WEP Warwick Evans Publishing

Transactions on Materials, Biotechnology and Life Sciences
ISSN: 2960-1932, eISSN: 2960-2319 | Volume 8
MMTCS 2025

# A Personalized Aerobic Exercise Intervention for Chinese Adolescents with Congenital Heart Disease: A Methodological Framework for a Three-Year Longitudinal Study

Zinong Zhu *

Suzhou Foreign Language School, Suzhou, China

* Corresponding Author email: zhuzinong3377@outlook.com

**Abstract.** The population of adolescents with congenital heart disease (CHD) is expanding. With medical advances, the group of people who survive to adolescence with CHD continues to grow. In China, the challenges are further magnified by a sedentary lifestyle as a result of academic pressures and parental over-protection, underscoring how timely exercise interventions that are both safe and efficacious are needed. To meet this need, this paper presents a methodological framework for a three-year longitudinal study aimed at assessing an individualized aerobic exercise intervention. Methods/Design: The proposed study is a single-arm pre-post intervention and will recruit a target sample size of 1,000 Chinese adolescents (ages 15-18 years) who have been diagnosed with CHD. The intervention is guided by the FITT (Frequency, Intensity, Time, Type) principle which prescribes 150 min/week of aerobic exercise at the individualized intensity level defined according to both Heart Rate Reserve (HRR) and Rate of Perceived Exertion (RPE). The primary outcome will include the changes in cardiorespiratory fitness and the Health-Related Quality of Life (HRQoL) scores. This study protocol will close this gap by providing a written, evidence-based and culturally relevant exercise protocol rather than just general advice. Although conducted as a foundational study, the research is intended to draw information on whether and how exercise can be safely applied to individuals with this condition aiming at improved clinical care for the vulnerable population. The results likely will affect future edits of clinical guidelines.

**Keywords:** Congenital Heart Disease; Exercise Intervention; Adolescents; Study Protocol.

## 1. Introduction

Congenital Heart Disease (CHD) is defined as both a structural and functional heart defect present at birth [1]. CHDs are the most common group of congenital abnormalities, affecting 90 per 10,000 newborns and approximately 130 million each year globally [2]. The survival rate of CHD patients has been greatly improved in recent decades as prenatal and other early diagnosis and medical instruments advanced, and considerable progress in intensive care and the adoption of cardiac surgery have been made, indicated by an infant mortality rate of 75% in children with CHD fifty years ago [3]. In contrast, more than 95% will survive until adulthood in 2005, prolonging longevity significantly [3]. This remarkable medical success has resulted in a growing population of adolescents and young adults living with CHD, who require lifelong management and face unique lifestyle challenges.

Especially among the adolescent population in China, living with congenital heart disease (CHD) often involves dual challenges stemming from societal and educational pressures. The sedentary behavior fostered by the time-demand-oriented learning and the deeply rooted overprotective parenting culture which restricts sports participation due to safety reasons have created a foundation for underestimating and underutilizing its therapeutic potential. [4, 5] In this context, a considerable vacuum exists for an intervention; the purpose is to have one that is not only medically functional but also culturally sensitive.

Therefore, this paper has gone to some length in proposing a theoretical framework for an ideal aerobic exercise intervention for Chinese adolescents with CHD. This study aims to determine if a safe, effective, and feasible strategy to increase fitness outcomes can lead to the improvement of quality of life in this particular, at risk patient population.

## 2. Literature Review

### 2.1. Long-term Complications and Clinical Challenges in CHD Survivors

Although the symptoms of CHD patients have been largely alleviated or controlled, most of them still suffer from complications in varying degrees. Bouchardy et al. report that 15% of adults with congenital heart disease have atrial arrhythmias [6]. Lowe et al. report CHD adults diagnosed with pulmonary hypertension suffer significantly higher mortality and morbidity [7]. A surge in the need of re-operation for CHD patients in the last 20 years is reported by Ionescu-Ittu et al. [8]. A higher resting heart rate among CHD adults is found to be associated with low survival according to Hendriks et al. [9]. Central Nervous System (CNS) abnormalities are also observed among the population, measured by language, speech, behavioral signs and IQ scores [10]. Failure in right ventricular function, another important indicator of mortality and morbidity, remains a significant clinical issue among CHD patients [11]. The rate of Sudden Cardiac Death is 20-30 times higher in CHD patients, which contributes to 25% of their total death [12]. Other complications include valve regurgitation, increased risk for endocarditis, and other related diseases, often generating the need for lifelong medication [13, 14].

A combination of these outcomes means a surge in the population of children and adults with CHD and the long-term treatment for both pediatric and adult care for CHD patients, driving up the economic burden for healthcare provision [15]. An annual average of economic burden for all CHD patients in the US is 74 billion dollars [16], and the burden is even worse in those developing countries with high fertility rates [17].

### 2.2. Current Management Strategies and Their Limitations

So far, housekeeping measures of monitoring patient condition have proven paramount. Early detection and prevention of disease progression are accompanied by medication for symptom control or alleviation. These include cardiac surgery for severe cases, including using assisting devices, repair, replacement, or even heart transplantation [18]. Common medications include diuretics, ACE inhibitors, Cardiac Glycosides, Antiarrhythmic drugs, and anticoagulants [19].

Apart from continued costs, the side effects of drugs represent a problem. For example, irregular heartbeats are caused by cardiac glycosides and easy bleeding caused by anticoagulants, and post-operative morbidities often accompany the adoption of these conventional treatments [19]. The aforementioned shortcomings call for more comprehensive approaches in CHD prevention, progression monitoring, as well as management that provide a balance between comfort and effectiveness. Indeed, a plethora of novel complementary methods were devised over the last decades. As more patients survive to adulthood, new avenues are being explored, such as stem cell therapy [20], development of echocardiography, better post-operative care, minimizing invasive surgical techniques [21], and transnational service training programs to reduce healthcare disparities [22].

### 2.3. Exercise Intervention as a Promising Therapeutic Approach

One of the most interesting approaches is exercise intervention, an emerging field using physical activities to target the improvement of specific physical fitness components. These methodologies are rife with the potential to reduce mortality rates and enhance the quality of life of CHD patients [23]. Additionally, increasing attention has been regiven to cardiorespiratory fitness (CRF) as it is shown to be the strongest predictor for cardiovascular disease, outweighing traditional coronary heart disease risk factors, such as overweight and type II diabetes [24].

It is discovered that exercise, more specifically, a chronic aerobic exercise training program (ET), can generate a series of positive morphological and physiological improvements in CRF, for example, increase the end-diastolic diameter of the left ventricle, increase cardiac wall thickness, and increase contractile strength [25]. Its benefit can also be explained using the Fick equation: Cardiac Output (CO) = Oxygen Consumption ($VO_2$) / (Arterial $O_2$ Content [$CaO_2$] – Venous $O_2$ Content [$CvO_2$]). Cardiac output (CO) is also the product of stroke volume (SV) and heart rate (HR). A rise in CO caused by adaptations during exercise training is a crucial contributing factor to increasing maximal oxygen consumption (VO2 max), which is a direct way of measuring CRF nowadays, showing the potential of aerobic exercise in attenuating decline in cardiac function during aging [26].

It was postulated that systematic exercise intervention with appropriate intensity and moderate routine is beneficial for patients with congenital heart disease, whose cardiac function rehabilitation is a long-term challenge. Indeed, a strong negative correlation is shown between morbidity and exercise in CHD patients, and they benefit from better outcomes, including better aerobic and cardiorespiratory fitness, increased aerobic capacity or peak oxygen consumption, and accelerated recovery from cardiac surgery, as well as improvements in psychosocial functioning [4, 5, 27]. Therefore, physical exercises may provide complementation to conventional CHD treatments.

### 2.4. The Research Gap

However, public opinion and perception remain an obstacle. Patients, especially with CHD, tend to have relatively conservative views on exercise and have reduced exercise capacity and physical activity due to safety concerns, overprotection, and a sedentary lifestyle, making them difficult to adhere to regular exercise training and highlighting the underestimation and underusage of PA, causing the need for public awareness programs [4, 5]. The gap in the literature is found to be that most of the training references for CHD patients are relatively general, causing patients hard to locate a specific and personalized exercise plan that emphasize on the balance between safety and effectiveness, especially for those with valve defects.

## 3. Methodology

### 3.1. General Study Design

This study is designed as a single-arm, longitudinal, pre-post intervention study. The study design employs a longitudinal approach using stratified sampling among CHD patients with valve defects, with baseline measurements taken at the end of 9th grade, followed by a three-year senior high school period for aerobic exercise training implementation, and final assessment completed at the end of 12th grade for comparative analysis.

This study aims to design personalized exercise prescription by first assessing the suitable intensity of each participant using heart rate and Rate of Perceived Exertion (RPE) Scale and classify each individual into one of the intensity categories. The long-term effectiveness of sustained aerobic exercise on the adolescents after the period can later be measured by both physiological and psychological indicators, including CRF indicators, such as VO2 max and resting heart rate, and health-related quality of life (HRQoL) determined by a validated questionnaire.

### 3.2. Population and Eligibility Criteria

#### 3.2.1. Sample Population and Recruitment

Indeed, there is a high prevalence of valve defects among cases of congenital heart disease (CHD) and thus this would represent a suitable target in our study population. If feasible, we will randomly choose 1,000 adolescents with established CHD living in China. We have proposed a target sample size of 1,000 subjects in order to achieve sufficient statistical power for meaningful analysis; however, we acknowledge that recruitment may experience challenges due to the relatively low prevalence of CHD adolescents with isolated valvular defects and the required long-term commitment. Therefore, trade-offs might be needed and international partnerships could be employed. To guarantee a representative sample and address potential healthcare disparities, a random and stratified sampling approach will be applied across urban and rural schools.

#### 3.2.2. Inclusion Criteria

Students are required to meet a number of criteria to be considered for participation… For one, participants should be aged 15 to 18 and currently in the 9th through 12th grades. The study will also aim for a 1:1 male-female ratio to reach gender equity. In addition to this geographic diversity we are going to try and recruit from cities of different economic development. Finally, and most importantly, students and their legal guardians should provide consent (including full disclosures of the intent of the research and concerns of privacy) to be in the study at initiation.

#### 3.2.3. Exclusion Criteria

Criterion for exclusion is determined to conserve participant safety. Exclusion criteria include patients with chronic fatigue syndrome or potentially severe heart failure, lung diseases leading to limitation in oxygen uptake or post-exertional malaise (PEM), anemia and inflammatory disorders like rheumatoid arthritis [28, 29]. With other comorbidities and conditions that are likely to be worsened by the intervention, people will also not be included in this study. Conditions that may require a temporary abstention from high-intensity exercise include amenorrhea in women or recent cardiac thoracotomy or other major surgery; these cases will be monitored and handled on a case-by-case basis. Finally, they can take the basic post-cardiac surgery medications (such as anticoagulants), but almost all those that interfere with monitoring parameters (e.g., heart rate, $SpO_2$) will make them ineligible.

### 3.3. Intervention Protocol: The FITT Principle

The exercise prescription is structured based on the FITT principle, an acronym that represents frequency, intensity, time, and type in exercise. This framework provides a systematic tool to design and prescribe exercise programmes to improve specific health outcomes. In this case, each of the dimensions will be discussed in the context of valve defect CHD patients. The intervention is defined by these four dimensions. Regarding frequency, and considering the unique lifestyles and academic burden of high school students, participants are required to complete aerobic exercise on two to three days a week, usually during weekends. In terms of time, a total of 150 minutes of treadmill exercise is expected per week, and beginners are advised to split this total time evenly and incorporate short rests when feeling fatigued. For the type of exercise, given its established benefits for cardiorespiratory fitness and a strong safety profile, aerobic exercise using treadmill training is the focus of this intervention. According to Tran, the type and intensity of exercise that BAV patients can implement depends on their degree of aortic dilatation and valve dysfunction [30]. In case of repaired aortic dissection done previously, exercise with high intensity and resistance exercise training should be avoided [30]. Meanwhile, other complications related to valve defects or post-surgery should also be taken into account to determine exercise intensity, for example, pulmonary hypertension, cardiac rhythm issues, uncontrolled arrhythmias, an implanted pacemaker, or ischemia [30].

#### 3.3.1. Intensity Determination and Classification

Central to this study was the notion of prescribing intensity with an individualized approach to balancing safety and efficacy. The main difficulty in assessing exercise intensity is due to the fact that there are no well-defined guidelines about the minimum threshold for aerobic ET in coronary heart disease (CHD) patients [30]. Second, the specific absolute intensity of exercise that must be attained is also highly variable based on individual factors and baseline cardiorespiratory fitness (CRF) [30]. Most of the studies suggest a range of 60–80% HRmax, though this study is designed to use the HRR (heart rate reserve) method instead, which targets intensity referring to personal fitness levels [30].

To determine an optimal heart rate training zone, the resting heart rate (RHR) and maximum heart rate (MHR) are measured to calculate HRR using the formula: HRR = MHR - RHR. These results will then be combined with a subjective approach, the Rate of Perceived Exertion (RPE) scale, to assess how hard the physical activity feels on a scale ranging from 0 to 10, with higher numbers indicating greater effort. As detailed in Table 1, using these two indicators, a safe and effective intensity can be obtained for each participant.

**Table 1.** Exercise Intensity Categories Based on Various Methods of Exercise Prescription.

| **Intensity category** | **Aerobic training measure of intensity** | **Aerobic training subjective measures** |
| --- | --- | --- |
| Low (light) | 20–39% HRR or $VO_2R$<br>40–54% $HR_{max}$<br>20–39% $VO_{2max}$ | RPE: 8–10 |
| Moderate | 40–59% HRR or $VO_2R$<br>55–69% $HR_{max}$<br>40–59% $VO_{2max}$ | RPE:11–13 |
| Vigorous | 60–84% HRR or $VO_2R$<br>70–89% $HR_{max}$<br>60–84% $VO_{2max}$ | RPE: 14–16 |
| High | ≥85% HRR or $VO_2R$<br>≥90% $HR_{max}$<br>≥85% $VO_{2max}$ | RPE: ≥17 |

*Note: Those who fail to fall within any categories are deemed to be unfit for the said experiment and should thus not be recruited.*

### 3.4. Safety Monitoring and Clinical Oversight

Although clinical research results indicated that adverse effects from appropriately prescribed aerobic exercise are very uncommon in CHD populations [31, 32], when it comes to increasing ET intensity, safety is always the priority. Beyond heart rate and $VO_2$ max, careful monitoring of blood pressure, hemodynamic response, potential hypertensive or hypotensive reactions, and other body signals also need to be closely monitored. As illustrated in Figure 1, a systematic process adapted from established recommendations will be followed for each participant to ensure safety throughout the prescription and training process [30].

Furthermore, performing CPET before the programme, peak $VO_2$ levels assessment, risk precautions, regular interview, and follow-up with a CHD specialist are highly recommended [30].

### 3.5. Outcome Measures and Data Analysis

#### 3.5.1. Data Collection

Large-scale data collection in this study will be made feasible by using physical fitness and health report data which were collated through China’s domestic education system, between 9th grade (baseline) and 12th grade (follow-up), three years later. This method would give more wide-ranging and reliable CRF data. This data was justifiably acquired with informed consent and is to be made widely available on an appropriate platform for research purposes.

Further HRQoL data will be collected at regular intervals from baseline to the end of the three-year study period using a validated instrument (e.g., CDC HRQoL-14 questionnaire). This approach offers a way to measure exercise-related health outcomes that can be used broadly, quantifying not only objective measures of health but also subjective well-being beyond CRF. Age appropriate targeting could be enhanced further through future iterations by incorporating pediatric-specific tools (e.g., PedsQL).

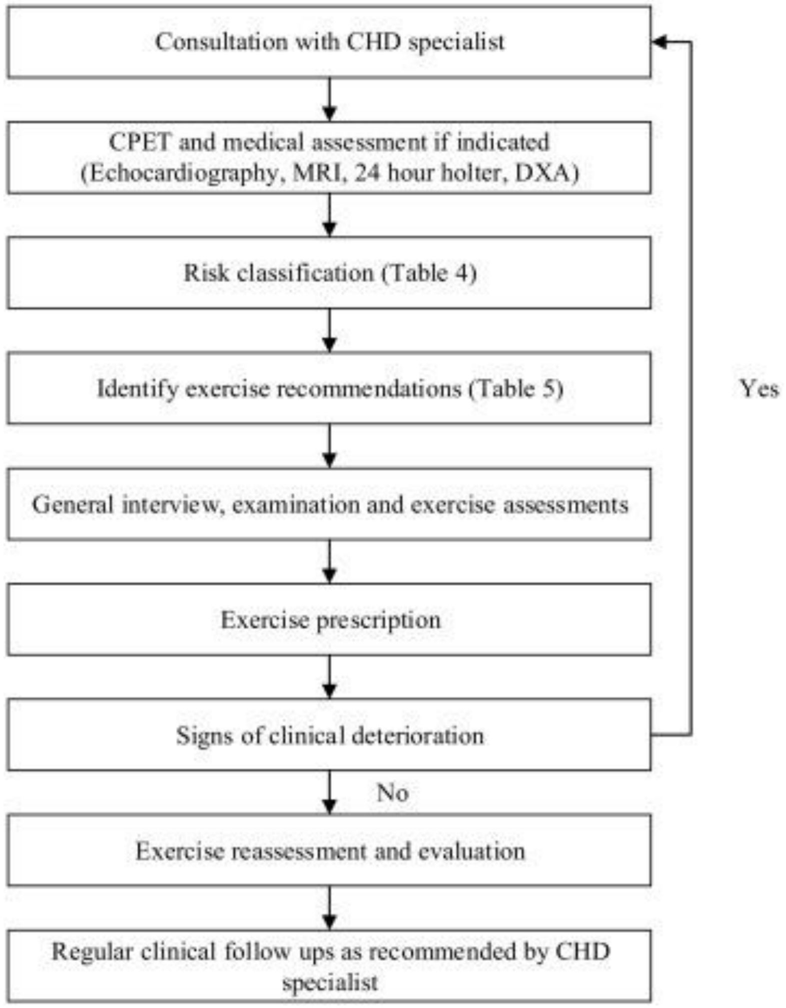


**Figure 1.** Recommended Process for Exercise Prescription and Training [30].

#### 3.5.2. Quantitative Analysis

For lack of a preexisting paradigm, a quantitative analysis framework is proposed. While a detailed statistical analysis plan will be finalized prior to data collection, the proposed approach is as follows: Initially, baseline characteristics of participants will be summarized using descriptive statistics. Subsequently, to evaluate the intervention's effectiveness, a repeated measures analysis of variance (ANOVA) or a mixed-effects model will be used to analyze the changes in CRF indicators and HRQoL scores from baseline to the 3-year follow-up. This statistical approach will allow for the tracking of changes over time within the participant group.

## 4. Discussion

### 4.1. Summary and Expected Outcomes

The proposed study will implement a three-year aerobic exercise training (ET) programme on Chinese high school students with valve defects and assess its overall effectiveness based on CRF-related factors and a health-related quality of life questionnaire. Throughout the study, ethical implications including privacy will be ensured, and participant safety will be guaranteed with the help of personalized ET intensity and thorough consideration of medical comorbidities related to CHD.

Based on the evidence presented in the literature review, it is hypothesized that through long-term, targeted aerobic ET, participants will achieve significant improvements in health indicators such as CRF on the basis of their existing conditions. From a clinical perspective, such findings would help researchers confirm and reassure the improvements of various indicators from aerobic ET for CHD patients in a more specific category—valve defects—in the long run, assisting clinicians and cardiologists in changing specified guidelines and building the mentality of patients. From a social implication perspective, as participants personally experience acceleration in their recoveries, it will lend credence to the effectiveness of the intervention. This may help promote wider public recognition of aerobic ET's potential therapeutic value, which can, to some extent, reduce the current stereotypes regarding exercise avoidance for this population.

### 4.2. Strengths of the Study

The proposed study possesses several key strengths. First, by focusing on adolescents with valve defects—specifically leveraging the prevalence of BAV as a target condition—it addresses a gap in the literature where most exercise interventions target the broad etiology of CHD rather than a specific disease. Second, the selection of the sample population in the study fully and pragmatically leverages the existing health assessment infrastructure of high school students within the context of China, thereby expanding the potential population size and enhancing feasibility. Third, in order to ensure safety while achieving the best performance, a simple but effective calculation method is adopted to help each participant individualize and select the most suitable ET intensity.

### 4.3. Limitations and Mitigation Strategies

Note that we need to consider some potential limitations of the study. The primary limitation of the study is the high target sample size required combined with potential difficulties in recruiting participants and ensuring they continue with their allocated intervention. Robust ethical and privacy safeguards are needed to help maintain the sample size; these must be fully explained, including detailed informed consent that ensures transparency in research objectives. Furthermore, due to academic pressures, lack of equipment and parental overprotection, it is not known whether Chinese high school students will be able to adhere to the prescribed treadmill standardized exercise training session (150 minutes per week) in a consistent manner. In practice, this could translate into alternative activities such as jogging around school athletic fields to maintain the heart rate in target zones. In addition to that, working with the appropriate government agencies or even healthcare facilities could provide all the necessary assistance.

Furthermore, the single-arm, pre-post design is a significant limitation, as the absence of a non-intervention control group means observed changes cannot be definitively attributed solely to the exercise program. However, as an initial exploratory study in a specific cultural and educational context, this design represents a pragmatic and foundational first step.

Finally, while the hypothesis is that participants can achieve improvements in health indicators, the extent of these improvements cannot be accurately predicted before conducting the experiment and may be relatively limited. Therefore, methods such as subjective questionnaires are employed to investigate other potential influences in case the objective ones are not significantly evident, coupled with anatomical-level qualification and quantification of heart condition.

### 4.4. Future Directions

In light of this foundational research, a number of fruitful directions for further investigation are apparent. It is necessary to investigate more thoroughly the action mechanisms of exercise in aortic valve defects, especially considering molecular pathways related to endocrine (by ET) and nervous systems, as well as the specificities observed for different CHD, like BAV. Second, alternative strategies for exercise intervention should be explored, such as changing from aerobic ET to resistance ET, adding high-intensity interval training or weight training, or even including other lifestyle modifications apart from exercise, with an emphasis on assessing both tolerance and safety. Third, to obtain results with higher validity, future studies should be designed as randomized controlled trials, employ a much larger sample size and prolong the period over which they are conducted. Finally, the potential universality of these findings could be assessed by building on the studies discussed above to include diverse demographics and international settings. After these trials are completed, other research should be dedicated to dissemination and translational research, such as publishing findings and creating exercise rehabilitation education programs for the general public. Finally, examining the neurobiological correlates of physical activity-related psychological benefits linked to CRF indicators represents another key area for future research.

## 5. Conclusion

In summary, this paper has identified a significant gap in the management of adolescents congenital heart disease based upon its certain socio-educational background of China. Current general physical activity recommendations often ignore the unique nature of these challenges, including significant academic demands and cultural overprotection from their parents.

The author therefore designed a full three-year longitudinal study, with the aim of implementing a personalized aerobic exercise intervention during this time. Their framework incorporates the FITT principle with objective physiological follow-up combined with subjective quality-of-life follow-up for a balance of both safety and efficacy.

The main value of this work does not come from specific empirical findings but instead the construction of a durable, theoretically sophisticated, culture-loaded framework. This framework provides a critical, detailed guide for clinicians, investigators and public health professionals who wish to deploy empirically proven programs in this context. In the end, if such a study could be effectively performed and validated, it would not only serve to improve the cardiorespiratory fitness of young CHD survivors but also empower them with the self-efficacy to manage their own health, profoundly increasing their life quality in forthcoming years.

## References


[1] K.K. Stout, C.J. Daniels, J.A. Aboulhosn, et al., 2018 AHA/ACC guideline for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, J. Am. Coll. Cardiol. 73 (2019) e81-e192.

[2] I. Nederend, M.R.M. Jongbloed, E.J.C. de Geus, N.A. Blom, A.D.J. Ten Harkel, Postnatal cardiac autonomic nervous control in pediatric congenital heart disease, J. Cardiovasc. Dev. Dis. 3 (2016) 16.

[3] C.A. Warnes, The adult with congenital heart disease: born to be bad?, J. Am. Coll. Cardiol. 46 (2005) 1-8.

[4] M. Gomes-Neto, M.B. Saquetto, C.M. da Silva e Silva, C.S. Conceição, V.O. Carvalho, 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. 37 (2016) 217-224.

[5] K. Dulfer, W.A. Helbing, E.M.W.J. Utens, The influence of exercise training on quality of life and psychosocial functioning in children with congenital heart disease: A review of intervention studies, Sports (Basel) 5 (2017) 13.

[6] J. Bouchardy, J. Therrien, L. Pilote, et al., Atrial arrhythmias in adults with congenital heart disease, Circulation 120 (2009) 1679-1686.

[7] B.S. Lowe, J. Therrien, R. Ionescu-Ittu, L. Pilote, G. Martucci, A.J. Marelli, Diagnosis of pulmonary hypertension in the congenital heart disease adult population impact on outcomes, J. Am. Coll. Cardiol. 58 (2011) 538-546.

[8] R. Ionescu-Ittu, A.S. Mackie, M. Abrahamowicz, et al., Valvular operations in patients with congenital heart disease: increasing rates from 1988 to 2005, Ann. Thorac. Surg. 90 (2010) 1563-1569.

[9] P.M. Hendriks, A.E. van den Bosch, J.A. Kors, et al., Heart rate: an accessible risk indicator in adult congenital heart disease, Heart 110 (2024) 402-407.

[10] G. Wernovsky, J. Newburger, Neurologic and developmental morbidity in children with complex congenital heart disease, J. Pediatr. 142 (2003) 6-8.

[11] Y.K. Cho, J.S. Ma, Right ventricular failure in congenital heart disease, Korean J. Pediatr. 56 (2013) 101-106.

[12] Z. Koyak, L. Harris, J.R. de Groot, et al., Sudden cardiac death in adult congenital heart disease, Circulation 126 (2012) 1944-1954.

[13] J.M. Saef, J. Ghobrial, Valvular heart disease in congenital heart disease: a narrative review, Cardiovasc. Diagn. Ther. 11 (2021) 818-839.

[14] C.M. Otto, R.A. Nishimura, R.O. Bonow, et al., 2020 ACC/AHA Guideline for the Management of Patients with Valvular Heart Disease, Circulation 143 (2020).

[15] C.A. Warnes, R. Liberthson, G.K. Danielson, et al., Task force 1: the changing profile of congenital heart disease in adult life, J. Am. Coll. Cardiol. 37 (2001) 1170-1175.

[16] D.M. Pickles, K. Keller, P. Andreu, N.J. Atay, The Cost of Complex Congenital Heart Disease in the US, Additional Ventures, IQVIA, 2024.

[17] J.I.E. Hoffman, The global burden of congenital heart disease, Cardiovasc. J. Afr. 24 (2013) 141-145.

[18] A. Arvanitaki, G. Diller, G. Giannakoulas, The right heart in congenital heart disease, Curr. Heart Fail. Rep. 20 (2023) 471-483.

[19] O.I. Woudstra, J.M. Kuijpers, F.J. Meijboom, et al., High burden of drug therapy in adult congenital heart disease: polypharmacy as marker of morbidity and mortality, Eur. Heart J. Cardiovasc. Pharmacother. 5 (2019) 216-225.

[20] K. Julian, N. Garg, N. Hibino, R. Jain, Stem cells and congenital heart disease: The future potential clinical therapy beyond current treatment, Curr. Cardiol. Rev. 19 (2023).

[21] P.P. Heinisch, S. Michel, D. Zimpfer, J. Hörer, Editorial: Emerging opportunities in congenital cardiac surgery, Front. Cardiovasc. Med. 10 (2023) 1343354.

[22] W.W. Lai, D. Vervoort, D. Bradley, et al., Pediatric and Congenital Cardiac Services: An Innovative and Empowering Approach to Global Training and Equitable Care, J. Am. Heart Assoc. 14 (2025) e040003.

[23] N.H. Amir, D.M. Dorobantu, C.A. Wadey, et al., Exercise training in paediatric congenital heart disease: fit for purpose?, Arch. Dis. Child. 107 (2022) 525-534.

[24] S. Kodama, Cardiorespiratory fitness as a quantitative predictor of All-Cause mortality and cardiovascular events in healthy men and women, JAMA 301 (2009) 2024.

[25] A.L. Baggish, K. Yared, F. Wang, et al., The impact of endurance exercise training on left ventricular systolic mechanics, AJP Heart Circ. Physiol. 295 (2008) H1109-H1116.

[26] A. Arbab-Zadeh, E. Dijk, A. Prasad, et al., Effect of aging and physical activity on left ventricular compliance, Circulation 110 (2004) 1799-1805.

[27] R. Yoshihara, Y. Kanejima, M. Kitamura, K. Ishihara, K.P. Izawa, Optimal exercise training for children with congenital heart disease: A systematic review, Am. Heart J. Plus 13 (2022) 100119.

[28] G. Liguori, American College of Sports Medicine, ACSM's guidelines for exercise testing and prescription, Lippincott Williams & Wilkins, 2020.

[29] D. Riebe, B.A. Franklin, P.D. Thompson, et al., Updating ACSM's recommendations for exercise preparticipation health screening, Med. Sci. Sports Exerc. 47 (2015) 2473-2479.

[30] D. Tran, A. Maiorana, J. Ayer, et al., Recommendations for exercise in adolescents and adults with congenital heart disease, Prog. Cardiovasc. Dis. 63 (2020) 350-366.

[31] C.A. Williams, C. Wadey, G. Pieles, G. Stuart, R.S. Taylor, L. Long, Physical activity interventions for people with congenital heart disease, Cochrane Library 2021 (2020).

[32] N. Duppen, T. Takken, M.T. Hopman, et al., Systematic review of the effects of physical exercise training programmes in children and young adults with congenital heart disease, Int. J. Cardiol. 168 (2013) 1779-1787.