Differential Impact of Physical Activity Type on Depression in Adults with Congenital Heart Disease: A Multi-center International Study

Running Title: Physical Activity and Depression in ACHD

Jong Mi Ko, MA,[a] Kamila S. White, PhD,[b] Adrienne H. Kovacs, PhD,[c,d] Kristen M. Tecson, PhD,[e] Silke Apers, PhD,[f] Koen Luyckx, PhD,[g] Corina Thomet, MSc,[h] Werner Budts, MD, PhD,[i,j] Junko Enomoto, PhD,[k] Maayke A. Sluman, MD,[l] Jou-Kou Wang, PhD,[m] Jamie L. Jackson, PhD,[n] Paul Khairy, MD, PhD,[o] Stephen C. Cook, MD,[p] Shanthi Chidambarathanu[q], Luis Alday, MD[r], Katrine Eriksen, MSc[s], Mikael Dellborg, MD, PhD[t,u,v], Malin Berghammer, PhD[v,w], Bengt Johansson, MD, PhD[x], Andrew S. Mackie, MD[y], Samuel Menahem, MD[z], Maryanne Caruana, MD[aa], Gruschen Veldtman, MD[ab], Alexandra Soufi, MD[ac], Susan M. Fernandes, LPD, PA-C[ad], Edward Callus, PhD[ae,af], Shelby Kutty, MD, PhD[ag], Philip Moons, PhD[f,v,ah] Ari M. Cedars, MD[a,*] on behalf of the APPROACH-IS consortium and International Society for Adult Congenital Heart Disease (ISACHD)

[a] Department of Internal Medicine, Division of Cardiology, The University of Texas Southwestern Medical Center, Dallas, Texas, USA

[b] Adult Congenital Heart Disease Center, Washington University and Barnes Jewish Heart & Vascular Center, University of Missouri, Saint Louis, MO, USA

[c] Peter Munk Cardiac Centre, University Health Network, University of Toronto, Toronto, Canada

[d] Knight Cardiovascular Institute, Oregon Health & Science University, Portland, OR, USA

[e] Baylor Heart and Vascular Institute, Dallas, Texas

[f] KU Leuven Department of Public Health and Primary Care, KU Leuven - University of Leuven, Leuven, Belgium

[g] School Psychology and Child and Adolescent Development, KU Leuven - University of Leuven, Leuven, Belgium

[h] Center for Congenital Heart Disease, Department of Cardiology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland,

[i] Division of Congenital and Structural Cardiology, University Hospitals Leuven, Leuven, Belgium

[j] KU Leuven Department of Cardiovascular Sciences, KU Leuven - University of Leuven, Leuven, Belgium

[k] Department of Adult Congenital Heart Disease, Chiba Cardiovascular Center, Chiba, Japan

[l] Department of Cardiology, Academic Medical Center, Amsterdam, the Netherlands

[m] Department of Pediatrics, National Taiwan University Hospital, Taipei, Taiwan

[n] Center for Biobehavioral Health, Nationwide Children's Hospital, Columbus, OH, USA

[o] Adult Congenital Heart Center, Montreal Heart Institute, Université de Montréal, Montreal, Canada

[p] Adult Congenital Heart Disease Center, Helen DeVos Children's Hospital, Grand Rapids, MI, USA

[q] Pediatric Cardiology, Frontier Lifeline Hospital (Dr. K. M. Cherian Heart Foundation), Chennai, India

[r]Division of Cardiology, Hospital de Niños, Córdoba, Argentina

[s]Department of Cardiology, Oslo University Hospital - Rikshospitalet, Oslo, Norway

[t]Adult Congenital Heart Unit, Sahlgrenska University Hospital/Östra, Gothenburg, Sweden

[u]Institute of Medicine, The Sahlgrenska Academy at University of Gothenburg, Sweden

[v]Centre for Person-Centred Care (GPCC), University of Gothenburg, Gothenburg, Sweden

[w]Department of Health Sciences, University West, Trollhättan, Sweden

[x]Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden

[y]Division of Cardiology, Stollery Children's Hospital, University of Alberta, Edmonton, Canada

[z]Monash Heart, Monash Medical Centre, Monash University, Melbourne, Australia

[aa]Department of Cardiology, Mater Dei Hospital, Birkirkara Bypass, Malta

[ab]Adult Congenital Heart Disease Center, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

[ac]Department of Congenital Heart Disease, Louis Pradel Hospital, Hospices civils de Lyon, Lyon, France

[ad]Department of Pediatrics and Medicine, Divisions of Pediatric Cardiology and Cardiovascular Medicine, Stanford University School of Medicine, Palo Alto, CA, USA

[ae]Clinical Psychology Service, IRCCS Policlinico San Donato, Milan, Italy

[af]Department of Biomedical Sciences for Health, Università degli Studi di Milano, Milan, Italy

[ag]Adult Congenital Heart Disease Center University of Nebraska Medical Center/ Children's Hospital and Medical Center, Omaha, NE, USA

[ah]Institute of Health and Care Sciences, University of Gothenburg, Gothenburg, Sweden

***Correspondence:** Ari Cedars, MD, The University of Texas Southwestern Medical Center, 2001 Inwood Road, WC5.824, Dallas, TX 75390; Phone: 214-645-7500; Fax: 214-645-7501; Email: Ari.cedars@utsouthwestern.edu

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Abstract

Objective: This study aimed to examine the association between physical activity (PA) and depression in a large international cohort of adults with congenital heart disease (ACHD) as data about the differential impact of PA type on depression in this population are lacking.

Methods: In 2018, we conducted a cross-sectional assessment of 3,908 ACHD recruited from 24 ACHD-specialized centers in 15 countries between April 2013 to March 2015. The Hospital Anxiety and Depression Scale was used to assess self-reported depressive symptoms and the Health-Behavior Scale-Congenital Heart Disease was used to collect PA information. Cochran-Armitage tests were performed to assess trends between depressive symptom levels and PA participation. Chi-Square and Wilcoxon Rank Sum tests were utilized to examine relations between depressive symptom levels and patient characteristics. Stepwise multivariable models were then constructed to understand the independent impact of PA on depressive symptoms.

Results: The overall prevalence of elevated depressive symptoms in this sample was 12% with significant differences in rates between countries ($p < 0.001$). Physically active individuals were less likely to be depressed than those who were sedentary. Of the 2 PA domains examined, sport participation rather than active commute was significantly associated with reduced symptoms of depression. After adjustment in multivariable analysis, sport participation was still significantly associated with 38% decreased probability of depressive symptoms ($p < 0.001$).

Conclusions: Sport participation is independently associated with reduced depressive symptoms. The development and promotion of sport-related exercise prescriptions uniquely designed for ACHD may improve depression status in this unique population.

Key Words: physical activity; depression; perceived health; prognosis; adult congenital heart disease

INTRODUCTION

A sedentary lifestyle has been consistently associated with premature death and the development of chronic illness, including cardiovascular disease, osteoporosis, diabetes mellitus, cancer, and depression.[1] Physical inactivity, however, is a modifiable risk factor and existing evidence has shown the protective effect of physical activity (PA) on overall health - both physical and psychological - in multiple patient groups, including adults with congenital heart disease (ACHD).[1,2,3,4,5,6] Specifically, depression has been demonstrated to have an adverse impact on the prognosis in patients with chronic heart disease (e.g., poor quality of life, higher rates of hospitalization or mortality, increased healthcare utilization, and shorter event-free survival).[7,8] We recently demonstrated that depression is a primary driver of patient-reported health status in ACHD.[9] Although existing studies have demonstrated an antidepressant effect of PA in other populations, the effect of PA on depressive symptoms in a large, diverse international cohort of ACHD has not been previously investigated.[4,10,11] Given the importance of both PA and depression on prognosis and health status, identifying the relationship between the two in ACHD has the potential to positively impact patient care. In the present study, we sought to identify independent associations between PA type and depression in a large international cohort of ACHD with the goal of better directing providers as to the impact of PA in ACHD care.

METHODS

Study Design, Patients, and Patient-Reported Outcome Metrics (PROMs):

In 2018, we performed a cross-sectional multi-institutional analysis of data derived from the *Assessment of Patterns of Patient-Reported Outcomes in Adults with Congenital Heart Disease –*

International Study (APPROACH-IS) study, which was conducted from April 2013 to March 2015. This study enrolled 4,028 ACHD from 24 centers in 15 countries across 5 continents. A detailed study protocol and a full list of demographic, clinical, and psychological variables have previously been summarized by Apers et al.[12] In investigating the relationship between depression and PA, we considered data from 2 PROMs employed in APPROACH-IS, both of which have previously been shown to have high reliability and validity. The Hospital Anxiety and Depression Scale (HADS) was used to assess the self-reported depressive symptoms experienced in the week prior to taking the survey. The total score ranges from 0 – 21 (scores 0-7 = "normal," 8-10 = "mild," and 11-21 = "moderate to severe"); scores ≥ 8 represent elevated symptoms of depression.[13] The Health-Behavior Scale-Congenital Heart Disease was used to collect PA information including activity domain (active commute [i.e., walking or cycling to work or school] and sport participation [i.e., any types of physical activities other than active commute performed regularly at different intensities]), intensity (i.e., minimal [e.g., yoga and darts], moderate [e.g., jogging and dancing] and vigorous [e.g., basketball and rowing]), and the time spent engaging in PA.[14] Individuals who both actively commuted or participated in sport were considered sport participants based on our previous finding on no association between active commute and perceived health status.[2] To limit inferences to participants healthy enough to be employed or attend school, our analysis included only those who were employed or were students. The amount of energy expended (MJ/h) during PA was calculated and considered as a continuous variable.[15] This analysis was approved by the institutional review board at Baylor University Medical Center.

Statistical Methods:

To assess trends in depressive symptom levels with physically active (either active commuters or sport participants) versus sedentary subjects, sport participants versus non-participants, and active commuters versus non-active commuters, we performed Cochran-Armitage tests for trend. To assess relations in depressive symptom levels with overall PA-related energy expenditure, we utilized Wilcoxon Rank Sum tests. To examine the relations between depressive symptom levels and patient characteristics (i.e., age, gender, marital status, having child[ren], number of children, student status, education level, employment status, New York Heart Association [NYHA] functional class, complexity of cardiac defect, history of congestive heart failure, arrhythmia, other medical conditions, cardiac device implantation, number of cardiac surgeries, number of cardiac admission, frequency of follow up, cognitive impairment, mood disorder, anxiety disorder, and other psychiatric disorder), we utilized Chi-Square and Wilcoxon Rank Sum tests. Then, to understand the independent impact of PA on depression, we constructed adjusted ordinal logistic mixed models with a cumulative logit link, using country as a random effect to account for similarities between respondents from the same country. We examined the cumulative logits, as described by Derr to assess the proportional odds assumption.[16] We built separate models for active commute and sport. We additionally adjusted the PA domain of sport for the list of significant covariates identified by Apers et al. (i.e., age, gender, employment, marital status, and NYHA class).[17] Finally, we built optimally-adjusted models for the effect of sport participation on depression via stepwise selection, which considered all variables having significant relations with depression in bivariate analyses and missing at a rate of < 5% (i.e., age, gender, having a child[ren], education level, employment status, congestive heart failure, arrhythmia, comorbidities, NYHA functional class, mood disorder, anxiety, other psychiatric disorder, frequency of follow up, and total admissions). Continuous variables are presented as

median [quartile 1, quartile 3]. Categorical variables are presented as frequency (percentage). Statistical significance was determined by p-value < 0.05. Analyses were performed using SAS 9.4 (Cary, NC).

RESULTS

The demographic, clinical, and psychological characteristics of 4,028 ACHD have been previously described.[17] Detailed information on the significant differences in patient characteristics within each PA domain and the rates of PA participation across countries, have also been reported.[2] Briefly, of 3,087 individuals, either employed or attending school, 1,084 (35%) actively commuted; the rates of active commute differed significantly by country (p <0.001), ranging from 18% (the United States) to 55% (France).[2] Of 3,955 patients who provided information on sport participation, 1,703 (43%) practiced sport(s); the rates of sport participation differed significantly by country (p < 0.001), ranging from 10% (India) to 66% (Norway).[2]

Prevalence of Elevated Depressive Symptoms:

Of 4,028 study participants, 3,908 (97%) who completed the HADS met inclusion criteria for this analysis and their characteristics were described in Supplemental Table 1. Of 3,908 patients, 12% reported having at least mild depressive symptoms, the prevalence of which significantly differed by country (p < 0.001), ranging from 6% (Norway) to 21% (Japan) (Table 1). The countries with the highest rates of depression were Japan, India, and Taiwan. In contrast, the countries with the lowest rates of depression were Norway, the Netherlands, and Malta.

Physical Activity and Depression:

The prevalence of elevated depressive symptoms (HADS scores ≥ 8) was lower in patients who were physically active (i.e., either active commuters or sport participants) compared to those who were sedentary (9% versus 17%, respectively, $p < 0.001$). Respondents who participated in sport had a lower prevalence of elevated depressive symptoms than those who did not participate in sport (7% versus 15%, respectively, $p < 0.001$), yet no significant difference in the prevalence of elevated depressive symptoms was found between active commuters and those who did not actively commute (8% versus 9%, $p = 0.48$) (Table 2).

Among those who participated in some form of PA, total PA energy expenditure correlated negatively with depressive symptoms ($p < 0.0001$). When total energy expenditure in each PA domain was separately evaluated, the amount of energy expended in sport was associated with depressive symptoms while that in active commute was not (Table 3).

Among sport participants, the proportion of patients who met World Health Organization recommended PA levels (i.e., 5 x 30 minutes of moderate-intensity or 3 x 20 minutes of vigorous-intensity activities per week) in the normal group (i.e., HADS < 8) was significantly higher than those in the elevated depressive symptom group (i.e., HADS ≥ 8) (72% versus 56%, $p < 0.001$) (Supplemental Table 2).[2] There were significant differences across countries in therms of the rate of sport participants meeting PA recommendations ($p < 0.001$) (Supplemental Table 2).

There was no significant relationship between active commute and depressive symptoms in bivariate analysis (OR=0.833; 95% CI 0.629 – 1.103; p = 0.20), whereas participating in sport was associated with a 38% decreased odds of depression severity, even after adjusting for confounders (fully adjusted OR=0.620; 95% CI 0.481 - 0.797; p < 0.001) (Table 4). Given that no significant association was found between depressive symptoms and active commute in an unadjusted analysis, adjusted analyses for active commute were not performed.

DISCUSSION

The present study is unique in that it is the first large international study to assess depression symptomatology in ACHD utilizing the same metrics between countries and that it not only examines the relationship between PA and depression in general, but also provides information on the differential impact of active commute versus sport participation on depression. We found that elevated symptoms of depression were more prevalent in patients who were sedentary compared to those who were physically active and that sport participation rather than active commute was associated with reduced symptoms of depression, suggesting that the promotion of sport participation in routine clinical care may decrease depression prevalence in ACHD.

In the present international study cohort, 12% of patients reported having elevated depressive symptoms and the prevalence of elevated symptoms of depression significantly varied by country. Based on the World Health Organization report on the global and regional estimates of prevalence of depression from 2017, depression prevalence varied by continents, Asia with the highest rates and Europe with the lowest rates.[18] Our study result was consistent with this finding. Large differences in depression prevalence between countries with similar annual

income such as Norway and Japan suggest that geographical factors (e.g., cultural perspective, healthcare and medical insurance system, availability and access to healthcare, social support, etc.) rather than economic status may have greater impact on such differences in this patient population.

The prevalence of depression in this study cohort is far greater compared to the world's population at large, in which it is estimated that prevalence of depression is 4%.[18] Although making a reasonable comparison between these numbers is difficult without a valid study design and statistical adjustments, a relatively high prevalence of depression in ACHD has consistently been reported.[19] A recent review of existing data on depression in ACHD also revealed that despite a high prevalence, depression is often unrecognized and untreated, and that it has been linked with poor perceived health status as well as adverse prognosis, including shorter survival and increased risk of mortality or hospitalization due to heart problems.[18,20,21] Persistent depressive symptoms were recently demonstrated to be responsible for unfavorable perceived health status and poor quality of life in young ACHD in a longitudinal study.[22] In support of this continuing into adulthood, we recently showed that among clinical, psychological, and demographic variables, depression was the primary driver of variability in self-assessed health status in ACHD.[9] Although the causal relationship is unclear, accumulating evidence suggests a potentially insidious role played by depression in negatively affecting patients' psychological and clinical health status. Given that perceived health measures are excellent predictors of prognosis in patients with heart failure having normal cardiac anatomy and the fact that in ACHD heart failure is a major cause of morbidity and mortality, identifying patients with

depression and factors associated with depression in the ACHD population carries the potential to have a major impact on overall care.[23,24]

PA is an effective alternative treatment approach for depression, in addition to pharmaco- and/or psycho-therapy. Regular physical exercise effectively reduces depressive symptoms in individuals with major depressive disorder or elevated depression symptoms with or without clinical comorbidities.[3,4,10,11] Recent meta-analyses of randomized clinical trials investigating exercise as an intervention to treat depression revealed that exercise significantly improved depression compared to no intervention, had a moderate additional beneficial effect when used as an adjunct treatment to pharmacotherapy alone, and had an effect size comparable to antidepressants or psychotherapy.[10,11] In one study, aerobic exercise specifically produced a large benefit in clinically depressed patients, with the greatest effect found among subjects supervised by exercise professionals.[11] In another study, supplementing the typical cardiac rehabilitation program with high-intensity resistance training reduced depression symptoms more effectively than the addition of flexibility training among depressed patients with cardiovascular disease.[25] These prior findings are consistent with those in the present analysis, that PA pursued in a programmatic or directed fashion may be beneficial in depressed patients.

There are several proposed mechanisms for the observed therapeutic benefits of PA in treating depression. Neurobiologically, exercise is associated with neurological changes similar to those triggered by antidepressant treatment, such as increased activity in serotonergic and noradrenergic neuromodulatory systems, an elevated level of brain-derived neurotrophic factor,

and an enhanced release of endogenous opioid neuropeptide (i.e., β-endorphin).[4,26] Relatively strenuous exercise consistently resulted in the increased level of β-endorphin.[27] Psychologically, regular aerobic exercise may enhance emotional recovery from or resilience to distress and thus promote mental health by minimizing the duration, intensity, or impact of rumination on negative thoughts or feelings, which together are risk factors for depression if left unchecked.[28] Socially, in a study of 1.2 million adults in the United States, team sport participation was associated with fewer days of poor mental health while in another study supervised exercise had a large therapeutic effect on depression in depressed individuals.[11,29] Further research to discover whether sport participation prescription to treat depression may result in the improvement of both depression and overall health in ACHD is warranted. To date, there are no trials investigating the relative efficacy of the various therapeutic approaches for depression management in the ACHD population.

Unlike the general population, ACHD may be more reticent to participate in exercise due to medical advice, overprotection of parents, or personal fear of exercise-induced sudden cardiac events. Added to these fears CHD-associated physical limitations resulting in reduced exercise capacity may weaken one's belief in having the ability to perform physically demanding activities, furthering a disinclination to exercise participation.[30,31,32] This may explain the high rate (70%) of patients failing to achieve the PA recommendations in the present study cohort.[2] Nevertheless, ACHD have expressed their willingness to exercise if properly instructed.[33] Moreover, a systematic review on the benefits of exercise training in patients with a full spectrum of CHD lesion complexity concluded that exercise is safe (e.g., no report of sudden cardiac death or incident arrhythmia) and that it improved objective physiologic exercise

response (e.g., improved ejection fraction, stroke volume and increase in PeakVO2, VO2 at ventilator threshold, muscle strength, and activity levels).[6, 34] Additionally, a previous meta-analysis has shown that the effectiveness of exercise training on depression was comparable to that of antidepressant medication in patients with normal cardiac anatomy and with chronic heart failure. Given that heart failure is the most common cause of mortality and morbidity in ACHD, exercise training may have potentially similar benefit on ACHD with heart failure.[35] Addressing specific needs of ACHD in the development of sport participation prescription may thus safely and effectively improve both physiologic and psychosocial state in this unique population.

Study Limitations:

There are several limitations to the present study. A recall and response bias is a potential problem in all self-reported PROMs which tend to yield results either higher or lower than objective measures. Depression assessed by HADS not by psychiatric interview might have underestimated the prevalence of depression in this study cohort. Some incomplete or incorrect clinical data may be present as all clinical data were collected by chart review. The results may not be generalizable to all ACHD as the study cohort was recruited only from ACHD-specialized centers. In this patient population, the specific activities recommended might vary depending on congenital heart disease type and this should be taken into consideration when interpreting the data. Confounding variables, such as geographic and cultural differences might have affected the results; however, the analysis helped control for these factors by treating country of origin as a random effect. Lastly, associations identified in the study cannot be used to draw firm conclusions about causation as the data were from a cross-sectional study, and are intended to be hypothesis-generating.

Conclusion:

Because depression worsens treatment response and prognosis, the prevention of and early treatment for depression is paramount to promoting mental and physical health in ACHD. Participation specifically in sport is strongly associated with reduced symptoms of depression among ACHD. The development and promotion of sport-related exercise prescriptions uniquely designed for ACHD may improve depression and by extension overall health status in ACHD.

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Table 1. The prevalence of elevated depressive symptoms

Country	Depression measured by HADS* ($p < 0.001$)		
	Normal (0-7)	Mild (8-10)	Moderate-Severe (11-21)
Overall	3440 (88%)	318 (8%)	150 (4%)
Argentina	139 (87%)	15 (9%)	6 (4%)
Australia	115 (90%)	11 (9%)	2 (1%)
Belgium	242 (89%)	21 (8%)	9 (3%)
Canada	448 (88%)	45 (9%)	15 (3%)
France	76 (83%)	12 (13%)	4 (4%)
India	152 (81%)	24 (13%)	12 (6%)
Italy	54 (90%)	5 (8%)	1 (2%)
Japan	202 (79%)	32 (12%)	23 (9%)
Malta	106 (92%)	6 (5%)	3 (3%)
Norway	160 (94%)	9 (5%)	2 (1%)
Sweden	413 (91%)	23 (5%)	17 (4%)
Switzerland	243 (89%)	18 (7%)	11 (4%)
Taiwan	204 (82%)	34 (14%)	10 (4%)
Netherlands	233 (92%)	16 (6%)	3 (1%)
USA	653 (89%)	47 (6%)	32 (4%)

*HADS= Hospital Anxiety and Depression Scale

Table 2. The association of physical activity with depression

Depression (HADS score)	Physically Active* (n=2,305)	Sedentary (n=1,537)	Physical Activity: Sport Participants Yes (n=1,664)	Physical Activity: Sport Participants No (n=2,182)	Physical Activity: Active Commuters Yes (n=1,041)	Physical Activity: Active Commuters No (n=1,964)
	($p < 0.001$)		($p < 0.001$)		($p = 0.48$)	
Moderate-Severe (11-21)	54 (2%)	90 (6%)	27 (2%)	117 (5%)	22 (2%)	45 (2%)
Mild (8-10)	150 (7%)	163 (11%)	84 (5%)	228 (10%)	62 (6%)	130 (7%)
Normal (0-7)	2101 (91%)	1284 (84%)	1553 (93%)	1837 (84%)	957 (92%)	1789 (91%)

*Either sport participants or active commuters
HADS= Hospital Anxiety and Depression Scale
P-values are for a test of trend.

Table 3. The association of energy expended in physical activity* with depression

Depression (HADS score)	Total Energy Expended in PA ($p < 0.0001$)	Energy Expended in Sport ($p = 0.0236$)	Energy Expended in Active Commute ($p = 0.7503$)
Moderate-Severe (11-21)	0.95 [0.63, 3.78]	3.78 [2.14, 9.19]	0.63 [0.32, 0.79]
Mild (8-10)	1.49 [0.63, 5.19]	4.78 [2.52, 9.58]	0.63 [0.32, 0.63]
Normal (0-7)	4.10 [1.26, 8.51]	6.04 [3.52, 10.08]	0.63 [0.32, 0.63]

*Calculated for those who participated in the specified type of activity.
HADS= Hospital Anxiety and Depression Scale; PA=physical activity (i.e., either participating in sport or commuting actively)
The amount of energy expended (MJ/h) was presented in medians [quartile 1, quartile 3].

Table 4. The association between physical activity and depression

Model	Odds Ratio	Lower	Upper	P-value
Active Commute	0.833	0.629	1.103	0.20
Sport	0.406	0.321	0.513	<0.001
Sport + partial adjustment 1*	0.628	0.489	0.808	<0.001
Sport + adjustment 2†	0.620	0.481	0.797	<0.001

*Covariates identified by Apers et al and considered in adjustment 1 are age, gender, employment, marital status, and NYHA functional class.[17]

†Covariates considered in adjustment 2 to build the optimal model via stepwise selection are having child(ren), employment status, mood disorder, anxiety disorder, other psychiatric disorder, and NYHA functional class.

Supplemental Table 1. Respondent characteristics (n=3908)

Characteristic	Median [quartile 1, quartile 3]; frequency (%)
Age [4]	32 [25, 42]
Sex (male)[15]	1843 (47%)
Marital status [19]	
Unmarried / Never married	1704 (44%)
Married or Living with partner	1989 (51%)
Divorced or Widowed	192 (5%)
Other	4 (>1%)
Child(ren) present [24]	1536 (40%)
Education level [38]	
Less than high school	214 (6%)
High school	1660 (43%)
College/University degree	1996 (51%)
Employment status [23]	
Part time or full-time work	2486 (64%)
Homemaker or Retired	316 (8%)
Unemployed or Disability	494 (13%)
Full-time student	317 (8%)
Other	272 (7%)
Considered religious/spiritual [93]	1855 (49%)
Complexity of CHD defect	
Simple	1012 (26%)
Moderate	1898 (49%)
Complex	998 (25%)
NYHA functional class [95]	
I	2051 (54%)
II	1336 (35%)
III	277 (7%)
IV	149 (4%)
History of other medical conditions [29]	1686 (43%)
History of arrhythmia [26]	1074 (28%)
Device implantation [454]	

None	3044 (88%)
ICD	148 (4%)
PM	262 (8%)
Number of surgeries [202]	1 [1, 2]
Frequency of follow-up [54]	2 [1, 3]
Total adult cardiac admissions [221]	0 [0, 1]
Cognitive impairment [29]	48 (1%)
Chart-documented mood disorder [22]	249 (6%)
Chart-documented anxiety disorder [12]	186 (5%)
Chart-documented other psychiatric disorder [16]	69 (2%)

Superscripts represent the number of missing data.
CHD=congenital heart disease; ICD=implantable cardioverter defibrillator; NYHA= New York Heart Association; PM=pacemaker

Supplemental Table 2. Proportions of sport participants meeting physical activity recommended level* in a normal and elevated depressive symptom group

Country	Depression ($p < 0.001$)	
	Normal (HADS < 8)	Mild-Severe (HADS ≥ 8)
Overall	1123 (72%)	62 (56%)
Argentina	39 (70%)	3 (75%)
Australia	48 (91%)	3 (100%)
Belgium	79 (65%)	1 (25%)
Canada	143 (66%)	4 (44%)
France	16 (40%)	3 (60%)
India	15 (75%)	4 (100%)
Italy	20 (100%)	2 (100%)
Japan	19 (42%)	7 (54%)
Malta	28 (82%)	1 (100%)
Norway	85 (83%)	5 (63%)
Sweden	196 (80%)	11 (58%)
Switzerland	115 (70%)	4 (50%)
Taiwan	46 (66%)	6 (43%)
The Netherlands	97 (73%)	2 (40%)

USA	177 (76%)	6 (50%)

*World Health Organization recommended physical activity levels (i.e., 5 x 30 minutes of moderate-intensity or 3 x 20 minutes of vigorous-intensity activities per week.[2]
HADS= Hospital Anxiety and Depression Scale