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Efficacy of a Transition Program in Adolescents and Young Adults With Congenital Heart Disease: The TRANSITION-CHD Randomized Controlled Trial

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ABSTRACT

Purpose:

Currently, nearly 90% of patients with congenital heart disease (CHD) reach adulthood in relatively good health. Structured transition programs have emerged to support adolescents and young adults in transitioning to adult care structures, improve their autonomy, and limit healthcare ruptures. The TRANSITION-CHD randomized controlled trial aimed to assess the impact of a transition program on health-related quality of life (HRQoL) in adolescents and young adults with CHD.

Methods:

From January 2017 to February 2020, 200 subjects with a CHD, aged 13e25 years, were enrolled in a prospective, controlled, multicenter study and randomized in two balanced groups (transition program vs. standard of care). The primary outcome was the change in PedsQL self-reported HRQoL score between baseline and 12-month follow-up, using an intention-to-treat analysis. The secondary outcomes were the change in disease knowledge, physical health (cardiopulmonary fitness, physical activity), and mental health (anxiety, depression).

Results:

The change in HRQoL differed significantly between the transition group and the control group (mean difference = 3.03, 95% confidence interval (CI) = [0.08; 5.98]; $p = .044$; effect size = 0.30), in favor of the intervention group. A significant increase was also observed in the self-reported psychosocial HRQoL (mean difference = 3.33, 95% CI = [0.01; 6.64]; $p = .049$; effect size = 0.29), in the proxy-reported physical HRQoL (mean difference = 9.18, 95% CI = [1.86; 16.51]; $p = .015$; effect size = 0.53), and in disease knowledge (mean difference = 3.13, 95% CI = [1.54; 4.72]; $p < .001$; effect size = 0.64).

Discussion:

The TRANSITION-CHD program improved HRQoL and disease knowledge in adolescents and young adults with CHD, supporting the generalization and systematization of similar preventive interventions in pediatric and congenital cardiology.

Medical, technical, and surgical advances over the past decades have dramatically improved the prognosis of patients with congenital heart disease (CHD), including severe forms. As a result, currently, more than 90% of children born with a CHD reach adulthood [1].

Nevertheless, while nearly all children are regularly followed in specialized pediatric cardiology settings, many teenagers and young adults with a CHD are prone to drop out of active healthcare. These patients are at risk of later reintegrating into the healthcare system, mostly from the emergency department, when facing complications [2]. Such lapses in care appear to be predictors of morbidity and poor outcomes in CHD, especially for minority populations [3].

Healthcare transition is defined as the process through which adolescents and young adults with chronic childhood illnesses are prepared to manage their lives and health in adulthood [4]. The outlined procedure concludes with the transfer, coinciding with the designated moment when the patient moves from the pediatric unit to the adult unit. This process involves a shift of responsibility for the management of family health care to the patient. In the past decade, structured programs dedicated to the CHD population have emerged to structure this transition [3,5]. Transition is an age and developmentally dependent process that addresses medical, psychosocial, educational, and vocational aspects. Overall, transition programs intend to promote patient autonomy, limit loss to followup, and ensure appropriate transfer of care.

Various transition programs have been tested worldwide in patients with CHD, with preliminary results from mostly noncontrolled studies suggesting an improvement in disease knowledge, self-empowerment, and continuity of care [6e9]. However, the impact of transition programs on patient-reported outcomes (PROs) has been poorly evaluated in studies with a high level of evidence [10]. Yet, the current low level of morbimortality in youth with CHD justifies the choice of PROs to evaluate the impact of preventive actions in this population [11]. Among the various PROs, health-related quality of life (HRQoL), which may be defined as “the sub-set of the important or most common ways in which health or health care impact upon wellbeing” [12], has been widely used in the CHD population and is associated with physical capacity, cognitive function, psychosocial status, and gender [13e15]. Nevertheless, only one study assessed the impact of a transition program on PROs in the CHD population, and none used HRQoL as the primary outcome [9].

The TRANSITION-CHD randomized controlled trial aimed to assess the impact of a transition program on the HRQoL of adolescents and young adults with CHD.

Methods

Study design and setting

As previously reported in the study design article, the TRANSITION-CHD trial is an open-label prospective, multicenter, randomized, controlled, parallel-arm study with a 12-month patient follow-up and a 2-year recruitment period [16]. After informed consent, participants were randomly allocated in a 1:1 ratio to either the intervention group (e.g., the transition program) or the control group. Subjects randomized in the control group underwent a routine,

non-modified follow-up with no formalized transition program during the 12-month study period. However, they were offered to participate in the transition program once the 12-month study period was over.

Randomization was stratified by age group (13-17 years and 18-25 years), centralized using a secure, web-based randomization system (Ennov Clinical Software, Paris, France) managed by the Clinical Research Unit of Montpellier University Hospital, independently from the investigators. All three tertiary care CHD centers from the Occitanie region, southern France, participated in the study (Montpellier University Hospital, Saint-Pierre- Institute, and Toulouse University Hospital), with a total of 17 investigators involved in patient screening and enrollment.

Study population

Patients with a CHD, defined by the international anatomic and clinical CHD classification [17], and aged 13-25 years old were prospectively recruited in the participating centers during an outpatient visit. Parents of minors and partners of adult patients were also invited to participate in group sessions, separate from those held for the patients. The TRANSITION-CHD study relied on a nonselective program; however, patients unable to understand the study information were not eligible, as well as patients with a severe intellectual disability that did not allow the completion of the HRQoL questionnaire.

Intervention

The TRANSITION-CHD program has been structurally developed following the educational objectives outlined in the current guidelines for transition care for patients with CHD [5]. This program was built in partnership with the two national CHD patient advocacy organizations (“ANCC” and “Petit Coeur de Beurre”), delivered in a single setting (Pediatric Rehabilitation Centre, Saint-Pierre-Institute, Palavas-Les-Flots, France), and broadcast to the patients and on social networks (<https://youtu.be/GwZahh9Nf78>). The TRANSITION-CHD program was previously described in a nonrandomized controlled pilot study [10], as well as in the study design paper of the current trial [16]. A single health educator (A.A.), i.e., an advanced practice nurse in pediatric cardiology holding board certification in patient education, supervised the program for all participating centers. To limit contamination bias, the health educator was not in charge of patients from the control group during the study period. Using a holistic approach, the overall aim of the transition program was to address, at every stage, the physical, psychological, and social components of life for young people living with a CHD.

In practice, the intervention was divided into three parts (Figure 1):

(1) First educational outpatient visit (1 hour): this individual interview with a health educator (e.g., a specialist nurse) aimed to determine the patient’s educational objectives and needs.

(2) Group session (1 day): dedicated to patients and their relatives, this group session included 5-8 patients of similar age ranges (13-17 years or 18-25 years) and involved two health educators, a pediatric cardiologist, an adult congenital cardiologist, a psychologist, and a patient advocacy organization delegate. The program of this group session was divided into four sections: medical aspects, “living with my disease,” an administrative workshop, and a

final individual interview with a cardiologist and a health educator to establish a personalized educational report.

(3) Transfer preparation outpatient visit: approximately 6 months after the group session, the patient underwent a medical visit with both a pediatric cardiologist and an adult congenital cardiologist to prepare for the transfer to the adult care setting.

Primary outcome

Assessing PROs in cardiovascular clinical trials is relevant and fully justified in the context of transitioning adolescents, given that the program was designed using a holistic approach [18]. The transition program aimed to comprehensively address the physical, psychological, and social aspects of the lives of youth with CHD. Among various PROs, HRQoL assessment integrates each of these facets into a single criterion that is both reproducible and sensitive to change. The primary outcome was the change between baseline (M0) and 12-month follow-up (M12) in the PedsQL self-reported HRQoL total score.

The PedsQL instrument is a generic HRQoL questionnaire including four multidimensional scales: physical functioning (eight items), emotional functioning (five items), social functioning (five items), and school functioning (five items). In addition to the four scores for these dimensions, two summary scores were calculated: total score (23 items) and psychosocial health summary score (15 items, corresponding to emotional, social, and school functioning). Each item uses a 5-point Likert scale from 0 (never) to 4 (almost always). Items are reversed scored and linearly transformed to a 0-100 scale, with higher scores indicating a better quality of life. Psychometric properties showed reliability, validity, and responsiveness to clinical change over time [19]. After translation and cultural adaptation, the psychometric properties of the French version of the PedsQL appeared to be acceptable [20,21]. Two versions of the PedsQL questionnaire (13-17 and 18-25 years old) were used for adolescents and young adults, respectively. The parent-reported HRQoL scores were also measured using the proxy version of the PedsQL for adolescents (aged 13-17 years old).

Secondary outcomes

The following outcomes were measured at baseline (M0), and 12-month follow-up (M12) and their changes over time were analyzed:

_ The level of disease knowledge was assessed using the Leuven Knowledge Questionnaire for CHD, which covers four domains in which patients with CHD should be knowledgeable to be able to adopt adequate health behavior: (1) the disease and its treatment; (2) the prevention of complications; (3) physical activities; and (4) reproductive issues [22].

_ The main cardiovascular health outcomes were assessed, given that adolescents with CHD are concerned by sedentary lifestyles, physical deconditioning, and long-term increased cardiovascular risk, even in noncomplex CHD [23e25]. Clinical outcomes included New York Heart Association functional class, healthcare usage (primary and secondary care contacts, hospitalization), and medication. Physical health outcomes included cardiopulmonary fitness evaluated by cardiopulmonary exercise testing to measure aerobic fitness (peak oxygen consumption), ventilatory anaerobic threshold, and ventilatory efficiency (VE/VCO₂ slope). Impaired aerobic fitness was defined as peak oxygen consumption <80% of predicted values [23,26]. As previously detailed, cardiopulmonary exercise test procedures in all participating

laboratories were harmonized before the study started [23,26e30]. The level of physical activity was assessed using the Ricci and Gagnon questionnaire, composed of nine items with a total score ranging from 9 to 45 ([9-18] = physical inactivity; [18-35] = moderate physical activity; [36-45]= intensive physical activity) [26,31].

_ Mental health outcomes were assessed, considering that perceived health competence predicts anxiety and depressive symptoms in adolescents with CHD [32]. The level of anxiety was assessed with the self-administered State and Trait Anxiety Inventory questionnaire for young adults and the State and Trait Anxiety Inventory-Children questionnaire for adolescents [33]. The level of depression was assessed with the self-administered Beck Depression Inventory questionnaire for young adults and the Child Depression Inventory questionnaire for adolescents [34,35].

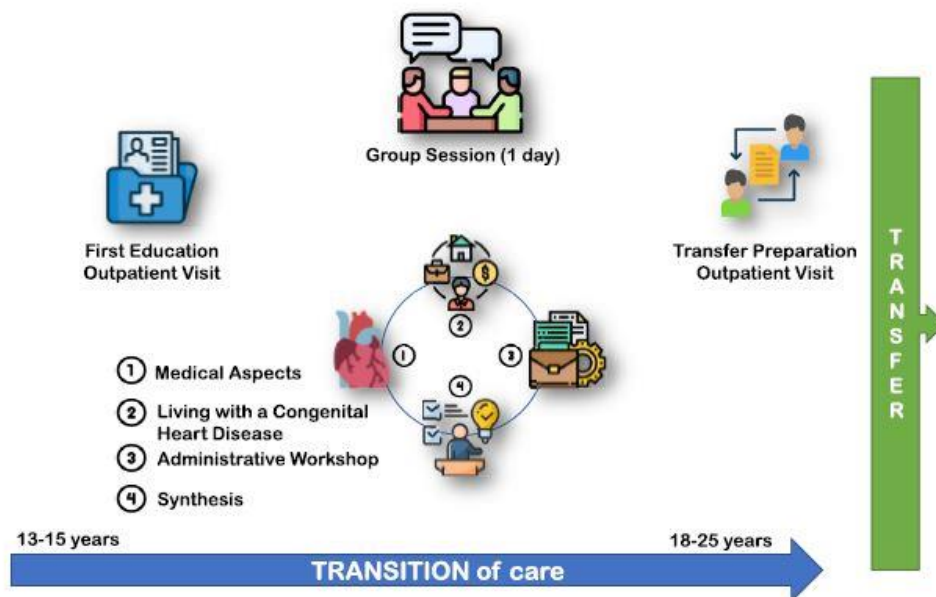


Figure 1. The TRANSITION-CHD program.

Statistical analyses

The minimum clinically relevant difference was estimated from our previous HRQoL in the CHD population [20,36e38]. The trial was designed to have 80% power to detect an absolute difference of seven points (+/-13.5 points) in the change of the selfreported HRQoL total score with a two-sided alpha-risk of 5%. We planned to enroll a total of 200 subjects (e.g., 100 patients in each group) and potentially lose 20% of follow-up or missing data on the primary outcome.

Baseline characteristics of the two groups were reported using mean and standard deviation or median and interquartile range for continuous variables and frequencies and percentages for categorical variables.

The primary analysis was performed according to the intention-to-treat (ITT) principle and involved all randomly assigned subjects with a complete baseline primary outcome assessment. When at least one of the four PedsQL multidimensional scores (physical, emotional, social, and school functioning) was missing at the final assessment visit, multiple linear imputation was implemented using a fully conditional specification method [39]. For

better stability, the number of imputations was 20 in the imputation process, and all baseline characteristics and follow-up data were used in the imputation model [39].

A sensitivity analysis was performed on complete data (patients with a complete baseline and final assessment of the primary outcome).

A per-protocol analysis was performed in randomized subjects with no significant protocol deviation (good compliance with the transition program and complete patient follow-up). In this study, the M12 assessment of the primary outcome was considered a protocol deviation if the delay exceeded 12 months (24 months after inclusion). Good compliance with the transition program was defined as a level of participation in the educational sessions above 80%.

For each score, the change between baseline and 12-month follow-up was evaluated by a covariate analysis adjusted for the score's baseline value, age, and allocated intervention group.

The effect size was estimated using Cohen's D method and expressed with its 95% confidence interval.

The statistical significance was set as 0.05, and analyses were conducted using Statistical Analysis Systems version 7.13 (SAS Enterprise Guide).

Ethics

The study was conducted in compliance with the Good Clinical Practices protocol and Declaration of Helsinki principles. It was approved by a drawn National Ethics Committee (South- Mediterranean IV 2016-A01681-50) and registered on [Clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03005626) (NCT03005626). Written informed consent was obtained from all patients and their parents or legal guardians for minors. Children's assent to participate in the study was also required.

Results

Population

From January 2017 to February 2020, the expected number of 200 patients were enrolled in the trial (mean age 18.6 +/-3.6 years, 49% female), of which 100 were randomly assigned to the TRANSITION-CHD intervention group and 100 were assigned to the control group. Eleven subjects were removed from the study analysis (missing data on the primary outcome at baseline, withdrawal of consent, and inclusion error). Therefore, the ITT analysis was performed on a total of 189 patients, with 95 subjects in the transition group and 94 subjects in the control group (Figure 2).

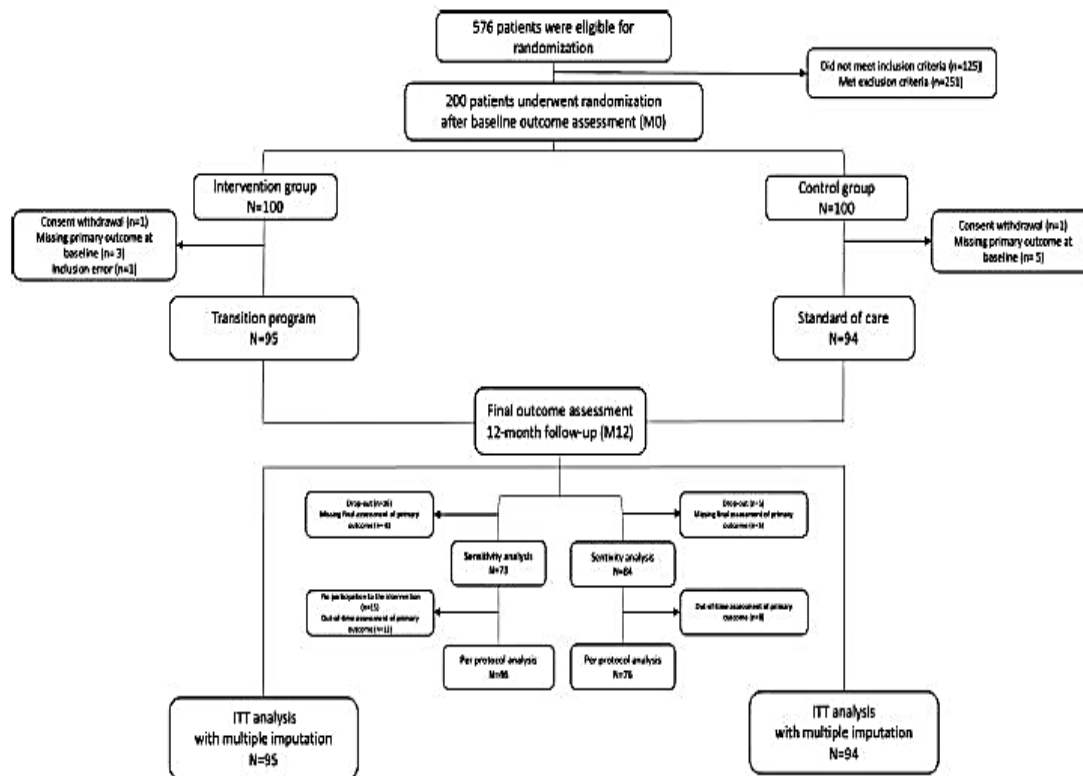


Figure 2. The TRANSITION-CHD randomized controlled trial flow chart. Drop-out: patient assigned to the transition group who did not participate in the intervention and did not complete final outcome assessment; out-of-time assessment of the primary outcome: completion of HRQoL questionnaire less than 6 months or more than 18 months after baseline assessment.

At baseline, both groups were balanced in terms of demographic data, except for height, as well as medical data, except for a higher number of subjects with a pacemaker in the transition group. Most patients did not have any symptoms of heart failure (New York Heart Association class I for 93% of subjects), and most types of CHD were represented. No significant group differences at baseline were observed for the primary and secondary outcomes (Table 1).

The sensitivity analysis was performed on 157 patients, as the primary outcome was not available for 32 subjects: lost to follow-up (N = 21) or missing data on the primary outcome at the final assessment (N = 11).

The per-protocol analysis was performed on 122 patients, as significant protocol deviation was observed for 35 subjects: poor participation in the transition program (N = 15) or significant delay (>12 months) in the final outcome assessment (N = 20).

Among patients randomized in the intervention group, a total of 31 “drop-out” patients did not participate in the therapeutic session, of which 16 were lost to follow-up and 15 underwent the final assessment without participating in the intervention (Figure 2). These drop-outs were significantly older than the participants (20.2 +/- 3.7 vs. 17.7 +/- 3.0 years, p = .004) and more independent than the participants (living in their parent’s house for 47% of them vs. 80%, p=017, respectively). No other parameters could discriminate the patients joining the program from the nonparticipants in the intervention group.

Change in the primary outcome (HRQoL)

In the ITT analysis, the PedsQL self-reported HRQoL total score, e.g., the primary outcome, between baseline and 12-month follow-up, increased more significantly in the transition group than in the control group (+ 3.85 points vs. + 0.82 points, $p = .044$, respectively, effect size = 0.30). Moreover, a significant increase was observed in the PedsQL self-reported psychological health summary score (+ 4.22 points vs. + 0.89 points, $p = .049$, effect size = 0.29), and in the PedsQL proxy-reported physical dimension (+ 5.98 points vs. - 3.20 points, $p = .015$, effect size = 0.53). A trend for an increase in the transition group for the PedsQL self-reported physical dimension was also observed (+ 3.14 points vs. + 0.30 points, $p = .149$, effect size = 0.21) (Table 2).

In the sensitivity analysis on patients with complete data on the baseline and final outcome assessments, a significant increase in the transition group was observed for the PedsQL proxy-reported physical dimension (+ 4.92 points vs. - 3.35 points, $p = .041$, effect size = 0.51). Nonsignificant trends were also observed for the PedsQL self-reported total and psychological scores (Table S1).

In the per-protocol analysis, no significant changes were observed in any of the HRQoL scores (Tables S2 and S3).

Change in the secondary outcomes

A significant improvement of the disease knowledge score was observed for the transition group in the ITT analysis (+ 4.36 vs. + 1.23, $p < .001$, effect size = 0.64) (Table 2), and in the per-protocol analysis (+ 4.90 vs. + 1.50, $p < .001$, effect size = 0.70) (Table S3).

No significant changes were observed in terms of clinical outcomes, physical capacity, level of physical activity, and mental health outcomes in ITT or per-protocol analyses (Table 2 and Table S3).

Assessment of contamination bias

The risk of contamination was limited as a large majority of patients enrolled in the trial (N=132, 90.4%) were referred to the institution delivering the transition program from an institution not offering any transition program and lacking an advanced practice nurse or health educator. Indeed, a single health educator supervised the program (A.A.), and only 15 (9.6%) patients previously followed in the institution where the transition program was delivered were enrolled in the trial, of which 8 were in the control group. The health educator was not in charge of these eight patients from the control group during the study period, further limiting contamination bias. The control group received no specific intervention for 1 year apart from routine care. Moreover, no clinically relevant increase in disease knowledge between baseline and final outcome assessment was observed in the control group (+1.4 +/-0.5 points).

Table 1
Baseline population characteristics

	Total population (N = 189)	Transition group (N = 95)	Control group (N = 94)
Sociodemographic characteristics			
Age (years)	18.6 ± 3.6	18.4 ± 3.4	18.9 ± 3.7
Male	96 (51)	55 (58)	41 (44)
Height (cm)	165.8 ± 10.1	167.9 ± 11.0	164.0 ± 8.9
Weight (kg)	57.8 ± 12.8	60.0 ± 14.7	55.8 ± 10.6
Body mass index (Kg/m ²)	20.9 ± 3.6	21.1 ± 4.0	20.7 ± 3.3
Level of education			
Middle school	89/172 (52)	41/82 (50)	48/90 (53)
High school	54/172 (31)	26/82 (32)	28/90 (31)
University	29/172 (17)	15/82 (18)	14/90 (16)
Living environment			
Alone	21/172 (12)	10/81 (12)	11/91 (12)
Couple	19/172 (11)	9/81 (11)	10/91 (11)
Parents house	124/172 (72)	59/81 (73)	65/91 (71)
Other	8/172 (5)	3/81 (4)	5/91 (5)
Clinical outcomes			
Prenatal diagnosis	14/126 (11)	9/64 (14)	5/62 (8)
NYHA functional class			
I	156/167 (93)	81/86 (94)	75/81 (93)
II	10/167 (6)	4/86 (5)	6/81 (7)
III	1/167 (1)	1/86 (1)	0/81 (0)
Type of CHD			
Transposition of the great arteries	14/157 (9)	6/73 (8)	8/84 (9)
Atrial septal defect	24/157 (15)	11/73 (15)	13/84 (15)
Ventricular septal defect	10/157 (6)	6/73 (8)	4/84 (5)
Conotruncal cardiopathy	25/157 (16)	13/73 (18)	12/84 (14)
Aortic valve disease	21/157 (13)	8/73 (11)	13/84 (15)
Pulmonary valve disease	14/157 (9)	5/73 (7)	9/84 (11)
Coarctation of the aorta	15/157 (10)	6/73 (8)	9/84 (11)
Univentricular heart	5/157 (3)	1/73 (1)	4/84 (5)
Atrioventricular septal defect	3/157 (2)	0/73 (0)	3/84 (4)
Heterotaxia and isomerism	10/157 (6)	5/73 (7)	5/84 (6)
Other	16/157 (10)	12/73 (16)	4/84 (5)
Cardiac surgeries	151/186 (81)	73/95 (77)	78/91 (86)
Cardiac interventional catheterization	56/186 (30)	25/95 (26)	31/91 (34)
Pacemaker	6/186 (3)	6/95 (6)	0/91 (0)
Patient under medication	54/184 (29)	30/94 (32)	24/90 (27)
Patient exposure to β -blockers	15/184 (8)	10/94 (11)	5/90 (6)
Cardiovascular comorbidity			
Thromboembolic	1/185 (1)	0/95 (0)	1/90 (1)
Arrhythmia	12/185 (6)	6/95 (6)	6/90 (7)
Other	61/185 (33)	28/95 (29)	33/90 (37)
comorbidities			
HRQL			
PedsQL self-reported scores			

Table 1
Continued

	Total population (N = 189)	Transition group (N = 95)	Control group (N = 94)
Psychological component	75.5 ± 16.3	75.1 ± 14.5	75.8 ± 18.0
Emotion	70.3 ± 21.3	71.3 ± 18.6	69.4 ± 23.8
Relation	83.3 ± 18.5	82.3 ± 18.3	84.3 ± 18.8
School	72.8 ± 18.8	71.7 ± 18.2	73.8 ± 19.4
PedsQL proxy-reported scores (N = 88) ^b			
Total score	72.7 ± 17.6	71.8 ± 16.7	73.7 ± 18.8
Physical component	77.9 ± 20.7	75.4 ± 21.2	80.8 ± 19.9
Psychological component	70.2 ± 18.2	69.7 ± 16.7	70.7 ± 19.9
Emotion	62.3 ± 21.8	64.3 ± 18.9	60.0 ± 24.8
Relation	79.6 ± 21.9	78.4 ± 22.1	81.0 ± 21.8
School	68.6 ± 20.2	66.4 ± 19.1	71.1 ± 21.3
Disease knowledge	20.5 ± 5.9	19.9 ± 5.8	20.8 ± 5.9
Physical health outcomes			
Physical capacity	133 (70)	63 (66)	70 (74)
Peak VO ₂ (mL/Kg/min)	32.1 ± 8.0	33.2 ± 8.1	31.2 ± 7.9
Percent-predicted peak VO ₂ (%)	79.6 ± 17.4	79.2 ± 18.9	78.0 ± 16.1
VAT (mL/Kg/min)	21.9 ± 6.7	22.6 ± 6.1	21.3 ± 7.2
Percent-predicted VAT (%)	53.9 ± 14.1	53.5 ± 13.9	54.2 ± 14.3
VE/VCO ₂ slope	29.7 ± 5.1	29.5 ± 4.7	29.9 ± 5.4
Peak VO ₂ <80% of predicted value	60/131 (46)	28/62 (45)	32/69 (46)
Level of physical activity			
Inactive	30/181 (17)	12/89 (13)	18/92 (20)
Active	148/181 (82)	75/89 (84)	73/92 (79)
Very active	3/181 (2)	2/89 (2)	1/92 (1)
Mental health outcomes			
Level of anxiety (STAI) ^a (N = 91)	38.5 ± 10.8	39.3 ± 9.7	37.7 ± 11.8
Level of anxiety (STAI-C) ^b (N = 98)	33.2 ± 7.7	32.0 ± 6.6	34.3 ± 8.5
Level of depression (BDI) ^a (N = 91)			
No depression	68/90 (76)	32/44 (73)	36/46 (78)
Mild depression	13/90 (14)	7/44 (16)	6/46 (12)
Moderate depression	6/90 (7)	4/44 (9)	2/46 (4)
Severe depression	3/90 (3)	1/44 (2)	2/46 (4)
Level of depression (CDI) ^b (N = 98)	10.4 ± 7.2	10.2 ± 6.9	10.7 ± 7.6

Values are means ± standard deviation (SD) or N(%).

BDI = Beck Depression Inventory; CDI = Child Depression Inventory; CHD = congenital heart disease; HRQoL = health-related quality of life; NYHA = New York Heart Association; STAI = State and Trait Anxiety Inventory; STAI-C = State and Trait Anxiety Inventory-Children; VAT = ventilatory anaerobic threshold; VE/VCO₂ = ventilatory efficiency; VO₂ = oxygen consumption.

^a Questionnaire for young adults.

^b Questionnaire for adolescents.

Table 2
Change in primary (HRQoL) and secondary outcomes in both groups with ITT analysis

	Transition group (N = 95)	Control group (N = 94)	Absolute difference [95% CI]	Effect size [95% CI]	p value
Change in HRQoL					
Change in PedsQL self-reported scores					
Total score	3.85 ± 1.06	0.82 ± 1.05	3.03 [0.08; 5.98]	0.30 [0.01; 0.58]	.044
Physical component	3.14 ± 1.41	0.30 ± 1.38	2.84 [-1.02; 6.70]	0.21 [-0.08; 0.50]	.149
Psychological component	4.22 ± 1.18	0.89 ± 1.19	3.33 [0.01; 6.64]	0.29 [0.00; 0.58]	.049
Change in PedsQL proxy-reported scores ^a					
Total score	3.18 ± 1.90	0.07 ± 1.80	3.11 [-2.16; 8.37]	0.24 [-0.16; 0.64]	.245
Physical component	5.98 ± 2.35	-3.20 ± 2.63	9.18 [1.86; 16.51]	0.53 [0.12; 0.93]	.015
Psychological component	2.41 ± 2.08	1.63 ± 1.89	0.77 [-4.78; 6.33]	0.06 [-0.34; 0.46]	.784
Change in level of disease knowledge	4.36 ± 0.59	1.23 ± 0.54	3.13 [1.54; 4.72]	0.64 [0.31; 0.96]	<.001
Change in physical outcomes					
Physical capacity					
Peak VO ₂ (ml/kg/min)	-0.76 ± 0.77	-0.94 ± 0.66	0.18 [-1.85; 2.22]	0.04 [-0.36; 0.43]	.859
Percent-predicted peak VO ₂ (%)	-3.85 ± 1.79	-1.18 ± 1.53	-2.67 [-7.40; 2.05]	-0.23 [-0.62; 0.17]	.264
VAT (ml/kg/min)	-0.42 ± 0.76	-1.21 ± 0.66	0.79 [-1.22; 2.79]	0.16 [-0.24; 0.55]	.439
Percent-predicted VAT (%)	-2.09 ± 1.86	-1.80 ± 1.61	-0.30 [-5.24; 4.65]	-0.02 [-0.42; 0.37]	.906
VE/VCO ₂ slope	0.20 ± 0.84	1.11 ± 0.74	-0.91 [-3.19; 1.38]	-0.16 [-0.56; 0.23]	.431
Level of physical activity					
Worsening	13/56 (23)	12/77 (16)	7.63 [-6.08; 21.34]	-	.355
Stability	39/56 (70)	55/77 (71)	-1.79 [-17.50; 13.93]	-	
Improvement	4/56 (7)	10/77 (13)	-5.84 [-15.94; 4.25]	-	
Change in mental health outcomes					
Change in level of anxiety (STAI) ^a	-1.83 ± 1.40	0.49 ± 1.16	-2.32 [-6.04; 1.40]	-0.33 [-0.83; 0.18]	.216
Change in level of anxiety (STAI-C) ^b	-2.05 ± 0.97	-1.25 ± 0.91	-0.80 [-3.48; 1.88]	-0.14 [-0.61; 0.33]	.551
Change in level of depression (BDI) ^a					
Improvement	4/29 (14)	6/38 (16)	-2.00 [-19.08; 15.09]	-	
Stability	19/29 (66)	27/38 (71)	-5.54 [-28.06; 16.99]	-	
Worsening	6/29 (21)	5/38 (13)	7.53 [-10.71; 25.78]	-	
Change in level of depression (CDI) ^b	-0.83 ± 1.16	-0.49 ± 1.02	-0.34 [-3.47; 2.78]	-0.06 [-0.56; 0.45]	.826

Values are means adjusted on age and baseline score's value ± standard error or N (%).

BDI = Beck Depression Inventory; CDI = Child Depression Inventory; CI = confidence interval; HRQoL = health-related quality of life; ITT = intention-to-treat; STAI = State and Trait Anxiety Inventory; STAI-C = State and Trait Anxiety Inventory-Children; VAT = ventilatory anaerobic threshold; VE/VCO₂ = ventilatory efficiency; VO₂ = oxygen consumption.

^a Questionnaire for young adults.

^b Questionnaire for adolescents.

Discussion

The TRANSITION-CHD randomized controlled trial demonstrated that the HRQoL of adolescents and young adults with CHD was significantly improved by a structured transition program. The expected number of 200 subjects was included in the study, of which 189 subjects were analyzed in the ITT analysis, as defined in the study protocol [16]. A significant difference in the primary outcome was observed, e.g., the change in HRQoL selfreported PedsQL total score between baseline and 12-month follow-up, with a mean group difference of three points and an effect size of 0.3, in favor of the transition intervention.

The positive impact of this transition program on a global evaluation of the quality of life is a step forward in research evaluating preventive interventions in youth with cardiac diseases. The use of a PRO as a primary endpoint, as well as the assessment of its variation over a fairly long period of 1 year, contribute to the value of these results.

The holistic approach adopted by the transition program could elucidate why the benefits associated with the intervention in the trial surpassed values previously reported for the minimal clinically important difference [40]. Notably, the mean HRQoL increase in the transition group observed in this study (+ 3.85) was close to the reported minimal clinically important difference for the PedsQL instrument (+ 4.3) [41].

This holistic intervention may have additionally played a role in fostering positive effects on various dimensions of HRQoL, including physical health, social functioning, and proxy reports.

In this study, despite the statistical significance, the magnitude of the difference in HRQoL change (mean difference of 3 with an effect size of 0.3) may appear limited or even non-clinically relevant. However, we believe that this result remains important, given the preventive nature of this program dedicated to young people and considering the decrease in quality of life in adults with CHD [15].

Our findings complement those of the recently conducted STEPSTONES randomized controlled trial in a cohort of 114 adolescents with CHD, which found a favorable increase in patient empowerment associated with the transition intervention (mean difference of 3.44 and effect size of 0.397) [9]. Indeed, transition programs are commonly designed to improve transition readiness and therefore increase the level of patient empowerment [42]. Nevertheless, no impact on HRQoL, used as a secondary outcome, was observed in the STEPSTONES trial. These two transition programs are structurally similar and were originally built using a holistic approach, aiming to address a wide spectrum of patient potential needs [9, 10]. Nevertheless, our transition program has specific characteristics: (1) referral of patients by several tertiary care centers to a single site delivering the transition program, with supervision by a single health educator who is an advanced practice nurse trained both in pediatric cardiology and patient education; (2) organization of distinct group sessions for both patients and relatives, led by the same multidisciplinary team; and (3) program delivered at a pediatric cardiac rehabilitation center, facilitating an active promotion of physical activity [11]. Overall, the beneficial effects on HRQoL and patient empowerment observed in these two randomized controlled trials support the relevance of the major worldwide efforts made over the past decade by multidisciplinary healthcare teams and patient organizations for adolescents with CHD transitioning to adulthood [3, 5].

Moreover, the change in HRQoL self-reported psychological score was significantly better in the transition group, with a mean group difference of 3.3 points. In this study, nearly 10% of the overall patient cohort at baseline reported symptoms of moderate to severe depression in the Beck Depression Inventory questionnaire, which is concordant with the literature concerning children and adolescents with CHD [43]. The presence of a psychologist in a multidisciplinary team involved in transition programs is important. Even if individual mental health care cannot be implemented during a transition group session, the identification of difficult psychosocial situations in some adolescents or young adults must lead to structured psychological support, following educational workshops.

Additionally, the change in HRQoL proxy-reported physical score was significantly better in the transition group, with a mean group difference of 9.2 points. The TRANSITION-CHD program may have helped patients and families deconstruct prebuilt concepts around the risk related to sports practice in CHD [44]. One of the main educational aims of the transition group session dedicated to families was to limit parental barriers to their child's physical

activity, which may have contributed to this positive change in their child's proxy-reported physical wellbeing. As a potential consequence, at baseline, cardiopulmonary fitness was impaired in about half of the patients enrolled in the trial, and nearly one in five patients was physically inactive. The TRANSITION-CHD program has been intrinsically built with strong educational objectives in favor of the promotion of physical activity in young patients with CHD [11]. Indeed, young patients with low levels of physical activity are particularly affected by being overweight or obese, [29] whereas aerobic fitness is expected to be normal or subnormal in most children with CHD [23]. Physical inactivity and sedentary behaviors precipitate many children with CHD into the vicious circle of physical deconditioning, which negatively affects their quality of life [11, 13]. Ultimately, physically inactive adolescents are at higher risk for a sedentary lifestyle in adulthood [45], leading to substantial cardiovascular morbidity in the long term [25].

Finally, a significant improvement in disease knowledge in the transition group has been observed, which is consistent with the previous studies [8,9]. Indeed, patients' lack of knowledge about their disease leads to a deficit of self-efficacy and adherence to care, potentially impacting their quality of life. It can also become an obstacle to patients' implications and adherence to the decisions concerning their health [46,47]. Conversely, good patient knowledge about the disease is usually associated with less anxiety and a better quality of life [48]. In the TRANSITIONCHD program, the health educators used various educational tools oriented towards patient disease knowledge and autonomy, such as 3D printed heart models, card games of clinical symptoms, or a spinning wheel of questions on everyday life [49]. Such educational support should probably be repeated throughout the patient's life, using different age-appropriate tools, to improve the long-term prognosis.

Study limitation

The heterogeneous nature of the patients enrolled in the trial made it impossible to evaluate the impact of the TRANSITIONCHD program on specific subgroups of complex CHD, for which the effect could be even greater. Indeed, larger effect sizes could have been observed in targeted populations.

In addition, the wide age range among patients meant that the messages delivered had to be adapted, addressing topics relevant to the age groups concerned. As a result, the potential impact of the intervention is likely to be biased when comparing results between adolescents and young adults.

No significant changes were observed in the major cardiovascular secondary outcomes, such as cardiopulmonary fitness, or in the major mental health outcomes, such as anxiety and depression. Moreover, this study was not designed to assess long-term outcomes, such as adherence to care or cardiovascular morbidity. Ongoing randomized controlled trials with specific interventions have been initiated by our group to address these aspects in adolescents and young adults with CHD [18,21].

Despite the active support of the TRANSITION-CHD study group (e.g., 17 investigators, one study coordinator, three clinical research associates, and two patient organization delegates), 30% of patients enrolled in the intervention group did not fully participate in the transition program, and the per-protocol analysis failed to reach statistical significance. Commonly, conducting patient education programs remains challenging, both in clinical research and in

real life. Therefore, after the end of the trial, these difficulties in terms of patient adherence led our group to adapt the TRANSITION-CHD program into a “hybrid” model, combining in-person and videoconference transition individual and group sessions.

Conclusion

In the TRANSITION-CHD randomized controlled trial, HRQoL of adolescents and young adults with CHD was significantly improved by a structured transition program between baseline and 12-month follow-up. A positive change in favor of the transition intervention was observed in the primary outcome, e.g., the HRQoL self-reported global wellbeing, but also in the HRQoL self-reported psychological wellbeing, the HRQoL proxy-reported physical wellbeing, and the level of disease knowledge. In the global field of preventive cardiology, transition programs dedicated to adolescents and young adults with CHD are the gateway to patient-specific interventions, such as cardiac rehabilitation or psychological support. Further studies will have to determine the impact of transition programs on long-term prognosis.

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