ORIGINAL ARTICLE

WILEY Congenital Heart Disease

Modifiable cardiovascular risk factors in adolescents and adults with congenital heart disease

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Abstract

Objective: Individuals with congenital heart disease (CHD) may be at higher risk of acquired cardiovascular disease than the general population due to their underlying physiology and/or surgical sequelae. We sought to assess the prevalence of cardiovascular disease risk factors in youth and adults with CHD.

Methods: We assessed cardiovascular health as per the Cardiovascular Health in Ambulatory Care Research Team (CANHEART) health index in patients with CHD aged 15+ years who attended cardiology outpatient clinics. Participants self-reported smoking behavior, fruit and vegetable consumption, physical activity, and whether they had diabetes and hypertension. Individual health indices were categorized into ideal/not ideal, and sum of individual health indices was categorized as poor, intermediate or ideal cardiovascular health as per CANHEART criteria.

Results: We included n = 102 adults (35.4 ± 12.9 years, 46% female) and n = 88 youth (17.2 ± 1.1 years, 41% female). Most individuals reported to be nonsmokers (88% youth vs 86% adults) and to consume \geq 5 servings of fruit and vegetables per day (83% vs 85%, respectively). More adults than youth were overweight/obese (52% vs 22%, p < 0.001) though more adults than youth reported meeting age-specific physical activity guidelines (84% vs 55%, p < 0.001). According to CAN-HEART health index criteria, 32% of youth and 27% of adults were in ideal cardiovascular health.

Conclusions: A low proportion of individuals with CHD are in ideal cardiovascular health, suggesting a need to promote healthy lifestyles during adolescence and throughout adulthood in these individuals.

KEYWORDS

adolescent, adults, child, congenital heart disease, health behavior, obesity

1 | INTRODUCTION

Congenital heart disease (CHD) is the most common congenital defect that occurs in approximately 1 in 100 live births.¹ Advances in preoperative care, surgical techniques, and postoperative management of children with CHD have resulted in significant improvements in survival and life expectancy,² and adults with CHD now outnumber children by 2:1.³ However, intrinsic structural and functional abnormalities, surgical sequelae or disturbances in cardiac rhythm may place individuals with CHD at increased cardiovascular risk compared with the general population.⁴ It is well documented that the atherosclerotic process originates in childhood;^{5,6} children with CHD who have undergone coronary manipulation (ie, status postarterial switch operation, Ross procedure, etc.) or have intrinsic coronary abnormalities (ie, pulmonary atresia with intact ventricular septum) may have additional predisposition for early or accelerated coronary artery disease.⁷ Our understanding regarding the role of modifiable cardiovascular risk factors on longterm outcomes in CHD is limited and continues to evolve with an aging CHD population. However, studies have consistently reported that adults with CHD present with modifiable risk factors at rates that warrant attention.^{8–14} While it is well established that cardiovascular risk factors track from childhood to adulthood in the general population,^{15,16} data on modifiable risk factor prevalence in youth with CHD are scarce, 17,18 and largely focused on the troubling prevalence of overweight and obesity in these children. $^{19-25}$

The Cardiovascular Health in Ambulatory Care Research Team (CANHEART) health index is a tool that was developed to monitor the prevalence of cardiovascular risk factors in the Canadian population; it encompasses information on health status (weight, blood pressure, and diabetes) and health behaviors (smoking, physical activity, and diet).²⁶ The CANHEART health index has already provided insight into spatial, temporal, and demographic variations in the cardiovascular health status among Canadians.²⁶ The aim of the current study was to utilize the CANHEART health index to assess the prevalence of cardiovascular disease risk factors in youth and adults with CHD.

2 | METHODS

2.1 Sample and protocol

We recruited a convenience sample of patients with CHD attending regularly scheduled clinic visits for routine follow-up. Youth aged >15 years were recruited from cardiology outpatient clinics at BC Children's Hospital (Vancouver, BC) or Stollery Children's Hospital (Edmonton, AB). Adults were attending a CHD clinic at the Mazankowski Alberta Heart Institute (Edmonton, AB). Participants completed a brief selfadministered questionnaire regarding their health and health behaviors during clinic visits between August 2014 and March 2016. Nurses measured height (0.1 cm) and weight (0.1 kg). Pertinent medical records, including cardiac diagnosis, were obtained from patient charts. Cardiac diagnosis was categorized as CHD (mild, moderate, or complex²⁷); noncongenital cardiovascular diseases were excluded (n = 17). All data were centrally stored and managed using REDCap, a secure browser-based electronic data capture system.²⁸ We obtained institutional ethics approvals and informed written consent; written assent was additionally obtained for participants <18 years. The study conformed with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards, except that this study was not registered in a public database.

2.2 Questionnaire and CANHEART health index

Normal weight was categorized as BMI <25 kg/m², or according to age-sex-specific International Obesity Task Force (IOTF) criteria for those aged <18 years.²⁹ Classification of the combined overweight/ obesity category (as used in the present analyses) is comparable between the IOTF method and the other widely used US Centers for Disease Control method, although it is of note that estimates of obesity specifically tend to be lower by the IOTF method.³⁰ Participants self-reported their health behaviors regarding cigarette smoking, physical activity, and fruit and vegetable consumption in a brief self-administered questionnaire. Adults additionally reported whether they had diabetes and/or hypertension. Details regarding assessments of individual health behaviors and indices, as well as corresponding categorization of responses into ideal/not ideal are shown in Table 1.

CANHEART health index score was calculated in accordance with MacLagen et al.,²⁶ with youth being defined as 15 to 19 years and adults defined as \geq 20 years. CANHEART health index score was calculated as the sum of individual indices (range: 0 to 4 in youth; 0 to 6 in adults), and grouped as poor (\leq 2 in youth or \leq 3 in adults), intermediate (3 in youth and 4 to 5 in adults), or ideal health (4 in youth and 6 in adults).

2.3 Statistical analysis

Descriptive statistics (frequencies (%), mean \pm SD, and median [IQR]) were calculated for applicable variables. Between-group differences (ie, by sex, age groups (in adults defined as 20 to 25, 26 to 40, or \geq 41 years), and cardiac diagnosis) were assessed by independent *t*-tests, Pearson's chi-squared, or Fisher's exact test. Analyses were carried out using Stata (v.14.1, Stata Corp LP, College Station, Texas) and significance was set at *P* < .05.

3 | RESULTS

We included 88 youth (17.2 \pm 1.1 years, 41% female) and 102 adults (35.4 \pm 12.9 years, 46% female) with complete data. In the youth sample, CHD disease categories were relatively evenly represented among the n = 88 individuals with CHD (32% mild, 40% moderate, and 28% complex). In the adult sample, moderate CHD was the most common category (47% vs 30% mild and 23% complex). Detailed cardiac diagnoses are listed in Table 2. General demographic sample characteristics for youth and adult samples are provided in Table 3. Adults had significantly greater BMIs (26.3 vs 22.5 kg/m², *P* < .001), and were more frequently overweight (30% vs 10%) and obese (22% vs 11%, *P* < .001) compared with the youth sample. Group mean BMI and prevalence of weight categories was no different by sex in adults, but in youth, more females than males were overweight/obese (33% vs 13%, *P* = .026).

3.1 Cardiovascular health

The prevalence of individual cardiovascular health indices is shown in Table 3 and Figure 1. Most reported to be nonsmokers (88% youth and 86% adults) and to consume \geq 5 servings of fruit and vegetables per day (83% youth and 85% adults); there were no significant differences between prevalence of "ideal status" for these indices between youth and adults, or by sex. More adults than youth reported to be meeting age-specific physical activity guidelines (84% vs 55%, *P* < .001). In adults, there were no differences in meeting physical activity guidelines by sex. In youth, males more frequently reported to be meeting physical activity guidelines compared with females (63% vs 42%, *P* = .044). In the adult sample, 19% reported to have hypertension, which was no different by sex. Diabetes was rare (<2%), but only occurred in females.

3.2 | CANHEART health index

CANHEART health index scores and prevalence of cardiovascular health categories in youth and adult samples are shown in Table 3 and

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TABLE 1 Assessment of individual health indicators and corresponding CANHEART health index scoring

		CANHEART health index		
	Assessment	Ideal	Not ideal	
Overweight/obesity	Measured in clinic: Height (cm) and weight (kg) BMI calculated (kg/m ²)	Normal weight:	Overweight or obese:	
		 BMI < 25 kg/m² (adults) BMI = "normal" by IOTF cut-points (youth) 	 BMI ≥ 25 kg/m² (adults) BMI = "overweight" or "obese" by IOTF cut-points (youth) 	
Smoking	Self-report (select one drop-down option): "Do you smoke or have you ever tried a cigarette?"	Nonsmoker:	Smoker:	
		 Nonsmoker or quit ≥12 months ago (adults) Never tried smoking (youth) 	 Current smoker or quit <12 months ago (adults) Tried smoking, quit smoking, or current smoker (youth) 	
Physical activity	Self-report (free text): "How much physical activity do you get in an average day?" Moderate-to-vigorous activity in minutes	Meets activity guidelines:	Does not meet activity guidelines:	
		 ≥ 30 min/d (adults) ≥ 60 min/d (youth) 	 < 30 min/d (adults) < 60 min/d (youth) 	
Fruit and vegetable consumption	Self-report (select one drop-down option each): "How many servings of fruit and vegeta- bles do you eat in an average day?"	Meets fruit and vegetable consumption guidelines:	Does not meet fruit and vegetable consumption guidelines:	
		• \geq 5 servings per day	• < 5 servings per day	
Hypertension (adults only)	Self-report (select one drop-drown option): "Have you been told by a doctor or nurse that you have problems with your blood pressure?"	No hypertension:	Hypertension:	
		• No or not sure (adults)	• Yes (adults)	
Diabetes (adults only)	Self-report (select one drop-drown option): "Do you have diabetes (either type 1 or 2)?"	No diabetes:	Diabetes:	
		• No or not sure (adults)	• Yes (adults)	

Abbreviations: BMI, body mass index; IOTF, International Obesity Task Force.

Figure 1. The distribution of CANHEART cardiovascular health categories differed significantly between youth and adult samples (P = .019). In both adults and youth, approximately 30% were in ideal health, but fewer adults were classified as being in poor health and more in intermediate health compared with youth. This finding is at least in part due to the different CANHEART scoring mechanism for adults and youth, where, for example, the absence of hypertension and diabetes—which is not assessed in youth—already provides half of the needed "points" to be classified as intermediate vs poor health. In adults, there were no significant differences in CANHEART health index score or cardiovascular health categories by sex or according to age group. In youth, more females than males were in poor health (36% vs 13%) and fewer were in intermediate health (36% vs 52%, P = .043).

3.3 Associations between severity of CHD diagnosis and cardiovascular risk factors

In neither adult nor youth samples were there significant associations between the severity of CHD diagnosis and the following individual cardiovascular risk factors: BMI (kg/m²), weight status, smoking, physical activity, and fruit and vegetable consumption (all P > .05). In adults, hypertension was more common in individuals with a CHD diagnosis of "moderate" severity (29%) vs individuals with "mild" (6%), or "complex" (13%) diagnoses (P = .039). It is of note that the greater prevalence of hypertension in the "moderate" group was not attributable to individuals with coarctation of the aorta, as the prevalence of this

specific diagnosis did not differ significantly between individuals with vs without hypertension (16% vs 11%, P = .692).

We were unable to assess associations between CHD diagnosis and diabetes, as only one adult had diabetes (with transposition of the great arteries). Hypertension and diabetes were not assessed in youth in the current study. There were no significant associations between severity of CHD diagnosis and the prevalence of CANHEART categories or CANHEART health index score in either age group.

4 | DISCUSSION

Youth and adults with CHD presented with a range of cardiovascular risk factors in our study. Overall, only 1 in 3 individuals with CHD was in ideal cardiovascular health as per CANHEART criteria.²⁶ We found expected sex-differences for physical activity in youth but not for any other risk factor in either age group.

4.1 Overweight and obesity in individuals with CHD

Excess body weight predisposes to a myriad of noncommunicable diseases such as cardiovascular disease, diabetes, and many cancers,³¹ and has reached pandemic proportions in the general population.³² Obese adults with CHD are more likely to have metabolic syndrome than obese adults without CHD.¹¹ In children and youth with CHD, significant associations between obesity and elevated blood pressure,²² and cardiometabolic risk factors²⁰ have been reported. Although the long-term

TABLE 2 Distribution and classification of cardiac diagnosis in the current sample (n = 190)

Cardiac diagnosis	Youth (n = 88)	Adult (n = 102)
Simple Ventricular septal defect Mitral valve disease Atrial septal defect Bicuspid aortic valve Mild pulmonary stenosis Patent ductus arteriosus Mild aortic stenosis	27 7 5 4 3 3 3 2	31 4 3 12 4 3 5 0
Moderate Tetralogy of Fallot Coarctation of the aorta Moderate/severe aortic stenosis Ostium primum atrial septal defect Ebstein's anomaly Atrioventricular septal defect Severe mitral valve regurgitation Interrupted aortic arch Double chamber right ventricle Moderate tricuspid regurgitation Interrupted aortic arch Dilated thoracic aorta Partial anomalous pulmonary venous return (or drainage) Moderate/severe pulmonary valve stenosis Anomalous left coronary artery from pulmonary artery Aortic valve replacement	36 10 6 3 2 2 1 1 1 1 1 1 1 1 0 0 0 0	48 16 12 9 1 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
Complex Transposition of the great arteries Single ventricle Double outlet ventricle Pulmonary atresia Truncus arteriosus Fontan Conduit Tricuspid atresia Isomerism	25 13 4 2 2 2 1 1 1 0 0	23 11 1 2 4 1 0 0 1 3

Note. CHD severity was categorized in accordance with consensus guidelines.²⁷

impact of childhood obesity in individuals with CHD is yet unknown due to a lack of sufficient long-term follow-up data, it is likely that obesity can exacerbate future cardiovascular risk by conspiring with the underlying congenital substrate.^{8,10} Therefore, mounting reports of overweight and obesity in CHD populations are concerning. In our study, we found that 52% of adults and 23% of youth with CHD were overweight or obese, which is remarkably similar to Canadian national data (using the same IOTF criteria for youth).^{26,33,34} These findings align with what has been reported elsewhere: that prevalence of overweight and obesity in both adults^{9,11,13,14} and youth¹⁹⁻²⁵ with CHD is common and similar to the general population. Although we found no significant differences in BMI or weight status according to CHD severity, it is of note that weight status is a complex issue in CHD; several studies reported that prevalence of underweight is significantly higher in both youth^{19,21} and adults^{9,13} with CHD compared with the general population (particularly in complex types of CHD such as univentricular hearts), although it is of note that prevalence of underweight was low in our youth and adult samples with CHD. There have been reports that there appears to be a weight status gradient across the CHD spectrum, with overweight/obesity being more common among simpler types of CHD in both youth^{21,22,25} and adults.^{10,14} Failure

to thrive, or decreased growth trajectories early in life, continue to be an issue particularly in complex types of CHD.^{35,36} Historically, this phenomenon has led to routine endorsements of high caloric intake in children with CHD, which could explain abnormal growth patterns throughout adolescence, where gains in weight but not stature accelerates.²³ This accelerated weight gain, in combination with inadequate physical activity, predisposes for overweight and obesity at an early age. The double disease burden of underweight and obesity in CHD populations is further complicated by recent research that reported on the "obesity paradox," where having a higher BMI was associated with lower all-cause and cardiac mortality in adults with CHD.³⁷ More long-term follow-up data are needed to better understand the role of weight status—both underweight and overweight/obesity—on long-term health in individuals with CHD.

4.2 Physical activity—the most important health behavior in CHD?

Physical activity—defined as "any bodily movement produced by skeletal muscles that results in energy expenditure"³⁸—is one of the most important health behaviors, as it significantly reduces risk for

TABLE 3	Sample characteristics and cardiovascular health in youth
and adult	amples

	Youth	Adult
Sample characteristics n Female Age (years) Height (cm) Weight (kg) BMI (kg/m ²)	$8836 (41%)17.2 \pm 1.1170.6 \pm 10.365.6 \pm 14.222.5 \pm 4.6$	$102 \\ 47 (46\%) \\ 35.4 \pm 12.9^{a} \\ 170.1 \pm 10.8 \\ 76.4 \pm 17.9^{a} \\ 26.3 \pm 5.3^{a} \\$
BMI weight category Underweight Normal weight Overweight Obese	9 (10%) 60 (68%) 9 (10%) 10 (11%)	2 (2%) ^a 47 (46%) ^a 31 (30%) ^a 22 (22%) ^a
CHD severity Mild Moderate Severe	28 (32%) 35 (40%) 25 (28%)	31 (30%) 48 (47%) 23 (23%)
Cardiovascular health Ideal weight Nonmoker Physically active (age-specific guidelines) ^b Fruit and vegetables No hypertension (adults) No diabetes (adults) CANHEART health index score ^c Poor health ^d Intermediate health ^e Ideal health ^f	69 (78%) 77 (88%) 48 (55%) 73 (83%) - - 3.0 ± 0.9 20 (23%) 40 (45%) 28 (32%)	$\begin{array}{c} 49 \ (48\%)^{a} \\ 88 \ (86\%) \\ 86 \ (84\%)^{a} \\ 87 \ (85\%) \\ 83 \ (81\%) \\ 101 \ (99\%) \\ 4.8 \pm 1.0 \\ 10 \ (10\%)^{a} \\ 64 \ (63\%)^{a} \\ 28 \ (27\%) \end{array}$

Note. Data are presented as n (%) or (mean \pm SD).

^aSignificantly different between youth with CHD and adults with CHD at P < .05.

^bDaily minutes of moderate-to-vigorous physical activity: \geq 60 minutes in youth; \geq 30 minutes in adults.

^cScored between 0 and 4 in youth, and 0 and 6 in adults; higher score indicates better health.

^dThe presence of 0–3 ideal health indices among adults and 0–2 ideal health indices among youth.

^eThe presence of 4–5 ideal health indices among adults and 3 ideal health indices among youth.

^fThe presence of all ideal health indices (6 among adults; 4 among youth).

cardiovascular disease, type 2 diabetes and some cancers.³⁹ A recent consensus statement by the American Heart Association recognizes the importance of physical activity in patients with CHD, and recommends that most individuals with CHD should aim to achieve the same physical activity guidelines as the general population.⁴⁰ For adults, the recommended minimum is 150 minutes of moderate-to-vigorous physical activity per week,⁴¹ which is typically operationalized as a minimum of 30 min/day. For children, the recommended minimum is considerably higher at 60 minutes of moderate-to-vigorous physical activity every day.⁴² Activities of moderate-to-vigorous intensities typically refers to an energy cost of \geq 3 metabolic equivalents (multiples of resting metabolism), which includes brisk walking, some types of occupational activity and household chores, as well as a wide range of sports and exercises.⁴³

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It is generally thought that physical activity levels are lower in individuals with CHD,^{10,40} and the increasing prevalence of overweight and obesity in these individuals is frequently attributed to low physical activity levels stemming from real and perceived physical activity restrictions. However, we documented a notably higher proportion of adults with CHD met age-specific physical activity guidelines (≥30 min/d moderate-to-vigorous physical activity) when compared with national 2011 data (84% vs 55%).²⁶ This finding aligns with other studies that have reported higher sport participation in adults with CHD compared with the general population.^{9,14} For youth with CHD, however, we found no differences in the proportion of youth meeting agespecific physical activity guidelines (>60 min/d) compared with national 2011 data (all \sim 55%).²⁶ Our observation that a greater proportion of adults than youth (with or without CHD) met physical activity guidelines (by self-report) is likely predominantly due to the lower physical activity guidelines for adults (≥30 min/day) compared with youth (\geq 60 min/day), rather than adults with CHD being more active than youth with CHD.

These contrasting findings are partly explained by methodological differences. The Canadian Community Health Survey from which we draw national data for comparison,²⁶ conducted detailed assessments of health behaviors by computer-assisted interviews. Such an approach was beyond the scope of our study, which utilized a simplified selfreport question for each health behavior (see Table 1). Recall error and social desirability are also important considerations that may contribute to the overestimation of prevalence of health behaviors. For example, in the US-based National Health and Nutritional Examination survey, 51% of adults met physical activity guidelines based on self-report, but only 5% did when physical activity was measured objectively by accelerometry.⁴⁴ Recent studies that have used objective measures of physical activity in youth⁴⁵ and adults⁴⁶ with CHD found physical activity levels to be broadly comparable to the general population. While encouraging, these data need to be viewed in the context of the global physical inactivity crisis,47 and furthermore, we lack data confirming that the minimum "dose" recommended in general physical activity guidelines is also sufficient to achieve meaningful cardiovascular risk reduction in individuals with CHD.

4.3 Additional health behaviors in CHD

In light of an increasing and aging CHD population with alarming rates of overweight and obesity, it is critically important that an increased emphasis is placed on a broader assessment of health behaviors. Several recent studies have assessed a range of health behaviors in adults and children/youth with CHD, revealing evolving epidemiologic patterns. The prevalence of smoking in both adults^{9,12,14} and youth⁴⁸ with CHD has consistently been reported to be lower than in the general population. Similarly, we found that smoking was less common in adults and youth with CHD compared with the general Canadian population²⁶ (14% vs 25% in adults; 12% vs ~19% in youth). Encouragingly, a large proportion of both adults and youth with CHD in our study reported to consume \geq 5 servings of fruit and vegetables daily (~85%), which was much higher than national data (~40%).²⁶ We are aware of only

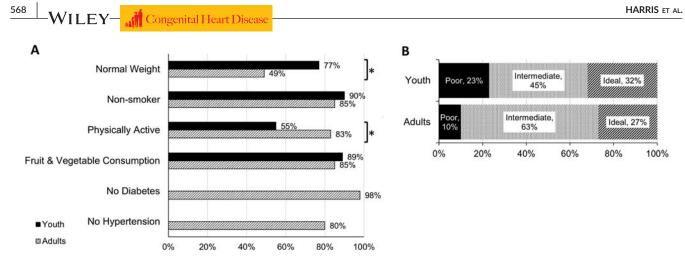


FIGURE 1 Prevalence of individual cardiovascular health indices (A) and CANHEART health index categories (B) and in youth and adult samples with CHD. CHD, congenital heart disease. *Significantly different between youth and adults with CHD at p<0.05. CANHEART health index categories: Poor—the presence of 0–3 ideal health indices among adults and 0–2 ideal health indices among youth; Intermediate—the presence of 4–5 ideal health indices among adults and 3 ideal health indices among youth; ideal—the presence of all ideal health indices (6 among adults; 4 among youth)

one other study that conducted a comprehensive dietary assessment in children with CHD, and found a lower fruit and vegetable consumption and a poorer overall diet quality, including frequent sugar-sweetened beverage consumption, compared with the general population.¹⁸ Regardless of the paucity of data on dietary patterns in CHD, annual screening of dietary quality is recommended for the management of adult CHD, alongside screenings of weight status, physical activity, and smoking.¹⁰

4.4 | A call for routine cardiovascular risk factor screening in pediatric cardiology

Our data adds to a growing body of evidence that children with CHD already present with modifiable cardiovascular risk factors at alarming rates that mirror the general population. It is well established that obesity¹⁵ and physical activity¹⁶ track from childhood into adulthood in the general population. For the CHD population, the traditional endorsement of high caloric intake in the early years, followed by a lack of dietary monitoring, and further exacerbated by physical activity restrictions (real or perceived), has the potential to fuel a future obesity epidemic among the growing and aging CHD population. A lack of time and dedicated focus to performing cardiovascular risk factor screening and counseling by pediatric cardiologists was identified as a prominent issue over a decade ago⁴⁹; yet the concerning data that we and others present on the changing landscape on cardiovascular risk profiles in children with CHD evidently calls for more decisive action from pediatric cardiologists.

4.5 | Study limitations

Our sample was a convenience sample of individuals attending cardiology outpatient clinics at one of three sites, and as such, may not be nationally representative. Although height and weight were measured directly, we used a simple self-report questionnaire to assess health behaviors. Recall error and social desirability are known limitations of self-report, and lead to marked overestimates of heath behaviors, such as physical activity.44 Although we compared our results to age-specific national data, we did not include control groups for either age group. Our adult sample included a wide age range (35.4 ± 12.9 years; absolute range: 20–79 years), and while we did not find any significant differences in CANHEART health index by age in our study, future research should explore the potential role of surgical era, impact of significant life transitions on health behaviors, and survival bias in adults with CHD. We did not assess other health behaviors such as alcohol consumption or recreational drug use, which others reported to be slightly lower in individuals with CHD compared with the general population.^{14,48} We also did not perform any blood work to assess cardio-metabolic risk factors, such as triglycerides, high-density lipoprotein levels, or fasting glucose. The cross-sectional observational study design limits insight into the prognostic value of cardiovascular risk factor screening in the CHD population; long-term tracking and interventional studies are clearly warranted to inform future practice on routine cardiovascular risk factor screening in individuals with CHD.

5 | CONCLUSION

This study of adolescents and adults with CHD demonstrates that there are modifiable cardiovascular risk factors present in almost 70% of the CHD population. Identifying these risk factors should be a top priority for caregivers. Intervention for modifiable risk factors presents an important opportunity to optimize their cardiovascular health status.

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CONFLICT OF INTEREST

All authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

The article was approved by all authors.

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