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CLINICAL RESEARCH

Lifetime cumulative activity burden is associated with symptomatic heart failure and arrhythmic risk in patients with arrhythmogenic right ventricular cardiomyopathy: a retrospective cohort study

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Aims

Sports-related physical activity is associated with an increased risk of ventricular dysfunction and arrhythmias in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC). However, there are currently no standardized strategies for activity assessment. Thresholds for harmful levels of physical activity suggested by previous studies vary substantially and neither lifetime activity burden nor continuous modelling approaches were considered.

Methods and results

For this single-centre retrospective study, ARVC patients were interviewed to assess sports-related and non-sports-related physical activity between the age of 10 years and the last follow-up. Activity data were aggregated to the median metabolic equivalent of task—hours (METh) per week for each year. The association between cumulative physical activity burden and clinical study endpoints was investigated using Cox regression models. A total of 124 patients (median age: 39.5 years, 48% male) were included in the analysis, of whom 93 had been diagnosed with definite ARVC. Study participants reported a median overall activity of 202.3 METh/week, with 38.7 METh/week attributed to sports-related activity. In the continuous model, cumulative overall activity burden was associated with the occurrence of symptomatic heart failure [hazard ratio (HR) per 100 METh/week: 1.017, 95% CI (1.003, 1.032), $P = 0.015$], sustained ventricular tachycardia [HR: 1.021, 95% CI (1.006, 1.037), $P = 0.007$], and implantable cardioverter defibrillator interventions [HR: 1.017, 95%CI (1.000, 1.034), $P = 0.048$]. This finding was consistent when considering sports-related activity separately as a predictor variable, whereas the resulting hazard ratios did not show a significant association for non-sports-related physical activity.

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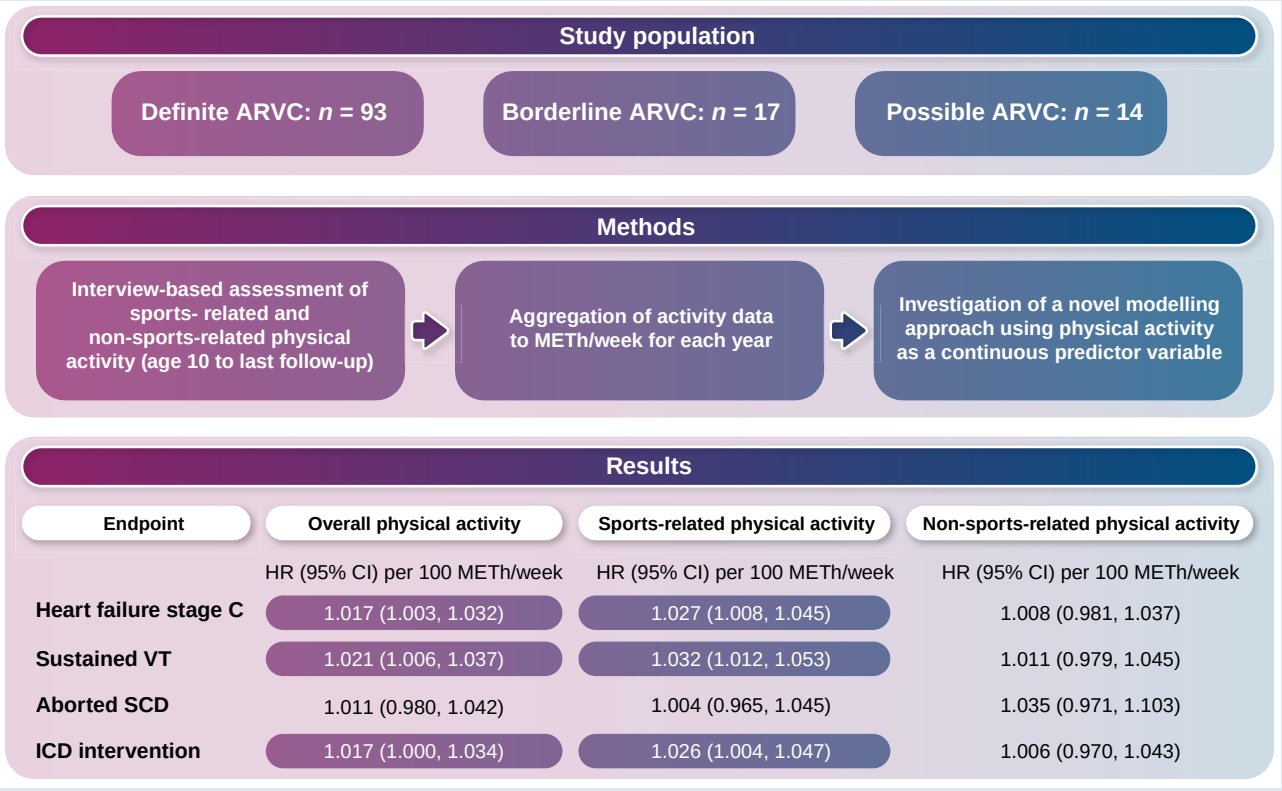
Conclusion This study demonstrates for the first time that cumulative physical activity as a continuous predictor variable is associated with symptomatic heart failure and arrhythmic risk in ARVC patients. Collaborative research is required in larger cohorts to investigate the influence of potential confounders on event occurrence and to develop threshold recommendations for clinical practice.

Graphical Abstract



Endpoint	Overall physical activity	Sports-related physical activity	Non-sports-related physical activity
	HR (95% CI) per 100 METh/week	HR (95% CI) per 100 METh/week	HR (95% CI) per 100 METh/week
Heart failure stage C	1.017 (1.003, 1.032)	1.027 (1.008, 1.045)	1.008 (0.981, 1.037)
Sustained VT	1.021 (1.006, 1.037)	1.032 (1.012, 1.053)	1.011 (0.979, 1.045)
Aborted SCD	1.011 (0.980, 1.042)	1.004 (0.965, 1.045)	1.035 (0.971, 1.103)
ICD intervention	1.017 (1.000, 1.034)	1.026 (1.004, 1.047)	1.006 (0.970, 1.043)

ARVC, arrhythmogenic right ventricular cardiomyopathy; CI; confidence interval; HR, hazard ratio; ICD, implantable cardioverter defibrillator; METh, metabolic equivalent of task—hours; SCD, sudden cardiac death; VT, ventricular tachycardia.

Keywords Arrhythmogenic right ventricular cardiomyopathy • Physical activity

What's new

- This study is the first to investigate the association of cumulative sports-related and non-sports-related physical activity with clinical outcome parameters in arrhythmogenic right ventricular cardiomyopathy patients utilizing a novel statistical modelling approach.
- The results indicate that physical activity burden as a continuous predictor variable is associated with new-onset symptomatic heart failure and arrhythmic risk.
- Further collaborative research is required to investigate the influence of potential confounders on event occurrence and to develop threshold recommendations for clinical practice.

Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a heritable heart disease affecting approximately 1 in 5000 to 1 in 2000 persons in Europe.[1,2] Multiple pathogenic variants, most commonly in genes encoding desmosomal proteins, have been associated with ARVC.[3] Characteristic histopathological and macroscopic features are fibro-adipose dysplasia and scarring of myocardial tissue, focal aneurysms, and progressive loss of contractile function.[1] These changes most commonly affect the right ventricle (RV), although patients may also present with left ventricular involvement.[1,4–6] Typical clinical manifestations of ARVC include heart failure, ventricular arrhythmias, and sudden cardiac death (SCD), but penetrance in variant carriers is often incomplete.[1]

Physical activity, in particular high-intensity sports-related activity, has been shown to be associated with the onset of symptoms and poor outcomes in affected individuals.[7–14] Previous studies have found a higher risk of biventricular dysfunction,[8,11] symptomatic heart failure,[7] ventricular arrhythmias,[7,10,11,14,15] and SCD[9] among ARVC patients who were classified as 'athletes'. In addition, variant carriers participating in regular endurance training are more likely to meet diagnostic criteria for ARVC.[7,15,16] However, physical activity assessment and study participant characterization regarding activity intensity and volume lacks standardization. Previous analyses have employed a variety of methodological strategies to evaluate the participants' exercise level, including questionnaire-based self-

assessment, assessment of aerobic intensity, and quantification of exercise burden by multiplication of reported metabolic equivalent of task (MET) units with activity duration.[7,8,10,11,14,15] Not only the cut-off values that have been proposed for defining 'athletic' individuals but also consideration of non-sports-related physical activity, timeframe of activity analysis, and study endpoints are heterogeneous. These factors currently limit a more precise risk estimation associated with the individual history of physical activity and the development of personalized physical activity recommendations for ARVC patients.[17,18]

In order to address these limitations, we assessed both sports-related and non-sports-related physical activity burden in a large cohort of ARVC patients from the age of 10 years onwards. We investigated the relationship of activity burden with clinical endpoints using a novel modelling approach with cumulative activity as a continuous predictor variable to account for the longitudinal nature of the data.

Methods

Study design and population

This retrospective study was conducted at LMU University Hospital in Munich, Germany, between January 2020 and August 2023. Patients ≥16 years of age diagnosed with definite, borderline, or possible ARVC according to the 2010 Modified Task Force Criteria[16] were eligible and screened for study participation.

Data acquisition

ARVC patients usually visit our cardio-genetic outpatient clinic every 6–12 months for regular follow-ups.[17] Routine device examinations are performed every 6 months unless patients experience symptoms or implantable cardioverter defibrillator (ICD) interventions occur. Information from the main clinical database was supplemented by patient inquiry and external documentation provided by study participants, if needed. Clinical data were interpreted and validated by the study team. Patients who had received a heart transplantation were excluded from the analysis at the last follow-up. Proband status was defined as being the first person in a family to be diagnosed with definite, borderline, or possible ARVC based on typical symptoms or other diagnostic findings suggestive of disease.[16] Genetic testing was performed by a specialized external core facility according to guideline recommendations.[19]

Assessment of physical activity

Physical activity data were collected in a standardized two-stage interview conducted either in person or via telephone by an experienced team member from the cardio-genetic outpatient clinic. A complete transcript of the questionnaire is available in the Supplementary Appendix. Patients completed a preliminary questionnaire (Stage I) covering various aspects of personal and professional life, e.g. occupation, leisure activities, sports club memberships, possession of sports or fitness equipment, and ownership of pets. This surrogate information for specific sports-related and non-sports-related activities was used to reduce potential bias in the comprehensive assessment of physical activity during the main interview (Stage II). Physical activity was assessed from the age of 10 years to the time of the interview. The unprocessed activity data underwent review by a senior physician from the study team and was categorized as sports-related or non-sports-related physical activity, based on the primary intent provided by the study participant. Each type of activity was transcribed into the MET units based on the 2011 Compendium of Physical Activity.[20] MET units were multiplied by the activity's respective average duration (in hours per week) within each year. The dynamic component (low vs. moderate vs. high) of sports-related activity was defined according to the 2005 Bethesda Conference Classification of Sports.[21] Recommendations regarding minimum physical activity were derived from the 2007 Physical activity and public health: Updated recommendation for adults from the American College of Sports Medicine and the American Heart Association.[22] Previously proposed definitions of athlete status and high-level physical activity were adapted and applied to the present dataset for comparability purposes and as proof of concept.[7,8,11,14,23–25]

Study endpoints

For statistical analysis regarding the association of cumulative physical activity and the study endpoints, we used data exclusively from the subgroup of patients diagnosed with definite ARVC to minimize confounding by diagnostic criteria. The study endpoints included (i) heart failure stage C, (ii) occurrence of sustained ventricular tachycardia (VT), (iii) aborted SCD, and (iv) appropriate ICD intervention.

Statistical analysis

Statistical analyses were performed using R® (version 4.3.1). Continuous variables were reported as a median with interquartile ranges (25th and 75th percentile). Categorical variables were reported as absolute numbers and percentages. Cox proportional hazards models were employed for the time-to-event outcomes. We chose these models to assess the association between cumulative physical activity and the hazard of these outcomes. The primary modelling strategy focused on the time until the first event for each participant. In each Cox model, we examined the influence of cumulative physical activity as the predictor variable and interpreted the hazard ratio (HR) for its impact on event occurrence. In two exploratory models, the association between physical activity burden and outcomes was adjusted for sex (male) and genotype [presence of a pathogenic/likely pathogenic variant in the plakophilin-2 (PKP2) or desmoplakin (DSP) gene or both], respectively. Cumulative physical activity in METh/week was rescaled by dividing it by 100 to reduce the range.

Ethical standards

The study was approved by the local ethics committee (AZ 19-889) and was conducted in accordance with the Declaration of Helsinki. All study participants provided written informed consent.

Results

Study population

During recruitment, 396 patients were screened for study participation, and 125 patients fulfilled diagnostic criteria for definite, borderline, or possible ARVC and completed the interview.[16] One patient withdrew consent after the interview. For the final analysis, 124 patients were included, of whom 93 had been diagnosed with definite ARVC, 17 with borderline ARVC, and 14 with possible ARVC at the time of the interview (*Figure 1*). The median duration of follow-up from the first clinical visit to the interview was 5.1 years (IQR 2.1, 11.2). Detailed baseline characteristics are presented in *Table 1* and Supplementary material online, *Table S1*. The median age of study participants was 39.5 years (IQR 29.0, 55.2), with 48% being male. Sixty-four per cent had an implanted ICD. The most frequently reported initial symptoms included palpitations, dyspnoea, and syncope. In the definite, borderline, and possible groups, 14, 76, and 100% of patients, respectively, were asymptomatic at the time of diagnosis. In the overall study population, 88% of patients underwent genetic testing, revealing a pathogenic/likely pathogenic variant in the PKP2 gene in 51% and in the DSP gene in 24%. Baseline characteristics of study participants categorized into 'athletes' and 'non-athletes' according to the definition proposed by Saberniak and colleagues[8] in patients with pathogenic/likely pathogenic variants in the PKP2 or DSP gene, and in male and female patients, are presented in Supplementary material online, *Tables S2–S4*.

Characterization of physical activity

From the age of 10 years until their last follow-up or heart transplantation, study participants reported a median of 202.3 METh/week (IQR 172.9, 226.8) in total physical activity, with a median of 38.7 METh/week (IQR 23.5, 66.4) attributed to sports-related activities and 157.0 METh/week (IQR 135.9, 172.7) to non-sports-related

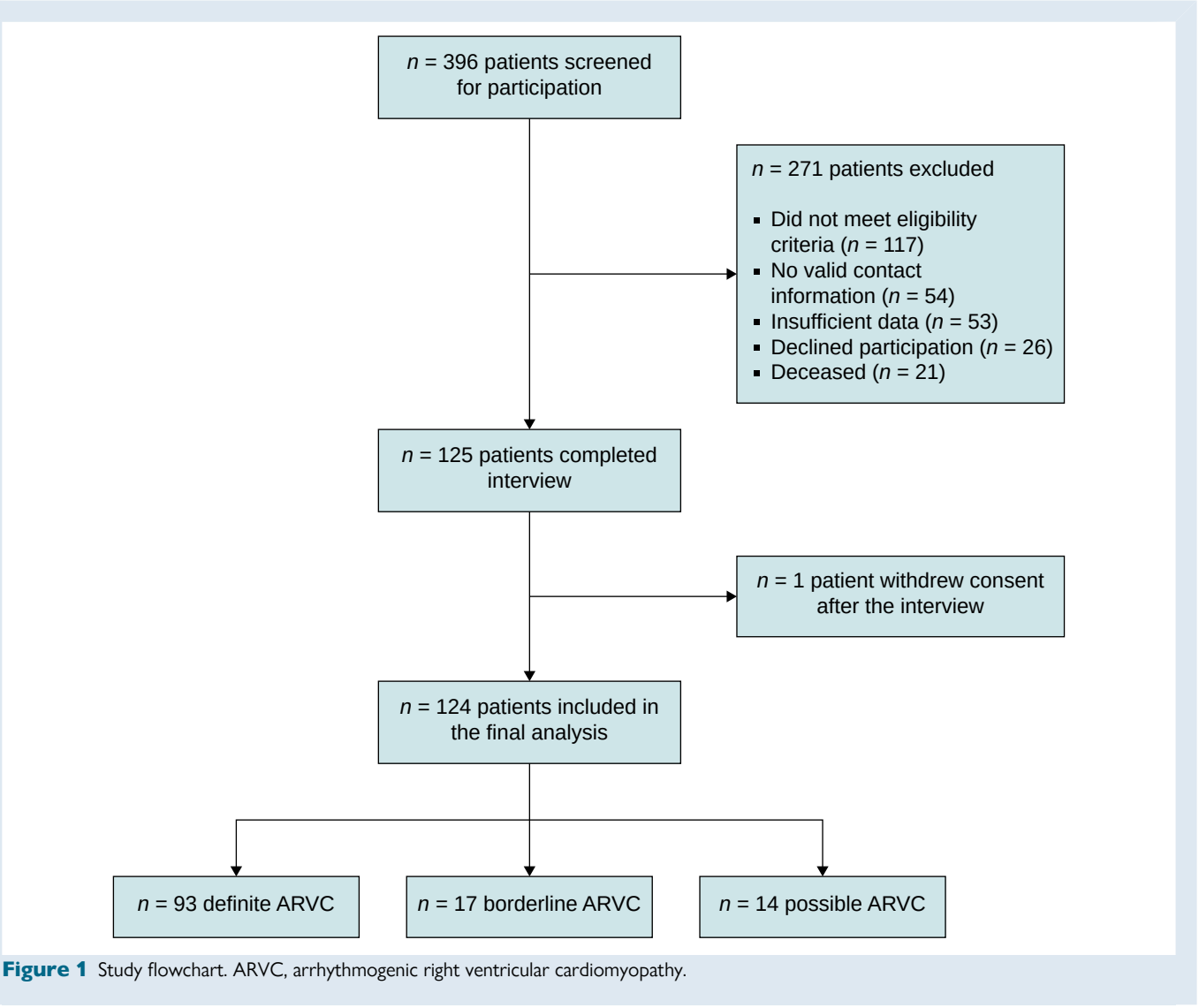


Figure 1 Study flowchart. ARVC, arrhythmogenic right ventricular cardiomyopathy.

activities (*Figure 2*). After diagnosis, patients with definite ARVC reported a decrease in sports-related activity by a median of 24.6 METh/week (IQR 10.6, 55.1), whereas non-sports-related activity increased by 14.8 METh/week (IQR −2.1, 37.9) when compared to the period between age 10 and ARVC diagnosis. In the borderline and possible groups, the median differences between sports-related METh/week before vs. after ARVC diagnosis were less pronounced, at 17.4 METh/week (IQR 14.0, 38.7) and 3.5 METh/week (IQR −1.1, 7.1), respectively. Patients diagnosed with definite and borderline ARVC reported a reduction in sports-related activity with moderate and high dynamic components after diagnosis. All patients met or exceeded the recommended minimum level of physical activity both before and after diagnosis.[22] In the overall population, 73% of patients met the criteria for 'athlete' status according to Wang *et al.*,[24] 67% according to Saberniak *et al.*,[8] 48% according to Gasperetti *et al.*,[23] and 68% according to James *et al.*[7] (*Table 2*). Thirty-nine per cent of patients diagnosed with definite ARVC exceeded 63 METh/week in the year before ICD implantation.[25] Across all groups, the majority of patients engaged in high-intensity (≥6 MET) and long-duration (≥2.5 h/week) sports-related activities within 3 years preceding ARVC diagnosis, as per the definition by Lie *et al.*[11] Descriptive analysis of physical activity in 'athletes' and 'non-athletes' as defined by Saberniak *et al.*[8] in patients with pathogenic/likely pathogenic variants in the PKP2 or DSP gene, and in male and female patients, are presented in Supplementary material online, *Figure S1* and Supplementary material online, *Tables S5–S7*.

Clinical outcomes

At the last follow-up or the year preceding heart transplantation, 92% of patients with definite ARVC and 65% with borderline ARVC reported experiencing exertional dyspnoea (*Table 3*). A total of 13 patients received a heart transplant. Within the definite group, 70% experienced sustained ventricular arrhythmias, and 24% suffered cardiac arrest. Appropriate ICD interventions were documented in 49% of patients with definite ARVC. Outcome parameters in 'athletes' and 'non-athletes' as defined by Saberniak *et al.*[8] in patients with pathogenic/likely pathogenic variants in PKP2 or DSP gene and in male and female patients are shown in Supplementary material online, *Tables S8–S10*.

Impact of physical activity burden

In the main prespecified Cox proportional hazards model, the HR for the association of cumulative overall activity per 100 METh/week exceeded 1 for all main study endpoints, i.e. for symptomatic heart failure

Table 1 Baseline characteristics in the overall population and in subgroups of patients with definite, borderline, or possible ARVC

Demographics at the last follow-up	**Overall: *n* = 124**	**Definite: *n* = 93**	**Borderline: *n* = 17**	**Possible: *n* = 14**
Age (years), median (IQR)	39.5 (29.0, 55.2)	44.0 (30.0, 56.0)	38.0 (34.0, 45.0)	31.0 (21.8, 39.5)
Sex (male), *n* (%)	59 (48)	49 (53)	5 (29)	5 (36)
Body mass index (kg/m^2), median (IQR)	23.6 (21.2, 26.5)	23.9 (21.2, 26.6)	22.8 (20.5, 27.6)	23.2 (21.3, 25.0)

Cardiovascular risk factors and comorbidities at the last follow-up	**Overall: *n* = 124**	**Definite: *n* = 93**	**Borderline: *n* = 17**	**Possible: *n* = 14**
Hypertension, *n* (%)	22 (18)	17 (18)	4 (24)	1 (7)
Diabetes mellitus, *n* (%)	6 (5)	4 (4)	2 (12)	0 (0)
Dyslipidemia, *n* (%)	30 (24)	25 (27)	3 (18)	2 (14)
Smoking history, *n* (%)	27 (22)	22 (24)	4 (24)	1 (7)
Positive family history for SCD/CPR, *n* (%)	70 (56)	49 (53)	13 (76)	8 (57)
Coronary artery disease, *n* (%)	3 (2)	2 (2)	1 (6)	0 (0)
Previous PCI, *n* (%)	1 (1)	1 (1)	0 (0)	0 (0)
Previous myocardial infarction, *n* (%)	1 (1)	1 (1)	0 (0)	0 (0)
Previous myocarditis, *n* (%)	15 (12)	14 (15)	1 (6)	0 (0)
Valvular disease, *n* (%)	19 (15)	17 (18)	2 (12)	0 (0)
Atrial fibrillation, *n* (%)	16 (13)	15 (16)	0 (0)	1 (7)
Stroke/TIA, *n* (%)	6 (5)	5 (5)	1 (6)	0 (0)
Chronic kidney disease, *n* (%)	8 (6)	8 (9)	0 (0)	0 (0)

Device therapy	**Overall: *n* = 124**	**Definite: *n* = 93**	**Borderline: *n* = 17**	**Possible: *n* = 14**
ICD implantation during follow-up, *n* (%)	79 (64)	75 (81)	4 (24)	0 (0)

Cardiovascular medication at the last follow-up	**Overall: *n* = 111[a]**	**Definite: *n* = 80**	**Borderline: *n* = 17**	**Possible: *n* = 14**
Mexiletine, *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)
Flecainide, *n* (%)	1 (1)	1 (1)	0 (0)	0 (0)
Beta-blocker (excluding sotalol), *n* (%)	62 (56)	51 (64)	11 (65)	0 (0)
Sotalol, *n* (%)	22 (20)	22 (28)	0 (0)	0 (0)
Amiodarone, *n* (%)	5 (5)	5 (6)	0 (0)	0 (0)
ACE inhibitor, *n* (%)	11 (10)	7 (9)	4 (24)	0 (0)
Angiotensin receptor blocker, *n* (%)	11 (10)	10 (12)	1 (6)	0 (0)
Angiotensin receptor neprilysin inhibitor, *n* (%)	7 (6)	7 (9)	0 (0)	0 (0)
Aldosterone antagonist, *n* (%)	14 (13)	12 (15)	1 (6)	1 (7)
SGLT-2 inhibitor, *n* (%)	8 (7)	7 (9)	1 (6)	0 (0)
Diuretic, *n* (%)	10 (9)	7 (9)	3 (18)	0 (0)

Last available cardiac imaging		**Overall: *n* = 111[a]**	**Definite: *n* = 80**	**Borderline: *n* = 17**	**Possible: *n* = 14**
Echocardiography	RV basal diameter (mm), median (IQR)	40.0 (40.0, 48.0)	42.0 (40.0, 52.0)	40.0 (40.0, 40.0)	37.5 (32.2, 40.0)
	RV length (mm), median (IQR)	70.0 (70.0, 79.0)	70.0 (70.0, 87.0)	70.0 (70.0, 70.0)	70.0 (70.0, 70.0)
	RVOT PSAX distal (mm), median (IQR)	29.0 (25.0, 37.5)	34.0 (25.2, 39.0)	25.0 (24.2, 28.2)	25.0 (24.0, 25.0)
	RV FAC (%), median (IQR)	45.0 (36.0, 45.0)	45.0 (32.5, 45.0)	45.0 (42.5, 45.0)	45.0 (41.8, 45.8)
	RV wall motion abnormalities, *n* (%)	45 (41)	43 (54)	0 (0)	2 (14)
	TAPSE (mm), median (IQR)	21.0 (19.0, 24.0)	21.0 (18.0, 23.0)	22.0 (20.0, 26.0)	21.0 (20.0, 24.5)
	Significant tricuspid regurgitation (Grade ≥ III), *n* (%)	2 (2)	2 (3)	0 (0)	0 (0)
	LV ejection fraction (%), median (IQR)	60.0 (55.0, 60.0)	60.0 (54.5, 60.0)	60.0 (59.0, 60.0)	60.0 (59.2, 60.0)

Continued

Table 1 *Continued*

Last available cardiac imaging		Overall: $n = 111$[a]	Definite: $n = 80$	Borderline: $n = 17$	Possible: $n = 14$
	LVEDD (mm), median (IQR)	46.0 (43.0, 48.2)	46.0 (43.0, 50.0)	46.0 (43.0, 48.0)	46.0 (44.2, 46.0)
	IVSd (mm), median (IQR)	8.4 (8.0, 9.5)	8.8 (8.0, 9.7)	8.0 (7.0, 9.0)	8.0 (8.0, 8.6)
Cardiac MRI	RVEDVi (mL/m^2), median (IQR)	97.0 (87.0, 120.0)	107.0 (92.0, 130.0)	87.0 (78.5, 92.8)	78.5 (63.5, 93.0)
	RV ejection fraction (%), median (IQR)	46.0 (36.0, 50.0)	40.0 (31.0, 50.0)	51.0 (48.5, 56.5)	51.0 (47.5, 58.5)
	RV wall motion abnormalities, *n* (%)	61 (55)	53 (66)	6 (35)	2 (14)
	Local RV aneurysm, *n* (%)	16 (14)	14 (17)	1 (6)	1 (7)
	RV LGE, *n* (%)	32 (29)	24 (30)	7 (41)	1 (7)
	LVEDVi (mL/m^2), median (IQR)	80.0 (74.0, 85.0)	80.0 (78.5, 88.0)	81.0 (71.0, 86.0)	72.5 (67.5, 78.2)
	LV ejection fraction (%), median (IQR)	60.0 (55.0, 63.0)	60.0 (54.2, 62.0)	61.0 (57.8, 63.5)	60.0 (55.5, 62.5)

ARVC diagnosis		Overall: $n = 124$	Definite: $n = 93$	Borderline: $n = 17$	Possible: $n = 14$
Time of definite ARVC diagnosis[b] (age in years), median (IQR)		N/A	34.0 (25.0, 50.0)	N/A	N/A
Proband status, *n* (%)		79 (64)	75 (81)	2 (12)	2 (14)
Onset of symptoms (age in years), median (IQR)		29.0 (22.2, 45.0)	27.5 (22.0, 45.0)	34.0 (27.0, 42.0)	N/A
Initial symptoms	Aborted sudden cardiac death, *n* (%)	21 (17)	21 (23)	0 (0)	0 (0)
	Palpitations, *n* (%)	49 (40)	46 (49)	3 (18)	0 (0)
	Syncope, *n* (%)	25 (20)	23 (25)	2 (12)	0 (0)
	Chest pain, *n* (%)	13 (10)	11 (12)	2 (12)	0 (0)
	Dyspnoea, *n* (%)	43 (35)	42 (45)	1 (6)	0 (0)
	None, *n* (%)	40 (32)	13 (14)	13 (76)	14 (100)

Genotype	Overall: $n = 124$	Definite: $n = 93$	Borderline: $n = 17$	Possible: $n = 14$
Plakophilin-2 (PKP2), *n* (%)	63 (51)	45 (48)	8 (47)	10 (71)
Desmoplakin (DSP), *n* (%)	30 (24)	19 (20)	8 (47)	3 (21)
Desmoglein-2 (DSG2), *n* (%)	6 (5)	5 (5)	0 (0)	1 (7)
Desmocillin-2 (DSC2), *n* (%)	2 (2)	2 (2)	0 (0)	0 (0)
Laminin subunit alpha 4 (LAMA4), *n* (%)	1 (1)	1 (1)	0 (0)	0 (0)
Sodium voltage-gated channel 58 (SCN58), *n* (%)	1 (1)	1 (1)	0 (0)	0 (0)
Titin (TTN), *n* (%)	1 (1)	1 (1)	0 (0)	0 (0)
Ryanodine receptor 2 (RYR2), *n* (%)	1 (1)	1 (1)	0 (0)	0 (0)
Multiple variants, *n* (%)	9 (7)	8 (9)	0 (0)	1 (7)
Gene elusive, *n* (%)	11 (9)	10 (11)	0 (0)	1 (7)
No genetic testing performed, *n* (%)	15 (12)	14 (15)	1 (6)	0 (0)

ACE, angiotensin-converting enzyme; ARVC, arrhythmogenic right ventricular cardiomyopathy; CPR, cardiopulmonary resuscitation; FAC, fractional area change; ICD, implantable cardioverter defibrillator; IQR, interquartile range; IVSd, end-diastolic interventricular septum thickness; LGE, late gadolinium enhancement; LV, left ventricle; LVEDD, left ventricular end-diastolic diameter; LVEDVi, left ventricular end-diastolic volume index; MRI, magnetic resonance imaging; PCI, percutaneous coronary intervention; PLAX, parasternal long-axis view; PSAX, parasternal short-axis view; RV, right ventricle; RVEDVi, right ventricular end-diastolic volume index; RVOT, right ventricular outflow tract; SCD, sudden cardiac death; SGLT, sodium–glucose-linked transporter; TAPSE, tricuspid annular plane systolic excursion; TIA, transient ischaemic attack.
[a]Data shown for patients who did not undergo heart transplantation until the last follow-up ($n = 111$).
[b]According to the 2010 Task Force Criteria.[16]

[HR per 100 METh/week: 1.017, 95% CI (1.003, 1.032), $P = 0.015$], sustained VT [HR per 100 METh/week: 1.021, 95% CI (1.006, 1.037), $P = 0.007$], aborted SCD [HR per 100 METh/week: 1.011, 95% CI (0.980, 1.042), $P = 0.498$], and ICD interventions [HR per 100 METh/week: 1.017, 95% CI (1.000, 1.034), $P = 0.048$], indicating a higher risk of event occurrence with higher cumulative activity except for aborted SCD (*Table 4A*). This finding remained consistent upon separate analysis of sports-related activity, whereas the HRs for clinical endpoint occurrence associated with non-sports-related activity may only suggest a trend (HR estimators >1) for higher event risk without reaching statistical significance. For all endpoints except aborted SCD, the numeric HRs for event occurrence were higher for sports-related compared to non-sports-related activity (*Table 4A*). In two separate exploratory models, event occurrence in the context of cumulative activity was analyzed adjusted for sex (*Table 4B*) and common genotypes (presence of PKP2 or DSP pathogenic/likely pathogenic variant or both) (see Supplementary material online, *Table S11*). Both secondary adjusted analyses did not show a significant association between

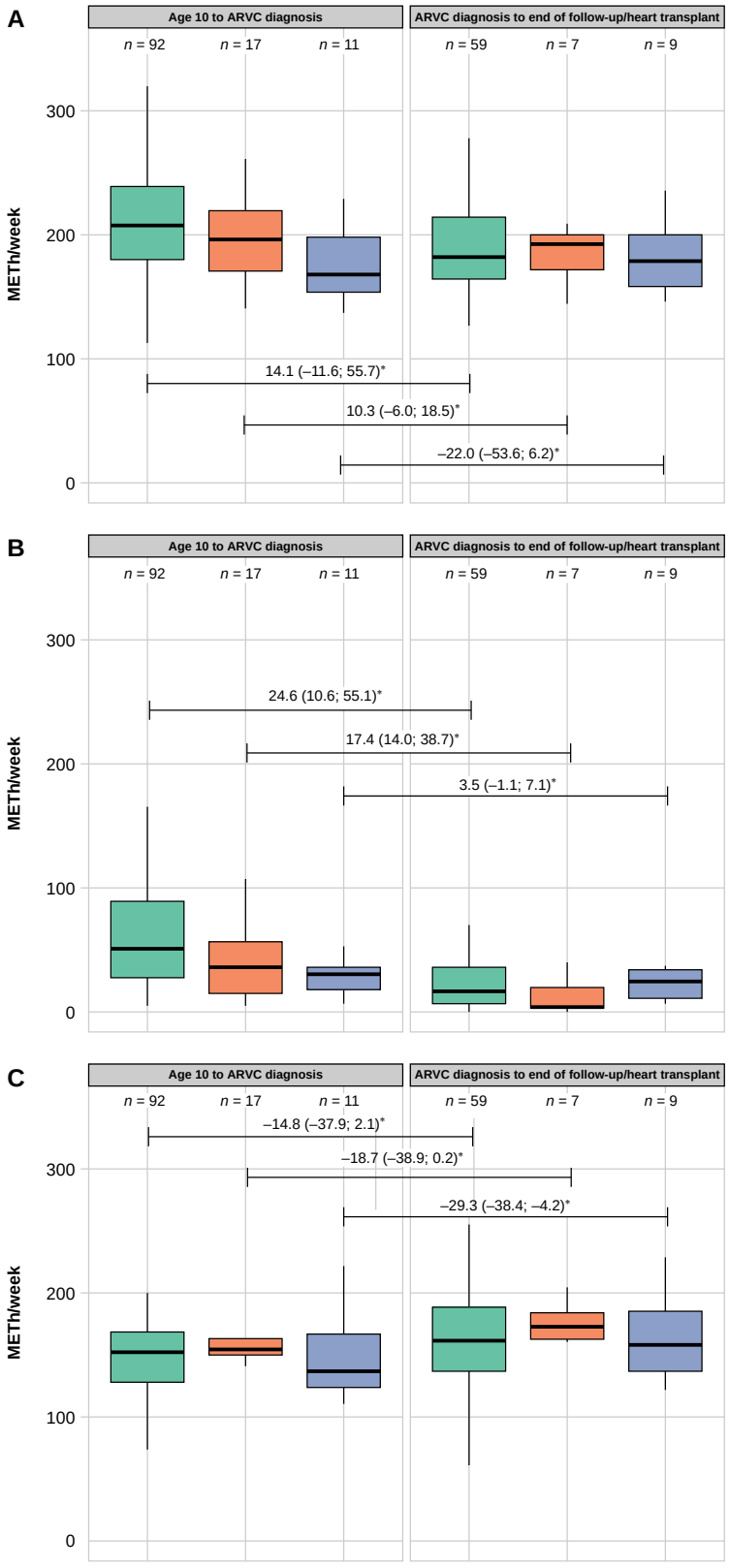


Figure 2 Physical activity levels before and after ARVC diagnosis in patients with definite, borderline, and possible ARVC. (*A*) Overall, (*B*) sports-related, and (*C*) non-sports-related physical activity, shown for patients with definite (green, first and fourth boxplots from the left), borderline (orange, second and fifth boxplots from the left), and possible ARVC (blue, third and sixth boxplots from the left). *indicates median difference (interquartile range) of METh/week before vs. after ARVC diagnosis. ARVC, arrhythmogenic right ventricular cardiomyopathy; METh, metabolic equivalent of task—hours.

Table 2 Physical activity in the overall population and in subgroups of patients with definite, borderline, or possible ARVC. The number of patients with sufficient data for categorization is indicated below

Dynamic component of sports-related physical activity		**Overall: *n* = 124**	**Definite: *n* = 93**	**Borderline: *n* = 17**	**Possible: *n* = 14**
Aggregated sports-related activity with low dynamic component (definition according to Mitchell *et al.*[21]) (METh/week), median (IQR)	Before ARVC diagnosis	0.5 (0.0, 2.7) *n* = 120	0.6 (0.0, 2.5) *n* = 92	0.5 (0.0, 2.4) *n* = 17	0.1 (0.0, 3.6) *n* = 11
	After ARVC diagnosis	0.4 (0.0, 4.3) *n* = 75	0.2 (0.0, 3.9) *n* = 59	0.0 (0.9, 1.1) *n* = 7	3.3 (0.0, 5.7) *n* = 9
Aggregated sports-related activity with moderate dynamic component (definition according to Mitchell *et al.*[21]) (METh/week), median (IQR)	Before ARVC diagnosis	18.5 (9.5, 29.8) *n* = 120	18.9 (11.3, 31.0) *n* = 92	19.4 (9.1, 28.7) *n* = 17	12.2 (7.4, 19.8) *n* = 11
	After ARVC diagnosis	9.6 (3.3, 19.2) *n* = 75	8.6 (3.2, 18.9) *n* = 59	3.6 (2.3, 17.7) *n* = 7	11.5 (5.5, 17.7) *n* = 9
Aggregated sports-related activity with high dynamic component (definition according to Mitchell *et al.*[21]) (METh/week), median (IQR)	Before ARVC diagnosis	18.4 (4.1, 48.8) *n* = 120	23.9 (5.6, 56.2) *n* = 92	8.1 (3.5, 23.5) *n* = 17	5.1 (1.8, 19.1) *n* = 11
	After ARVC diagnosis	0.0 (0.0, 6.8) *n* = 75	0.0 (0.0, 10.8) *n* = 59	0.0 (0.0, 1.4) *n* = 7	0.0 (0.0, 3.2) *n* = 9

Categorization according to minimum physical activity recommended by the AHA (Haskell *et al.*[22])		**Overall: *n* = 124**	**Definite: *n* = 93**	**Borderline: *n* = 17**	**Possible: *n* = 14**
Number of individuals below the recommended minimum of physical activity (<12.5 METh/week additional to light-intensity activities of daily living), *n* (%)	Before ARVC diagnosis	0 (0) *n* = 120	0 (0) *n* = 92	0 (0) *n* = 17	0 (0) *n* = 11
	After ARVC diagnosis	0 (0) *n* = 75	0 (0) *n* = 59	0 (0) *n* = 7	0 (0) *n* = 9
Number of individuals above recommended minimum of physical activity (≥12.5 METh/week additional to light-intensity activities of daily living), *n* (%)	Before ARVC diagnosis	120 (100) *n* = 120	92 (100) *n* = 92	17 (100) *n* = 17	11 (100) *n* = 11
	After ARVC diagnosis	75 (100) *n* = 75	59 (100) *n* = 59	7 (100) *n* = 7	9 (100) *n* = 9

Categorization according to previously proposed definitions of athlete status, exercise duration, and exercise intensity	**Overall: *n* = 124**	**Definite: *n* = 93**	**Borderline: *n* = 17**	**Possible: *n* = 14**
Athlete status (definition according to Wang *et al.*[24]: ≥18 METh/week within 3 years preceding ARVC diagnosis), *n* (%)	87 (73) *n* = 120	74 (80) *n* = 92	8 (47) *n* = 17	5 (45) *n* = 11
Athlete status (definition according to Saberniak *et al.*[8]: ≥24 METh/week during minimum 6 years preceding ARVC diagnosis), *n* (%)	80 (67) *n* = 120	69 (75) *n* = 92	6 (35) *n* = 17	5 (45) *n* = 11
Athlete status (definition according to Gasperetti *et al.*[23]: ≥36 METh/week within 3 years preceding ARVC diagnosis), *n* (%)	58 (48) *n* = 120	51 (55) *n* = 92	3 (18) *n* = 17	4 (36) *n* = 11
Athlete status (definition according to James *et al.*[7]: high dynamic exercise for ≥50 h/year preceding ARVC diagnosis), *n* (%)	82 (68) *n* = 120	68 (74) *n* = 92	7 (41) *n* = 17	7 (64) *n* = 11

Continued

Table 2 *Continued*

Categorization according to previously proposed definitions of athlete status, exercise duration, and exercise intensity	Overall: *n* = 124	Definite: *n* = 93	Borderline: *n* = 17	Possible: *n* = 14
High level of physical activity (definition according to Paulin *et al.*[25]: ≥63 METh/week in the year before ICD implantation), *n* (%)	29 (37)	29 (39)	0 (0)	0 (0)
	n = 79	*n* = 75	*n* = 4	*n* = 0
Long duration of sports-related activity (definition according to Lie *et al.*[11]: ≥2.5 h/week within 3 years preceding ARVC diagnosis), *n* (%)	107 (89)	83 (90)	14 (82)	10 (91)
	n = 120	*n* = 92	*n* = 17	*n* = 11
Short duration of sports-related activity (definition according to Lie *et al.*[11]: <2.5 h/week within 3 years preceding ARVC diagnosis), *n* (%)	13 (11)	9 (10)	3 (18)	1 (9)
	n = 120	*n* = 92	*n* = 17	*n* = 11
High-intensity sports-related activity (definition according to Lie *et al.*[11]: ≥6 MET within 3 years preceding ARVC diagnosis), *n* (%)	98 (82)	80 (87)	10 (59)	8 (73)
	n = 120	*n* = 92	*n* = 17	*n* = 11
Low-intensity sports-related activity (definition according to Lie *et al.*[11]: <6 MET within 3 years preceding ARVC diagnosis), *n* (%)	22 (18)	12 (13)	7 (41)	3 (27)
	n = 120	*n* = 92	*n* = 17	*n* = 11

AHA, American Heart Association; ARVC, arrhythmogenic right ventricular cardiomyopathy; ICD, implantable cardioverter defibrillator; IQR, interquartile range; MET, metabolic equivalent of task; METh, metabolic equivalent of task—hours.

cumulative physical activity and the four prespecified endpoints. In the subgroup analysis of male patients, the resulting HRs suggest a significant association between cumulative overall, sports-related, and non-sports-related physical activity with symptomatic heart failure, sustained ventricular arrhythmias, and ICD interventions (*Table 4C*).

Discussion

This study is the first to investigate the association of both sports-related and non-sports-related lifetime physical activity with clinical outcome parameters in ARVC patients utilizing a continuous statistical model. The results of this novel approach corroborate previous evidence for a correlation between a higher burden of cumulative physical activity and an increased risk of experiencing symptomatic heart failure, sustained ventricular arrhythmias, and ICD interventions. Surprisingly, we found no significant association between activity burden and aborted SCD, although this finding may be related to limited power or undetected confounding.

Recent pre-clinical studies have advanced our understanding of the pathophysiology of ARVC and the impact of physical activity on disease progression.[26–28] Most retrospective analyses investigating this relationship in ARVC patients have employed an interview-based strategy for assessing patients' (sports-related) physical activity.[7,8,10,11,14,25] This approach introduces the risk of multiple biases, such as the observer effect, response and social desirability bias, the halo effect, and others. Our interview-based collection of physical activity data may be limited by these inherent biases as well, although an attempt to mitigate potential confounding using a standardized two-step interview approach and by translating physical activity to MET units using a state-of-the-art database was applied.[20] A recent report from the EURObservational Research Programme Cardiomyopathy and Myocarditis Registry highlights that ARVC patients aged 10–18 years frequently experience arrhythmia-related symptoms or even major arrhythmic events.[29] This emphasizes the importance of extending risk factor analyses, including the assessment of physical activity, into adolescence. However, interpreting these data remains challenging and requires caution due to potential recency and recall biases.

Apart from the methodological variations related to collecting and processing activity data, previous studies have used different strategies to categorize study participants according to their activity profile, carrying additional risks of misclassification, loss of information, and loss of precision. Categorization of a continuous variable that is prone to non-differential measurement error (i.e. where the error is not related to the outcome) can often lead to differential misclassification (i.e. where the error is related to the outcome). The latter is prone to the introduction of more severe and unpredictable bias than the former.[30] Besides, previously used thresholds for defining 'athlete' status vary substantially (≥18 METh/week within 3 years preceding presentation[24] vs. ≥ 24 METh/week during a minimum of 6 years preceding presentation[8] vs. ≥ 36 METh/week within 3 years preceding presentation[23] vs. high dynamic exercise for ≥50 h per year preceding presentation[7]), which limits the comparability and reproducibility of study results. In fact, applying the abovementioned criteria to the present dataset yielded highly variable proportions of patients who would be classified as 'athletes'. This finding emphasizes the disadvantages of a categorical description of activity dose in this setting. In the present study, the high granularity of MET-based activity data collected from early adolescence onwards allowed for integration of physical activity as a continuous predictor into a modelling approach that is independent of the time of diagnosis, time of event occurrence, thresholds for activity duration and intensity, and other definitions of physical activity.

In theory, the underlying pathomechanism of physical activity-related ARVC disease progression equally applies to sports-related and non-sports-related high-intensity physical activity. In the present

Table 3 Clinical outcomes in the overall population and in subgroups of patients with definite, borderline, or possible ARVC

		Overall: $n = 124$	Definite: $n = 93$	Borderline: $n = 17$	Possible: $n = 14$
NYHA class at the last follow-up/year before heart transplantation	I, *n* (%)	27 (22)	7 (8)	6 (35)	14 (100)
	II, *n* (%)	71 (57)	60 (65)	11 (65)	0 (0)
	III, *n* (%)	25 (20)	25 (27)	0 (0)	0 (0)
	IV, *n* (%)	1 (1)	1 (1)	0 (0)	0 (0)
Heart transplantation, *n* (%)		13 (10)	13 (14)	0 (0)	0 (0)
Sustained ventricular tachycardia, *n* (%)		65 (52)	65 (70)	0 (0)	0 (0)
Aborted/resuscitated cardiac arrest, *n* (%)		22 (18)	22 (24)	0 (0)	0 (0)
Appropriate ICD intervention, *n* (%)		46 (37)	46 (49)	0 (0)	0 (0)
Ablation of ventricular tachycardia, *n* (%)		28 (23)	28 (30)	0 (0)	0 (0)

ARVC, arrhythmogenic right ventricular cardiomyopathy; ICD, implantable cardioverter defibrillator; NYHA, New York Heart Association.

Table 4A Association of cumulative physical activity (per 100 METh/week) and clinical endpoints between age 10 and last follow-up

	Overall physical activity		Sports-related physical activity		Non-sports-related physical activity	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Heart failure stage C	1.017 (1.003,1.032)	0.015	1.027 (1.008,1.045)	0.004	1.008 (0.981,1.037)	0.554
Sustained ventricular tachycardia	1.021 (1.006,1.037)	0.007	1.032 (1.012,1.053)	0.002	1.011 (0.979,1.045)	0.508
Aborted sudden cardiac death	1.011 (0.980,1.042)	0.498	1.004 (0.965,1.045)	0.842	1.035 (0.971,1.103)	0.297
ICD intervention	1.017 (1.000,1.034)	0.048	1.026 (1.004,1.047)	0.018	1.006 (0.970,1.043)	0.754

CI, confidence interval; HR, hazard ratio; ICD, implantable cardioverter defibrillator; METh, metabolic equivalent of task—hours.

analysis, non-sports-related physical activity constituted more than 75% of the cumulative overall physical activity, although subjective classification by study participants and potentially aggravated confounding during data collection limits the interpretation of these data. Due to underreporting in most previous studies, the impact of this portion of activity on ARVC progression is still unknown. Considering that many individuals are exposed to some form of occupational activity (e.g. construction work) or engage in moderate/high-intensity non-athletic leisure activities (e.g. gardening, home repair, household activities),[20] the associated risks are of high clinical relevance. In the separate analysis of non-sports-related physical activity, we found no significant association between cumulative activity and outcomes, although the observed HRs for all endpoints exceeded 1, suggesting a possible trend for higher risk associated with non-sports-related physical activity. Pending additional data from larger cohorts with higher statistical power, it remains unclear how best to advise ARVC patients regarding non-sports-related activities. Nonetheless, preliminary data from the present analysis at least suggest that non-sports-related activities should be included in patient-centred discussions on lifestyle changes, especially for patients engaged in regular high-intensity non-sports-related activities.

Regarding sports-related physical activity, our results are consistent with previously published data that demonstrated a higher risk of poor outcomes in individuals frequently engaging in athletic activities.[7–14] Although prospective studies have not been published, the available clinical and pre-clinical data indicate that the haemodynamic changes during intense activity contribute to anatomical and electrophysiological manifestations of ARVC.[1,8,26,31–34] Consequently, current guideline recommendations advise patients and variant-positive family members to avoid participation in competitive endurance and high-intensity exercise, a stance supported by the results of our analyses.[17,18] In the present cohort, a noticeable reduction of sports-related activity with moderate and high dynamic components after definite and borderline ARVC diagnosis suggests a high compliance with these recommendations. The numeric increase in non-sports-related activity reported after a definite ARVC diagnosis may be a direct consequence of these lifestyle changes.

Recently, Bosman and colleagues found that higher cumulative exercise within 3 years prior to ARVC diagnosis was associated with an increased risk of experiencing ventricular arrhythmias, which was in essence reproduced by our continuous modelling approach.[14] The authors have also shown that adding 'athlete' status (defined as >18 METh/week, >24 METh/week, or >36 METh/week within 3 years prior to diagnosis) to the established factors of the ARVC risk calculator did not improve risk prediction for ventricular arrhythmias.[14,35] This finding may be explained by the hypothesis that cumulative physical activity drives ARVC progression and thus directly influences other factors of the original model, such as non-sustained VT occurrence or RV dysfunction, and generally demonstrates the difficulties of investigating isolated impact of physical activity within a complex real-world setting. Our data indicate that activity burden before the occurrence of a first clinical event and ARVC diagnosis may be useful for risk assessment. However, accurate risk prediction seems to require comprehensive data collection and even more refined statistical modelling. Exploratory adjusted models incorporating non-modifiable baseline characteristics (sex or genotype) suggest that the observed association

Table 4B Association of cumulative physical activity (per 100 METh/week) and clinical endpoints between age 10 and last follow-up, adjusted for sex

		Overall physical activity		Sports-related physical activity		Non-sports-related physical activity	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Heart failure stage C	Cumulative exercise	1.012 (0.996, 1.029)	0.133	1.018 (0.99, 1.047)	0.214	1.009 (0.981, 1.038)	0.522
	Sex (m)	1.720 (0.708, 4.175)	0.231	1.763 (0.905, 3.432)	0.095	1.931 (0.799, 4.665)	0.144
	Cumulative exercise * sex (m)	1.002 (0.987, 1.018)	0.753	1.004 (0.969, 1.04)	0.816	1.002 (0.982, 1.023)	0.842
Sustained ventricular tachycardia	Cumulative exercise	1.016 (0.999, 1.035)	0.071	1.019 (0.984, 1.055)	0.286	1.017 (0.984, 1.051)	0.316
	Sex (m)	2.311 (0.834, 6.4)	0.107	2.201 (1.009, 4.801)	0.047	2.936 (1.047, 8.229)	0.041
	Cumulative exercise * sex (m)	1.002 (0.986, 1.019)	0.791	1.008 (0.967, 1.05)	0.708	0.999 (0.975, 1.023)	0.931
Aborted sudden cardiac death	Cumulative exercise	1.01 (0.977, 1.045)	0.544	0.971 (0.883, 1.068)	0.546	1.041 (0.977, 1.109)	0.212
	Sex (m)	2.142 (0.47, 9.752)	0.325	1.283 (0.381, 4.316)	0.687	2.842 (0.589, 13.713)	0.193
	Cumulative exercise * sex (m)	0.994 (0.965, 1.023)	0.665	1.033 (0.936, 1.142)	0.517	0.984 (0.942, 1.028)	0.468
ICD intervention	Cumulative exercise	1.007 (0.984, 1.03)	0.547	0.983 (0.929, 1.04)	0.545	1.009 (0.97, 1.049)	0.654
	Sex (m)	1.789 (0.514, 6.22)	0.360	1.639 (0.632, 4.253)	0.309	2.677 (0.745, 9.62)	0.131
	Cumulative exercise * sex (m)	1.009 (0.99, 1.029)	0.366	1.043 (0.983, 1.107)	0.167	1.004 (0.978, 1.031)	0.753

CI, confidence interval; HR, hazard ratio; ICD, implantable cardioverter defibrillator; m, male; METh, metabolic equivalent of task—hours.

Table 4C Association of cumulative physical activity (per 100 METh/week) and clinical endpoints between age 10 and last follow-up in subgroup of male patients

		Overall physical activity		Sports-related physical activity		Non-sports-related physical activity	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Heart failure stage C	Cumulative exercise	1.014 (0.999, 1.028)	0.059	1.02 (1.002, 1.04)	0.034	1.01 (0.983, 1.038)	0.476
	Sex (m)	1.943 (1.23, 3.071)	0.004	1.866 (1.174, 2.967)	0.008	2.086 (1.331, 3.27)	0.001
Sustained ventricular tachycardia	Cumulative exercise	1.018 (1.002, 1.034)	0.029	1.024 (1.003, 1.045)	0.023	1.017 (0.985, 1.05)	0.313
	Sex (m)	2.601 (1.535, 4.407)	<0.001	2.457 (1.442, 4.188)	0.001	2.823 (1.671, 4.769)	<0.001
Aborted sudden cardiac death	Cumulative exercise	1.007 (0.976, 1.04)	0.662	0.997 (0.956, 1.04)	0.882	1.037 (0.973, 1.106)	0.262
	Sex (m)	1.632 (0.685, 3.888)	0.269	1.724 (0.711, 4.18)	0.228	1.746 (0.741, 4.111)	0.202
ICD intervention	Cumulative exercise	1.013 (0.995, 1.031)	0.165	1.016 (0.994, 1.039)	0.156	1.011 (0.976, 1.048)	0.534
	Sex (m)	2.978 (1.569, 5.653)	0.001	2.854 (1.487, 5.477)	0.002	3.205 (1.696, 6.057)	<0.001

CI, confidence interval; HR, hazard ratio; ICD, implantable cardioverter defibrillator; m, male; METh, metabolic equivalent of task—hours.

between activity burden and clinical endpoints may be pronounced in certain subgroups, pointing towards possible influencing variables. However, these underpowered analyses must be interpreted with caution and should at this stage be considered hypothesis-generating. Furthermore, many modifiable factors influencing event risk over the disease course exist. Particularly after diagnosis, these factors include therapeutic interventions such as lifestyle recommendations, device therapy, and antiarrhythmic and other medications.

Consistent with previous analyses, a pathogenic/likely pathogenic variant in desmosomal genes was detected in a large proportion of patients.[3,14,36] Importantly, the underlying genotype has been shown to be associated with arrhythmic risk and clinical phenotype, further complicating the investigation of common risk factors in cohorts with heterogenous genotypes.[36–40] For example, recurrent myocardial inflammation, a higher rate of left ventricular dysfunction, and an increased risk of ventricular arrhythmias are characteristic features of DSP cardiomyopathy.[41] To address the heterogeneity of disease manifestation, Corrado and colleagues proposed modifications of the 2010 Task Force Criteria enabling the distinction between right-dominant, left-dominant, and biventricular forms within the spectrum of arrhythmogenic cardiomyopathies.[6,42] While the results from the present analysis may not be applicable to other cohorts with different predominant genotypes/phenotypes, or to patients in whom genetic testing was negative or not performed, further investigation into the relationship between cumulative physical activity and clinical endpoints in well-defined subgroups is essential for refining risk prediction and developing personalized management strategies.

Conclusion

The novel modelling approach employed for the present analysis provides further evidence for the association of cumulative activity burden with poor outcomes in ARVC patients. Assessment of both sports-related and non-sports-related activity with high granularity enabled for the first time the exploration of activity aggregates as a continuous rather than categorical parameter, which may increase the robustness and reproducibility of our findings. However, our analysis also demonstrates the methodological challenges of establishing an association or even causal relationship between physical activity and clinical endpoints in such complex long-term scenarios. In order to address the unanswered key question of which type and volume of physical activity is 'safe' for ARVC patients and variant carriers, future studies in larger cohorts have to account not only for the intricacies regarding individual physical activity but also for therapeutic interventions, lifestyle modifications, and the timing of clinical events. Until additional information becomes available, a patient's activity profile alone remains unsuitable for personalized risk prediction.

Supplementary material

Supplementary material is available at *Europace* online.

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Data availability

The data presented in this study are available on request from the corresponding author. The data are not publicly available due to ethical restrictions and legal constraints.

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