2=64%; SBP max: mean difference=−2.30 [95% CI, −10.67, 6.07], *P*=0.59, I^2=0%; HR resting: mean difference=1.28 [95% CI, −3.22, 5.77], *P*=0.58, I^2=0%; HR max: mean difference=−2.33 [95% CI, −10.23, 5.57], *P*=0.56, I^2=0%).

Peak VO_2

CHD patients who received exercise training intervention had similar postoperative physical fitness, measured by peak VO_2, as patients who did not receive exercise training (mean difference=−1.63 [95% CI, −3.63, 0.36]; *P*=0.11; I^2=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.[19] In addition,

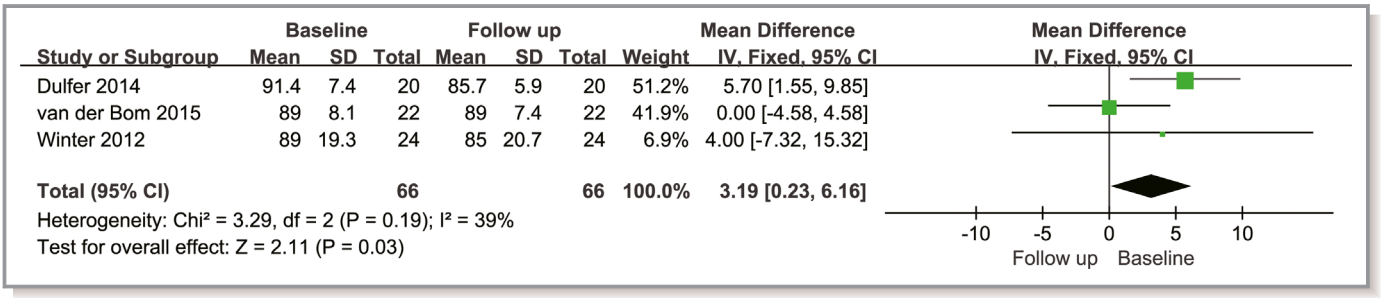


Figure 2. Forest plot for the role of exercise training in CHD postoperative patients with CHD-TAAQOL impact score[16,18,22] CHD indicates congenital heart disease; CHD-TAAQOL, CHD-TNO/AZL Adult Quality of Life.

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,[28–36] 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 VO_2, 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[18,19,22] and CHD-TAAQOL[16,18,22] scores. Our findings indicated an increase in CHD-TAAQOL (impact) scores after exercise training, which was consistent with a previous report.[22] 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,[37] while the mean age of subjects from the other 2 studies was over 31 years old.[16,18] The CHD-TAAQOL (impact) questionnaire principally contains routine cardiac testing and medical follow-up questions,[38] 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 questionnaires 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.[19] 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.[16] 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 VO_2 was unchanged after exercise training. Four of the included studies found that exercise contributed to peak VO_2 elevation.[16,19,20,23] 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 VO_2, which may have been because of a long follow-up period of up to 3 years,[18] suggesting that exercise may not be effective for long-term cardiopulmonary exercise capacity. Moreover, peak VO_2 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 VO_2 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.[19] NT-proBNP plays a role in predicting prognosis in patients with heart failure,[39,40] 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.[41] 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[42] or that NT-proBNP levels are positively correlated with age, although only among those older than 60 years.[43] Although we excluded 1 study in our analysis in which the follow-up time was 3 years,[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,[16,20] so we were unable to conduct a subgroup analysis. Studies have reported that arrhythmia is associated with the NT-proBNP level.[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.

Acknowledgments

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.

Sources of Funding

This work was supported by funding from the National Natural Science Foundation of China (81900281), the Maternal and Child Health Research Project of Jiangsu Province (F201755), the China Postdoctoral Science Foundation (2018M630585), the Key Project of Science and Technology Development Fund of Nanjing Medical University (2017NJMUZD060), the National Key Research and Development Program of China (2016YFC1101001, 2017YFC1308105), the Nanjing Medical University School Project (NMUC2018012A), and the Key Project supported by the Medical Science and Technology Development Foundation, Nanjing Department of Health (YKK18139).

Disclosures

None.

References

1. Fahed AC, Gelb BD, Seidman JG, Seidman CE. Genetics of congenital heart disease: the glass half empty. *Circ Res*. 2013;112:707–720.
2. Bouma BJ, Mulder BJ. Changing landscape of congenital heart disease. *Circ Res*. 2017;120:908–922.
3. van der Linde D, Konings EE, Slager MA, Witsenburg M, Helbing WA, Takkenberg JJ, Roos-Hesselink JW. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2011;58:2241–2247.
4. Marelli AJ, Ionescu-Ittu R, Mackie AS, Guo L, Dendukuri N, Kaouache M. Lifetime prevalence of congenital heart disease in the general population from 2000 to 2010. *Circulation*. 2014;130:749–756.
5. Oh H. Cell therapy trials in congenital heart disease. *Circ Res*. 2017;120:1353–1366.
6. Holst KA, Said SM, Nelson TJ, Cannon BC, Dearani JA. Current interventional and surgical management of congenital heart disease: specific focus on valvular disease and cardiac arrhythmias. *Circ Res*. 2017;120:1027–1044.
7. Warnes CA. Adult congenital heart disease: the challenges of a lifetime. *Eur Heart J*. 2017;38:2041–2047.

8. Cohen S, Earing MG. Neurocognitive impairment and its long-term impact on adults with congenital heart disease. *Prog Cardiovasc Dis*. 2018;61:287–293.
9. Cuypers JA, Utens EM, Roos-Hesselink JW. Health in adults with congenital heart disease. *Maturitas*. 2016;91:69–73.
10. Lui GK, Saidi A, Bhatt AB, Burchill LJ, Deen JF, Earing MG, Gewitz M, Ginns J, Kay JD, Kim YY, Kovacs AH, Krieger EV, Wu FM, Yoo SJ; American Heart Association Adult Congenital Heart Disease Committee of the Council on Clinical Cardiology and Council on Cardiovascular Disease in the Young; Council on Cardiovascular Radiology and Intervention; and Council on Quality of Care and Outcomes Research. Diagnosis and management of noncardiac complications in adults with congenital heart disease: a scientific statement from the American Heart Association. *Circulation*. 2017;136:e348–e392.
11. Pina IL, Apstein CS, Balady GJ, Belardinelli R, Chaitman BR, Duscha BD, Fletcher BJ, Fleg JL, Myers JN, Sullivan MJ; American Heart Association Committee on exercise, rehabilitation, and prevention. Exercise and heart failure: a statement from the American Heart Association Committee on exercise, rehabilitation, and prevention. *Circulation*. 2003;107:1210–1225.
12. Takken T, Giardini A, Reybrouck T, Gewillig M, Hovels-Gurich HH, Longmuir PE, McCrindle BW, Paridon SM, Hager A. Recommendations for physical activity, recreation sport, and exercise training in paediatric patients with congenital heart disease: a report from the exercise, basic & translational research section of the European Association of Cardiovascular Prevention and Rehabilitation, the European Congenital Heart and Lung Exercise Group, and the Association for European Paediatric Cardiology. *Eur J Prev Cardiol*. 2012;19:1034–1065.
13. Swift DL, Lavie CJ, Johannsen NM, Arena R, Earnest CP, O'Keefe JH, Milani RV, Blair SN, Church TS. Physical activity, cardiorespiratory fitness, and exercise training in primary and secondary coronary prevention. *Circ J*. 2013;77:281–292.
14. Ellison GM, Waring CD, Vicinanza C, Torella D. Physiological cardiac remodelling in response to endurance exercise training: cellular and molecular mechanisms. *Heart*. 2012;98:5–10.
15. Lavie CJ, Church TS, Milani RV, Earnest CP. Impact of physical activity, cardiorespiratory fitness, and exercise training on markers of inflammation. *J Cardiopulm Rehabil Prev*. 2011;31:137–145.
16. Winter MM, van der Bom T, de Vries LC, Balducci A, Bouma BJ, Pieper PG, van Dijk AP, van der Plas MN, Picchio FM, Mulder BJ. Exercise training improves exercise capacity in adult patients with a systemic right ventricle: a randomized clinical trial. *Eur Heart J*. 2012;33:1378–1385.
17. Duppen N, Kapusta L, de Rijke YB, Snoeren M, Kuipers IM, Koopman LP, Blank AC, Blom NA, Dulfer K, Utens EM, Hopman MT, Helbing WA. The effect of exercise training on cardiac remodelling in children and young adults with corrected tetralogy of fallot or fontan circulation: a randomized controlled trial. *Int J Cardiol*. 2015;179:97–104.
18. van der Bom T, Winter MM, Knaake JL, Cervi E, de Vries LS, Balducci A, Meregalli PG, Pieper PG, van Dijk AP, Bonvicini M, Mulder BJ, Bouma BJ. Long-term benefits of exercise training in patients with a systemic right ventricle. *Int J Cardiol*. 2015;179:105–111.
19. Novakovic M, Prokselj K, Rajkovic U, Vizintin Cuderman T, Jansa Trontelj K, Fras Z, Jug B. Exercise training in adults with repaired tetralogy of fallot: a randomized controlled pilot study of continuous versus interval training. *Int J Cardiol*. 2018;255:37–44.
20. Westhoff-Bleck M, Schieffer B, Tegtbur U, Meyer GP, Hoy L, Schaefer A, Tallone EM, Tutarel O, Mertins R, Wilmink LM, Anker SD, Bauersachs J, Roentgen P. Aerobic training in adults after atrial switch procedure for transposition of the great arteries improves exercise capacity without impairing systemic right ventricular function. *Int J Cardiol*. 2013;170:24–29.
21. Klausen SH, Andersen LL, Sondergaard L, Jakobsen JC, Zoffmann V, Dideriksen K, Kruse A, Mikkelsen UR, Wetterslev J. Effects of ehealth physical activity encouragement in adolescents with complex congenital heart disease: the prevail randomized clinical trial. *Int J Cardiol*. 2016;221:1100–1106.
22. Dulfer K, Duppen N, Kuipers IM, Schokking M, van Domburg RT, Verhulst FC, Helbing WA, Utens EM. Aerobic exercise influences quality of life of children and youngsters with congenital heart disease: a randomized controlled trial. *J Adolesc Health*. 2014;55:65–72.
23. Therrien J, Fredriksen P, Walker M, Granton J, Reid GJ, Webb G. A pilot study of exercise training in adult patients with repaired tetralogy of fallot. *Can J Cardiol*. 2003;19:685–689.
24. Gomes-Neto M, Saquetto MB, da Silva e Silva CM, Conceicao CS, Carvalho VO. Impact of exercise training in aerobic capacity and pulmonary function in children and adolescents after congenital heart disease surgery: a systematic review with meta-analysis. *Pediatr Cardiol*. 2016;37:217–224.
25. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*. 2009;339:b2700.
26. Wells GSB, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. Ottawa Hospital Research Institute. The newcastle-ottawa scale (nos) for assessing the quality of nonrandomised studies in meta-analyses. 2000. Available at: http://www.Ohri.Ca/programs/clinical_epidemiology/oxford.Asp. Accessed November 17, 2019.
27. Bandeira-Echtler E, Bergerhoff K, Richter B. Levothyroxine or minimally invasive therapies for benign thyroid nodules. *Cochrane Database Syst Rev*. 2014:CD004098.
28. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, Norris S, Falck-Ytter Y, Glasziou P, DeBeer H, Jaeschke R, Rind D, Meerpohl J, Dahm P, Schunemann HJ. Grade guidelines: 1. Introduction-grade evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011;64:383–394.
29. Guyatt GH, Oxman AD, Kunz R, Atkins D, Brozek J, Vist G, Alderson P, Glasziou P, Falck-Ytter Y, Schunemann HJ. Grade guidelines: 2. Framing the question and deciding on important outcomes. *J Clin Epidemiol*. 2011;64:395–400.
30. Balshem H, Helfand M, Schunemann HJ, Oxman AD, Kunz R, Brozek J, Vist GE, Falck-Ytter Y, Meerpohl J, Norris S, Guyatt GH. Grade guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol*. 2011;64:401–406.
31. Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, Montori V, Akl EA, Djulbegovic B, Falck-Ytter Y, Norris SL, Williams JW Jr, Atkins D, Meerpohl J, Schunemann HJ. Grade guidelines: 4. Rating the quality of evidence–study limitations (risk of bias). *J Clin Epidemiol*. 2011;64:407–415.
32. Guyatt GH, Oxman AD, Montori V, Vist G, Kunz R, Brozek J, Alonso-Coello P, Djulbegovic B, Atkins D, Falck-Ytter Y, Williams JW Jr, Meerpohl J, Norris SL, Akl EA, Schunemann HJ. Grade guidelines: 5. Rating the quality of evidence–publication bias. *J Clin Epidemiol*. 2011;64:1277–1282.
33. Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, Devereaux PJ, Montori VM, Freyschuss B, Vist G, Jaeschke R, Williams JW Jr, Murad MH, Sinclair D, Falck-Ytter Y, Meerpohl J, Whittington C, Thorlund K, Andrews J, Schunemann HJ. Grade guidelines 6. Rating the quality of evidence–imprecision. *J Clin Epidemiol*. 2011;64:1283–1293.
34. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, Alonso-Coello P, Glasziou P, Jaeschke R, Akl EA, Norris S, Vist G, Dahm P, Shukla VK, Higgins J, Falck-Ytter Y, Schunemann HJ; GRADE Working Group. Grade guidelines: 7. Rating the quality of evidence–inconsistency. *J Clin Epidemiol*. 2011;64:1294–1302.
35. Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, Alonso-Coello P, Falck-Ytter Y, Jaeschke R, Vist G, Akl EA, Post PN, Norris S, Meerpohl J, Shukla VK, Nasser M, Schunemann HJ; GRADE Working Group. Grade guidelines: 8. Rating the quality of evidence–indirectness. *J Clin Epidemiol*. 2011;64:1303–1310.
36. Guyatt GH, Oxman AD, Sultan S, Glasziou P, Akl EA, Alonso-Coello P, Atkins D, Kunz R, Brozek J, Montori V, Jaeschke R, Rind D, Dahm P, Meerpohl J, Vist G, Berliner E, Norris S, Falck-Ytter Y, Murad MH, Schunemann HJ; GRADE Working Group. Grade guidelines: 9. Rating up the quality of evidence. *J Clin Epidemiol*. 2011;64:1311–1316.
37. Kamphuis M, Zwinderman KH, Vogels T, Vliegen HW, Kamphuis RP, Ottenkamp J, Verloove-Vanhorick SP, Bruil J. A cardiac-specific health-related quality of life module for young adults with congenital heart disease: development and validation. *Qual Life Res*. 2004;13:735–745.
38. Pike NA, Evangelista LS, Doering LV, Koniak-Griffin D, Lewis AB, Child JS. Clinical profile of the adolescent/adult fontan survivor. *Congenit Heart Dis*. 2011;6:9–17.
39. Troughton R, Michael Felker G, Januzzi JL Jr. Natriuretic peptide-guided heart failure management. *Eur Heart J*. 2014;35:16–24.
40. Maisel AS, Duran JM, Wettersten N. Natriuretic peptides in heart failure: atrial and B-type natriuretic peptides. *Heart Fail Clin*. 2018;14:13–25.
41. Bolger AP, Sharma R, Li W, Leenarts M, Kalra PR, Kemp M, Coats AJ, Anker SD, Gatzoulis MA. Neurohormonal activation and the chronic heart failure syndrome in adults with congenital heart disease. *Circulation*. 2002;106:92–99.
42. Frankenstein L, Clark AL, Goode K, Ingle L, Remppis A, Schellberg D, Grabs F, Nelles M, Cleland JG, Katus HA, Zugck C. The prognostic value of individual NT-probnp values in chronic heart failure does not change with advancing age. *Heart*. 2009;95:825–829.
43. Zhang J, Wong KY, Clark AL, Cleland JG. Exploring the relation between changes in NT-probnp and renal function in patients with suspected heart failure using structural equation modelling. *Int J Cardiol*. 2017;233:67–72.
44. Ozmen C, Deniz A, Deveci OS, Cagliyan CE, Celik AI, Yildiz I, Yildiz PO, Demir M, Kanadasi M. Association among tenascin-C and NT-probnp levels and arrhythmia prevalence in heart failure. *Clin Invest Med*. 2017;40:E219–E227.

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':ti,ab OR 'Training, Exercise':ti,ab':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, Physical:ti,ab,kw OR Activity, Physical:ti,ab,kw OR Physical Activities:ti,ab,kw OR Exercise, Physical:ti,ab,kw OR Exercises, Physical:ti,ab,kw OR Physical Exercise:ti,ab,kw OR Physical Exercises:ti,ab,kw OR Acute Exercise:ti,ab,kw OR Acute Exercises:ti,ab,kw OR Exercise, Acute:ti,ab,kw OR Exercises, Acute:ti,ab,kw OR Exercise, Isometric:ti,ab,kw OR Exercises, Isometric :ti,ab,kw OR Isometric Exercises:ti,ab,kw OR Isometric Exercise:ti,ab,kw OR Exercise, Aerobic:ti,ab,kw OR Aerobic Exercise:ti,ab,kw:ti,ab,kw OR Aerobic Exercises:ti,ab,kw OR Exercises, Aerobic: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		128	⊕⊕⊖⊖	
Follow-up: 10/12/156 weeks		**2.14 higher**		(4 studies)	**low**[#,&]	
		(4.79 lower to 9.07 higher)				
SBP, max		The mean sbp, max in the intervention groups was		128	⊕⊕⊕⊖	
Follow-up: 10/12/156 weeks		**2.3 lower**		(4 studies)	**moderate**[#]	
		(10.67 lower to 6.07 higher)				
HR, rest		The mean hr, rest in the intervention groups was		128	⊕⊕⊕⊖	
Follow-up: 10/12/156 weeks		**1.28 higher**		(4 studies)	**moderate**[#]	
		(3.22 lower to 5.77 higher)				
HR, max		The mean hr, max in the intervention groups was		146	⊕⊕⊕⊖	
Follow-up: 10/12/156 weeks		**2.33 lower**		(5 studies)	**moderate**[#]	
		(10.23 to 5.57 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

[&] 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

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 **Before exercise training**	Corresponding risk **After exercise training**				
CHD-TAAQOL(impact) Follow-up: 10/12/156 weeks		The mean chd-taaqol(impact) in the intervention groups was **3.19 higher** (0.23 to 6.16 higher)		132 (3 studies)	⊕⊕⊕⊖ **moderate**[#]	
CHD-TAAQOL(Worries) Follow-up: 10/12/156 weeks		The mean chd-taaqol(worries) in the intervention groups was **2.91 lower** (9.88 lower to 4.07 higher)		132 (3 studies)	⊕⊕⊕⊖ **moderate**[#]	
CHD-TAAQOL(Symptoms) Follow-up: 10/12/156 weeks		The mean chd-taaqol(symptoms) in the intervention groups was **0.68 lower** (4.23 lower to 2.87 higher)		132 (3 studies)	⊕⊕⊕⊖ **moderate**[#]	
SF-36 (Mental health component) Follow-up: 10/12/156 weeks		The mean sf-36 (mental health component) in the intervention groups was		120 (4 studies)	⊕⊕⊕⊖ **moderate**[#]	

	2 lower (5.63 lower to 1.62 higher)		
SF-36 (Physical health component) Follow-up: 10/12/156 weeks	The mean sf-36 (physical health component) in the intervention groups was **0.37 higher** (4.56 lower to 5.29 higher)	120 (4 studies)	⊕⊕⊕⊖ **moderate**[#]

*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**	**No of Participants**	**Quality of the evidence**	**Comments**
	Assumed risk	Corresponding risk	**(95% CI)**	**(studies)**	**(GRADE)**	
	Before exercise training	**After exercise training**				
peak VO2		The mean peak vo2 in the intervention groups was		184	⊕⊕⊕⊖	
Follow-up: 10/12/24/156 weeks		**1.63 lower**		(6 studies)	**moderate**[#]	
		(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

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 **Before exercise training**	Corresponding risk **After exercise training**				
NT-proBNP Follow-up: 10/12/156 weeks		The mean nt-probnp in the intervention groups was **17.53 lower** (80.48 lower to 45.42 higher)		174 (5 studies)	⊕⊕⊖⊖ **low**[#,&]	

*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.

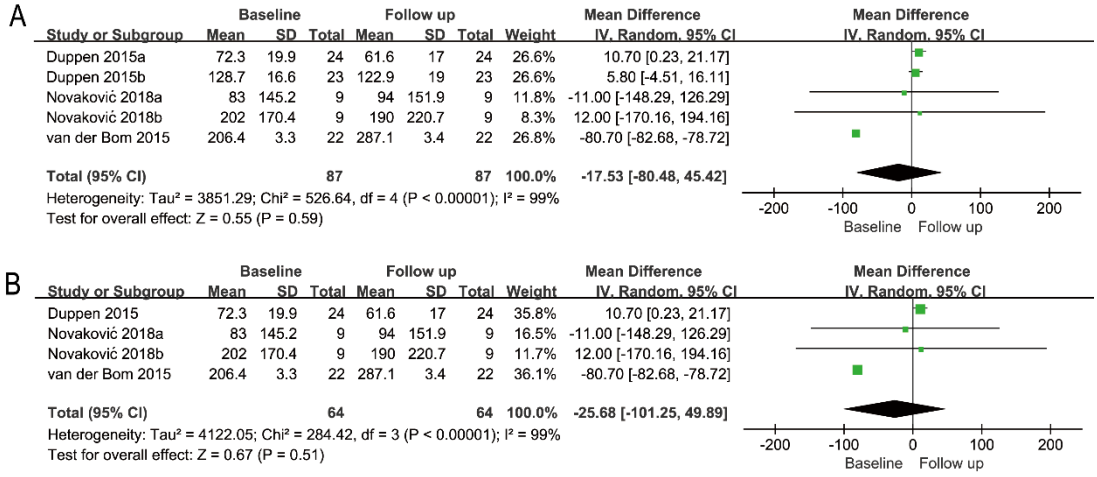
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

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

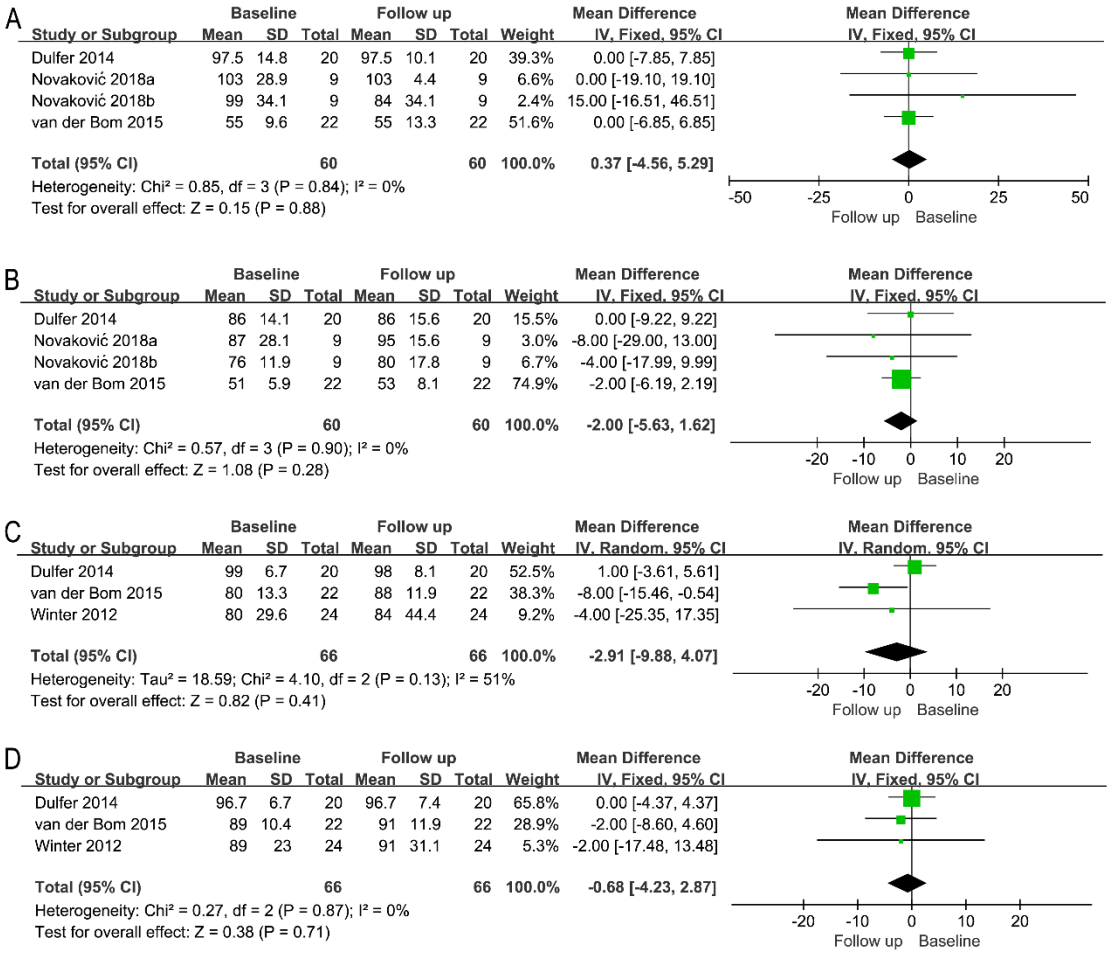
[&] due to very serious inconsistency (I2=99%) with differing directions of effect

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



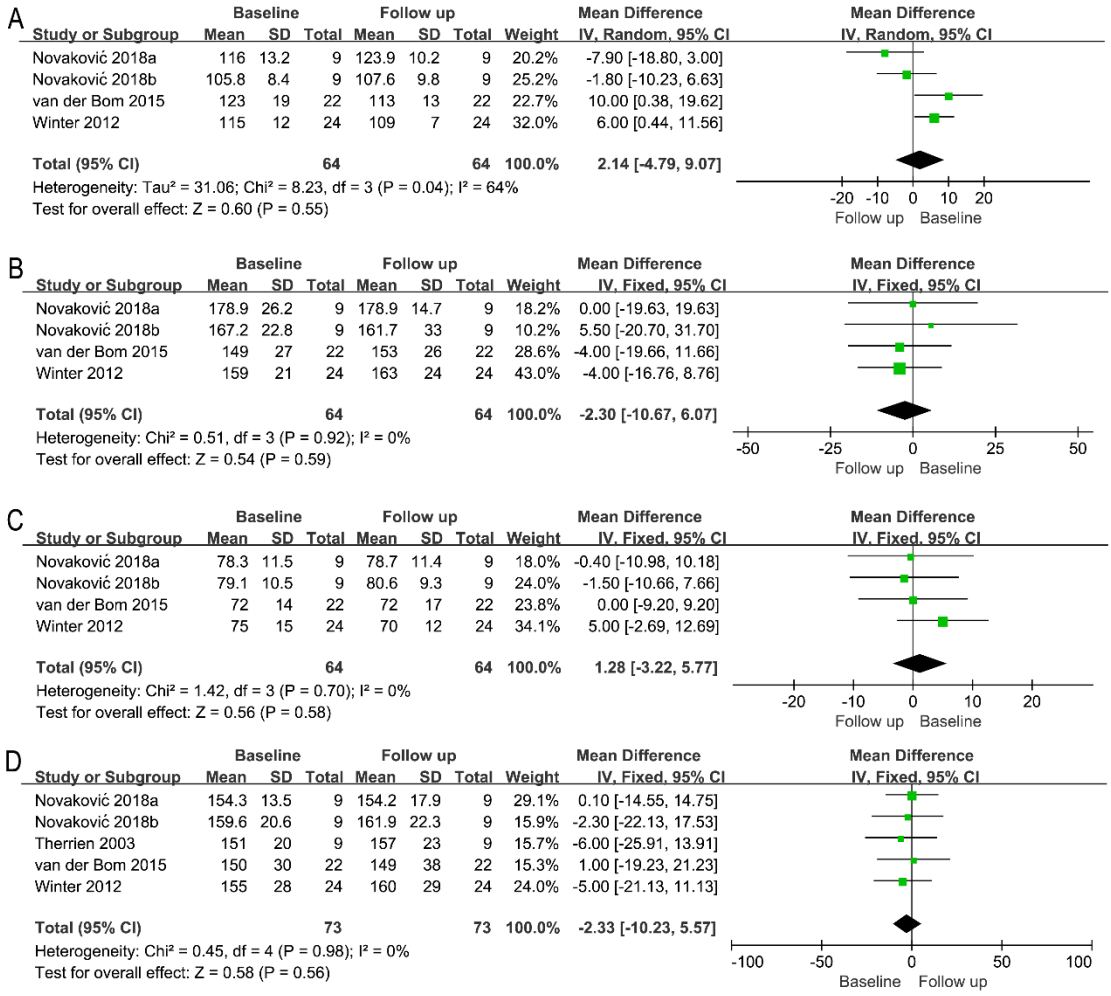
A. Overall population. B. Biventricular population.

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 (VO_2).

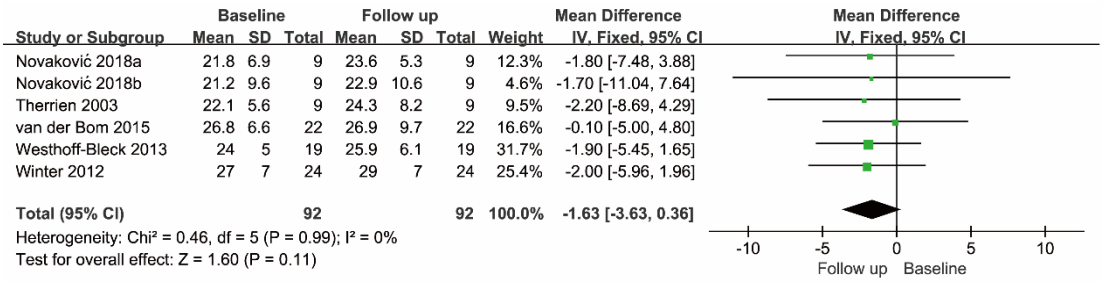
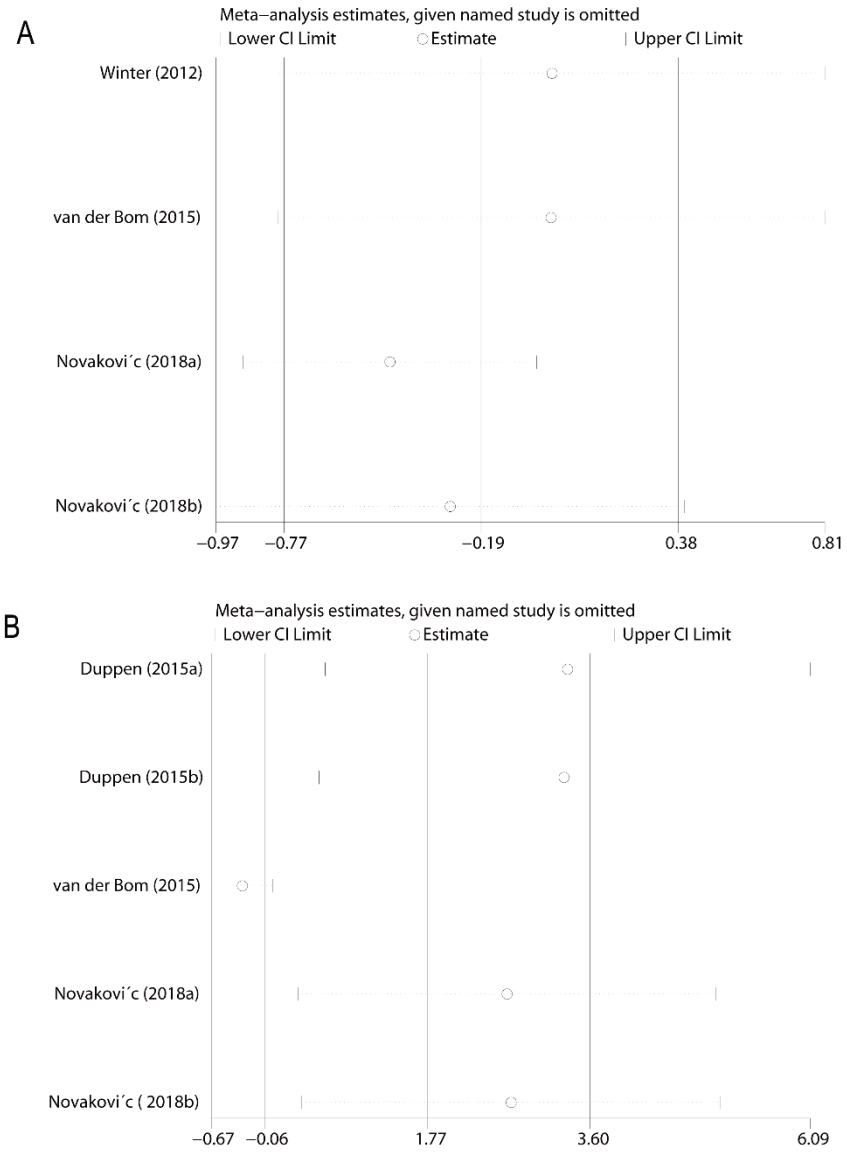


Figure S5. Sensitivity analysis for each outcome with high heterogeneity (I^2>50%).



A. The serum NT-proBNP. B. The SBP rest

Figure S6. Subgroup analysis for serum NT-proBNP.

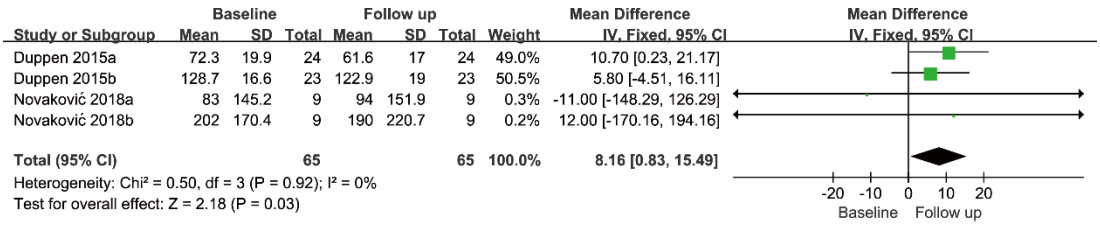
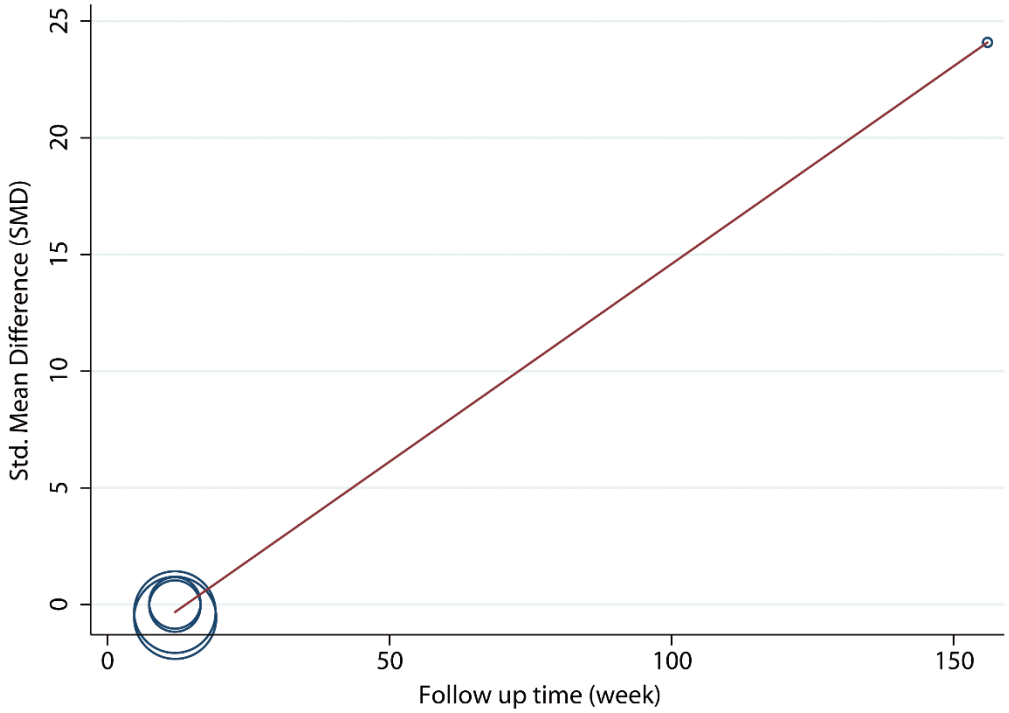
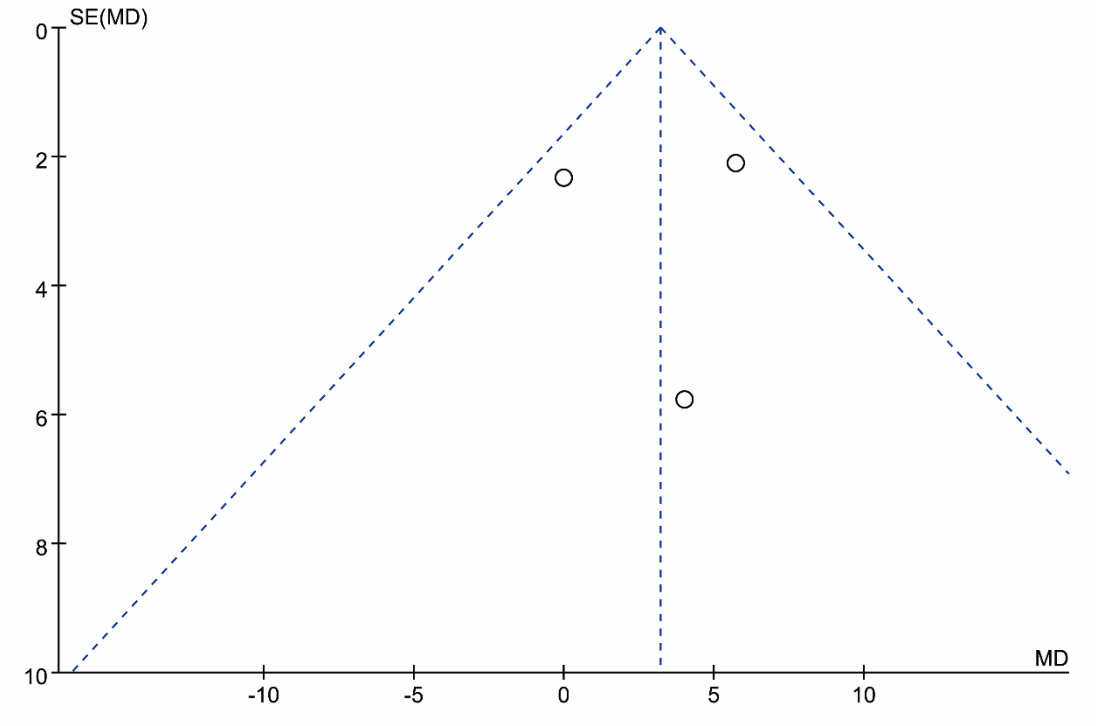


Figure S7. Meta-regression analysis of SMD in serum NT-proBNP levels after exercise training in postoperative patients with CHD correlated with the mean follow-up time of participants.



Circles represent each study, and the size of each circle represents the weight of the study in the meta-analysis. SMD, standardized mean difference.

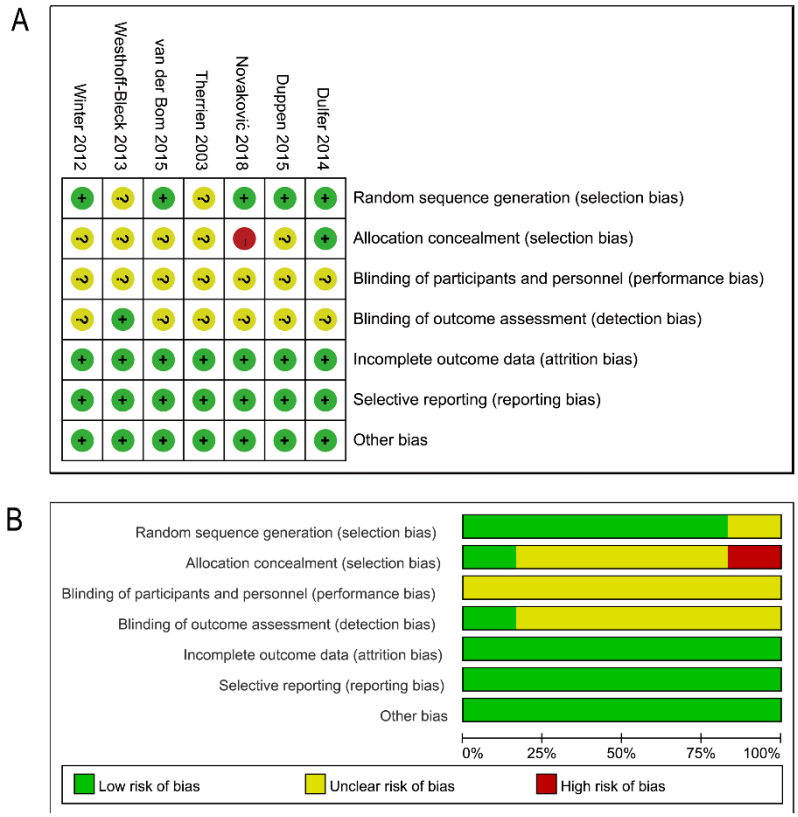
Figure S8. Funnel plots with pseudo 95% CIs for evaluating the publication bias of the included studies.



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:

1. Duppen N, Kapusta L, de Rijke YB, Snoeren M, Kuipers IM, Koopman LP, Blank AC, Blom NA, Dulfer K, Utens EM, Hopman MT, Helbing WA. The effect of exercise training on cardiac remodelling in children and young adults with corrected tetralogy of fallot or fontan circulation: A randomized controlled trial. International journal of cardiology. 2015;179:97-104
2. Novakovic M, Prokselj K, Rajkovic U, Vizintin Cuderman T, Jansa Trontelj K, Fras Z, Jug B. Exercise training in adults with repaired tetralogy of fallot: A randomized controlled pilot study of continuous versus interval training. International journal of cardiology. 2018;255:37-44
3. van der Bom T, Winter MM, Knaake JL, Cervi E, de Vries LS, Balducci A, Meregalli PG, Pieper PG, van Dijk AP, Bonvicini M, Mulder BJ, Bouma BJ. Long-term benefits of exercise training in patients with a systemic right ventricle. International journal of cardiology. 2015;179:105-111
4. Dulfer K, Duppen N, Kuipers IM, Schokking M, van Domburg RT, Verhulst FC, Helbing WA, Utens EM. Aerobic exercise influences quality of life of children and youngsters with congenital heart disease: A randomized controlled trial. The Journal of adolescent health : official publication of the Society for Adolescent Medicine. 2014;55:65-72
5. Winter MM, van der Bom T, de Vries LC, Balducci A, Bouma BJ, Pieper PG, van Dijk AP, van der Plas MN, Picchio FM, Mulder BJ. Exercise training improves exercise capacity in adult patients with a systemic right ventricle: A randomized clinical trial. European heart journal. 2012;33:1378-1385
6. Therrien J, Fredriksen P, Walker M, Granton J, Reid GJ, Webb G. A pilot study of exercise training in adult patients with repaired tetralogy of fallot. The Canadian journal of cardiology. 2003;19:685-689
7. Westhoff-Bleck M, Schieffer B, Tegtbur U, Meyer GP, Hoy L, Schaefer A, Tallone EM, Tutarel O, Mertins R, Wilmink LM, Anker SD, Bauersachs J, Roentgen P. Aerobic training in adults after atrial switch procedure for transposition of the great arteries improves exercise capacity without impairing systemic right ventricular function. International journal of cardiology. 2013;170:24-29