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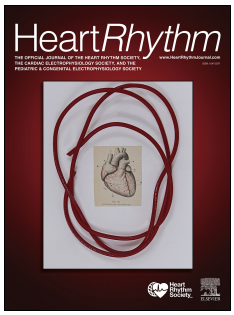

Endurance Exercise Promotes Episodes of Myocardial Injury in Individuals with a Pathogenic Desmoplakin (DSP) Variant

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Alan P. Jacobsen, M.B., B.Ch., B.A.O.;[1,2] Katia Chiampas, B.A.;[1] Steven A Muller, M.D.;[1,3,4] Alessio Gasperetti, M.D., Ph.D.;[1] Lisa R. Yanek, M.P.H.;[1] Richard T. Carrick, M.D., Ph.D.;[1] Catherine Gordon;[1] Crystal Tichnell, M.G.C., R.N.;[1] Brittney Murray, M.S.;[1] Hugh Calkins, M.D., F.H.R.S.;[1] Lili A Barouch, M.D.;[1] Cynthia A James, Sc.M., Ph.D.[1]

[1]Division of Cardiology, Department of Medicine, Johns Hopkins University, Baltimore, MD, USA
[2]Division of Cardiology, Department of Medicine, University of Utah, Salt Lake City, UT, USA
[3]Department of Cardiology, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, Netherlands
[4]Member of the European Reference Network for rare, low prevalence and complex diseases of the heart: ERN GUARD-Heart'(ERN GUARDHEART; http://guardheart.ern-net.eu)

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Corresponding author:
Alan P Jacobsen, Division of Cardiology, Department of Medicine, University of Utah, Salt Lake City, UT, USA
Email: alan.jacobsen@utah.edu
Twitter: @alanpjacobsen

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Abbreviations:
ACM: Arrhythmogenic Cardiomyopathy
ARVC: Arrhythmogenic Right Ventricular Cardiomyopathy
CI: Confidence Interval
HR: Hazard Ratio
ICD: Implantable cardioverter-defibrillator
IQR: Interquartile-range
METhr/wk: Metabolic hours/week
P/LP: Pathogenic/Likely pathogenic
SD: Standard deviation
VA: Ventricular arrhythmia

Abstract

Background

Desmoplakin (*DSP*) variants are associated with left-predominant or biventricular arrhythmogenic cardiomyopathy. Exercise promotes penetrance and sustained ventricular arrhythmias (VA) in right-sided arrhythmogenic right ventricular cardiomyopathy, but its effect is unknown in *DSP* variant carriers.

Objectives

To assess whether exercise is associated with clinical outcomes among individuals with a pathogenic or likely pathogenic (P/LP) *DSP* variant.

Methods

Adults with P/LP *DSP* variants were interviewed about physical activity from age 10. Endurance athletes were defined based on a mean exercise dose >24 metabolic equivalent hours/week (METhr/wk) of moderate to vigorous intensity exercise. Lifetime survival free from VA (ventricular tachycardia/fibrillation or appropriate ICD therapy), clinical heart failure (HF) (presentation to the emergency department or hospitalization with HF), and myocardial injury events characteristic of *DSP*-cardiomyopathy (symptoms, elevated troponin, imaging with non-obstructive coronaries) were examined with the Kaplan-Meier method and Cox regression models.

Results

Participants (N=100, 66% female, age 36 ± 15 years) were active with a median 28.4 METhr/wk (IQR 14.8-46) of pre-baseline evaluation exercise, and just 8 individuals continued athlete level exercise post-baseline evaluation. In multivariable analyses, endurance athletes (60%) had no worse survival free from VA [HR 1.00 (95% CI 0.5-1.98)] or clinical HF [HR 0.86 (95% CI 0.36-2.05)] but their risk for myocardial injury was elevated [HR 2.37 (95% CI 1.11-5.05)]. Furthermore, myocardial injury episodes were strongly associated with an elevated risk of both VA [HR 7.86 (95% CI 3.56-17.33)] and clinical HF [HR 10.28 (95% CI 2.95-35.83)] thereafter.

Conclusions

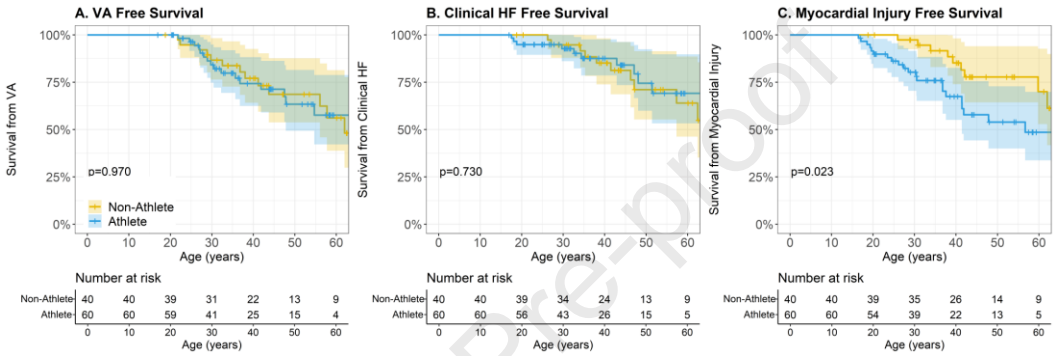
Endurance exercise may promote progression of *DSP*-cardiomyopathy by increasing risk of myocardial injury episodes, but the effect on VA and clinical HF is less clear. This study informs shared decision-making exercise and sports participation discussions.

Graphical Abstract

Endurance Exercise Promotes Episodes of Myocardial Injury in Individuals with a Pathogenic Desmoplakin (DSP) Variant

- Participants with a pathogenic or likely pathogenic desmoplakin variant
- N=100, 66% female, average age 36 ± 15 years
- 73% with phenotypic expression at presentation

- Physical exercise data were collected by telephone interview from age 10
- Exercise dose was quantified in metabolic equivalent hours per week (METhr/wk)
- Participants were classified as athletes or non-athletes based on an exercise dose >24 METhr/wk



VA=Sustained ventricular arrhythmia, HF=Heart failure

Introduction

Pathogenic and likely pathogenic (P/LP) variants in the gene encoding desmoplakin (*DSP*) are associated with arrhythmogenic cardiomyopathy (ACM) with left ventricular (LV) predominant or biventricular involvement.[1,2] Patients with *DSP*-cardiomyopathy experience high rates of ventricular arrhythmias (VA), heart failure (HF), and episodes of myocarditis-like myocardial injury.[3-6] Symptomatic episodes of acute myocardial injury are an important and distinguishing characteristic of *DSP*-cardiomyopathy, occurring in roughly one-fifth of individuals and characterized by chest pain and elevated troponin.[1,7] A high prevalence of subepicardial late gadolinium enhancement (LGE) in individuals with *DSP*-cardiomyopathy suggests that clinically silent myocardial injury episodes may occur as well.[4,8] It is unknown what triggers such events; however, intense exercise is hypothesized to play a role.[9]

Endurance exercise and frequent exercise have been shown to increase the risk of disease penetrance, VA, and HF in classical arrhythmogenic right ventricular cardiomyopathy (ARVC).[10] These adverse disease outcomes are more prominent in patients participating in higher intensity exercise and competitive sport, suggesting a dose-dependent relationship.[11-14] However, prior studies evaluating the relationship between exercise and adverse disease outcomes in ARVC have predominantly involved participants with Plakophilin-2 (*PKP2*) variants or gene-elusive ARVC. The relationship between exercise and ACM due to pathogenic variants in non-*PKP2* genes is not yet fully elucidated, and diverging results observed with different genes.[15-17] Clinical evidence exploring the effect of exercise on *DSP*-cardiomyopathy is limited to a single study that described clinical features found in individuals with a *DSP* variant and with a perfunctory exercise history noted no difference in ventricular function or VA among those who reported engaging in moderate and vigorous physical activity (N=42/80).[1]

Our study explores the relationship between exercise and clinical outcomes in individuals with known P/LP *DSP* variants. Specifically, we evaluated whether exercise dose, measured in metabolic equivalent hours per week (METhr/wk) was associated with lifetime risk of VA, clinical HF, or episodes of myocardial injury.

Methods

Study Population

The study population was recruited from the Johns Hopkins ARVC Registry, which prospectively enrolls ARVC/ACM patients and their family members. Registry participants with a P/LP *DSP* variant and were 18 years old or older were invited to participate in a telephone interview to document their exercise from age 10 up until the date of the interview. To the best of our knowledge, there was no overlap between participants in the current study and those from other studies that investigated exercise in patients with DSP variants.[1] Overlap of this cohort with participants in other studies of exercise in ACM is minimal due to the different genotype.[10]

Phenotypic expression (see below for definition for clinically affected) was not required for enrollment, which allowed for the inclusion of gene-positive, phenotype-negative individuals and those with overt *DSP*-cardiomyopathy. The Johns Hopkins School of Medicine Institutional Review Board approved all aspects of the study.

Genotype

All *DSP* genetic variants categorized as pathogenic or likely pathogenic underwent expert review by specialists in cardiac genetics in accordance with the American College of Medical Genetics and Genomics (ACMG) guidelines and previously published ACM-specific ACMG adjustments.[18]

Clinical Data

Clinical and demographic data were drawn from the Johns Hopkins ARVC Registry and supplemented with chart abstraction according to a set of standardized definitions as previously described.[6] Baseline evaluation was defined as the date of first clinical evaluation for ACM for those without symptoms or the date of first medical visit for a cardiac symptom related to ACM for those presenting symptomatically.

Clinical Outcomes and Definitions

The primary outcomes were lifetime first sustained VA (a composite of sustained VA, appropriate implantable cardioverter defibrillator (ICD) therapy, sudden cardiac death, and sudden cardiac arrest),[19,20] lifetime first clinical HF (presentation to the emergency department or hospitalization with clinical heart failure), lifetime first episode of myocardial injury (presentation with typical symptoms of myocardial injury such as dyspnea or chest pain, an elevated troponin, and imaging to exclude coronary artery disease).

Clinically affected was defined as the presence of any of the following clinical features in line with recent publications on the topic:[2]

1. Sustained VA as defined above

2. Clinical HF as defined above
3. Myocardial injury as defined above
4. ARVC by 2010 Task Force Criteria (TFC)
5. Dilated Cardiomyopathy (DCM): A dilated LV by TTE or CMR with EF <50%
6. Nondilated LV cardiomyopathy (NDLVC):[21] A nondilated LV with EF <50%, regional wall motion abnormalities or the presence of LGE on CMR
7. Absolute PVC count >500 on a 24-hour cardiac monitor

Exercise Data

An exercise history for all participants was obtained through a structured telephone interview according to previously published protocols (**Supplement**).[10-12] For each exercise activity, the duration was recorded (in hours per day, days per month, months per year, and total years), and exercise intensity in metabolic equivalents (METs) was determined using the 2011 Compendium of Physical Activities.[22] Only recreational and competitive exercise of at least moderate intensity, *i.e.,* requiring at least 3 METs, were considered as exercise in this study. The average exercise dose was calculated for each year from age 10 by multiplying the MET value of each exercise by its duration in hours. The average exercise dose per year of each activity was summed to obtain a total average exercise dose in metabolic equivalent hours (METhr) per year. This sum was subsequently divided by 52 to achieve an average exercise dose in metabolic equivalent hours per week (METhr/wk).

As current guideline documents recommend restricting vigorous physical exercise in those with a P/LP *DSP* variant, including those who are gene positive, phenotype negative,[23,24] we expected there to be a large difference in exercise dose prior to baseline evaluation as

compared with post-baseline evaluation. Therefore, average METhr/wk of exercise was calculated from age 10 to baseline evaluation (pre-baseline evaluation exercise) and from baseline evaluation to exercise interview or last clinical follow-up whichever came first (post-baseline evaluation exercise). Annual METhr/wk of exercise was calculated to treat exercise as a time dependent variable (see statistical analysis).

Endurance athletes were defined as having an exercise dose >24 METhr/wk, consistent with prior studies.[11,14] Greater than 24 METhr/wk equates to >4 hours per week of vigorous activity, *i.e.,* an activity requiring at least 6 METs, a standard clinical working definition for an athlete.[25] Each participant was defined as an endurance athlete (average exercise >24 METhr/wk) or non-athlete before and after baseline evaluation based on this definition. Additionally, to facilitate time-dependent analyses, the athlete status of each participant was calculated for each year of follow-up.

Statistical Analysis

Categorical variables were reported as frequency (%) and compared using the chi-square or Fisher's exact test. Continuous variables were summarized as either mean ± standard deviation or median [interquartile range (IQR)] and compared across groups using a Student's t-test or Mann-Whitney U-test as appropriate. Exercise dose in METhr/wk before and after baseline evaluation was compared by the Wilcoxon signed rank test.

Exercise exposure was evaluated in two complementary ways. First, we assessed whether athlete status before baseline evaluation was associated with our primary endpoints using the Kaplan-Meier method and Cox proportional hazards regression. Moreover, to minimize selection and ascertainment bias, we repeated the before-mentioned analyses separately for those with and

without phenotypic expression of *DSP*-cardiomyopathy. Second, as exercise dose in our cohort differed over time (**Supplemental Figure 1**), we also considered athlete status as a time-varying predictor. Additionally, as a sensitivity effort, we also considered average exercise in METhr/wk as a continuous variable and tested for an association between increasing exercise dose and clinical outcomes using both Cox and time-varying Cox proportional hazards regression.

Cumulative freedom from sustained VA, clinical HF, or myocardial injury were determined by the Kaplan-Meier method. For individuals without a clinical outcome, censoring was defined by the last clinical follow-up date or date of exercise interview, whichever came first. Differences in survival among endurance athletes and non-athletes were evaluated with a log-rank test. Event likelihood was compared between groups using Cox regression, including exercise dose (endurance athlete versus non-athlete in the primary analyses) and a covariate for sex due to the known higher clinical risk among women with *DSP*-cardiomyopathy.[4] As prior studies have suggested that myocardial injury episodes are associated with worse outcomes thereafter,[4] multivariable Cox regression for association between athlete status and both VA and HF were repeated with the inclusion of myocardial injury as a time-dependent outcome mediator. Intrafamilial clustering was incorporated in all models as a random effect. A p-value <0.05 was considered significant. SAS version 9.4 statistical software (SAS Inc., Cary, North Carolina) and R version 4.1.2 (Boston, MA, USA) were used.

Results

Participant Characteristics

Invitations to participate were emailed to 121 individuals enrolled in the Johns Hopkins ARVC/ACM Registry, and 105 interviews were completed. All individuals had a P/LP variant in the *DSP* gene. Three individuals were excluded due to the presence of concurrent pathogenic variants in other genes (*PKP2, DSC2, NEXN*), and two were excluded as the identified *DSP* variant was ultimately deemed to be a variant of uncertain significance.

Of the 100 patients included in the final analysis, the mean age at baseline evaluation was 36 ± 14 years; 66% were female, 47% were probands and 97% were white. At the time of baseline evaluation, 77% were clinically affected (13% VA, 5% clinical HF, 25% myocardial injury, 70% had ARVC, NDLVC or DCM, and 5% >500 PVCs). Additional demographic and clinical characteristics are shown in **Table 1**.

Over a median of 4.9 (IQR 2.2-9.1) years of follow up from baseline evaluation, there were no deaths in the cohort and four individuals had a cardiac transplant, all due to a combination of end-stage heart failure and arrhythmias. At last follow-up, 29% individuals experienced a sustained VA event, of which 45% (N=13/29) were life-threatening (>250 beats/minute).[26] The activities that individuals were engaged in at the time of VA are summarized in **Supplemental Table 1**. Twenty (20%) participants visited an emergency department or were admitted to hospital with clinical HF. Twenty-nine (29%) experienced an episode of symptomatic myocardial injury. Most participants with myocardial injury events had available CMR imaging (N=25/29, 86%) which typically had evidence of LGE in a subepicardial/midmyocardial pattern (N=17/25, 68%).

Exercise History Prior to Baseline Evaluation

The median exercise dose of moderate to vigorous intensity exercise prior to baseline evaluation was 28.4 METhr/wk (IQR 14.8-46) over 24 years (IQR 15-34) and sixty (60%) participants fulfilled our definition for endurance athlete prior to baseline evaluation. Overall exercise dose decreased with increasing age **(Supplemental Figure 1).** There were no significant differences between endurance athletes and non-athletes in proportion of female sex, proband status, clinically affected at baseline evaluation, type of presentation, ECG or CMR parameters **(Table 1)**.

Influence of Exercise on Outcomes

Ventricular Arrhythmias and Clinical Heart Failure – As shown in **Figure 1**, there was no difference in time to first VA or time to first clinical HF between participants who were endurance athletes versus non-athletes pre-baseline evaluation (p=0.97 and p=0.73 respectively). Additionally, time-varying survival as well as stratified analyses were similarly non-significant **(Supplemental Figures 2 and 3).** Furthermore, athlete status was not significantly associated with VA or clinical HF on both multivariable Cox proportional hazards regression (**Table 2**) and time-varying Cox regression (**Supplemental Table 2)**. Finally, sensitivity analyses considering exercise dose as a log transformed continuous variable were also non-significant **(Supplemental Table 3)**.

Myocardial Injury – There was a greater risk of incident symptomatic myocardial injury in endurance athletes compared to non-athletes (p=0.01, **Figure 1**). Athlete status was also associated with risk of myocardial injury on multivariable Cox proportional hazards regression

366 [(HR 2.37, 95% CI 1.11-5.05, p=0.03) **Table 2**], time-varying Cox regression (**Supplemental**
367 **Figure 2**, **Supplemental Table 2)**, and when stratified based on phenotypic expression
368 (**Supplemental Figure 3**). A trend towards dose-responsiveness was seen when pre-baseline
369 evaluation exercise dose was split into tertiles with participants who had done the most exercise
370 at the highest risk **(Figure 2)**.
371
372 Myocardial Injury as a Mediator for VA and HF – Multivariable Cox regression analyses for
373 association between athlete status and both VA and HF were repeated with inclusion of
374 myocardial injury as a time-dependent outcome mediator. Myocardial injury was a strong
375 independent risk factor for subsequent VA [(HR 7.86, 95% CI 3.56-17.33, p<0.001) **Table 3**] and
376 clinical HF (HR 10.28, 95% CI 2.95-35.83, p<0.001). The median time interval between an
377 initial episode of myocardial injury to subsequent VA or clinical HF event was 0 (IQR 0-4.6) and
378 1.1 (IQR 0.5-3.1) years, respectively. To visualize the possible combined effect of myocardial
379 injury and endurance athlete level exercise, we performed a time-dependent Kaplan-Meier
380 analysis. As shown in **Supplemental Figure 4**, while underpowered, risk of both VA and HF
381 events following myocardial injury appears to be most elevated among participants who
382 exercised >24 METhr/wk following a myocardial injury event.
383
384 *Exercise History and Clinical Outcomes Following Baseline Evaluation*
385 The median weekly exercise dose post initial baseline evaluation significantly decreased
386 to 0 (IQR 0-8.2) METhr/wk over 4.9 (IQR 2.2-9.1) years of clinical follow-up (p <0.001; **Figure**
387 **3**). Only 38 (38%) individuals participated in any regular moderate or vigorous intensity exercise
388 post-baseline evaluation with just eight individuals fulfilling the endurance athlete definition

post-baseline evaluation (*i.e.,* had a mean >24 METhr/wk of post-presentation exercise). Individuals who continued any regular exercise at a moderate or vigorous level post baseline evaluation were younger [median age 23 versus 35 years old (p=0.01)] and more likely to have been identified through asymptomatic family screening [57% versus 25% (p=0.01)]. Clinical outcomes among individuals who continued any exercise at moderate or high intensity are summarized in **(Supplemental Table 4)**.

Discussion

Main Findings

Our study represents the first systematic assessment of the effect of exercise participation on adverse disease-specific events in a cohort of 100 individuals with a P/LP *DSP* variant, followed for nearly 5 years of clinical follow-up. Enrolled patients were active with a median weekly exercise dose >4 times the AHA minimum exercise recommendation of 7.5METhr/wk[27] over the two decades prior to baseline evaluation. While high levels of moderate to vigorous exercise was not an independent risk factor for either incident VA or clinical HF events, exercise was associated with the development of symptomatic myocardial injury episodes **(Graphical Abstract)**. Participants who experienced myocardial injury had a markedly increased risk for subsequent VA and clinical HF events thereafter.

Myocardial Injury

Newly recognized in this study is our finding that endurance athletes are at increased risk for symptomatic myocardial injury episodes typical of *DSP*-cardiomyopathy. This association

remained statistically significant after adjustment for known risk factors (female sex)[4] and was further bolstered by a trend towards a dose-responsive relationship between exercise and myocardial injury. Furthermore, the association between exercise and myocardial injury events was present when athlete status was considered as a time-varying predictor.

While the exact mechanism of these episodes remains unclear, a number of lines of evidence suggest they likely represent inflammatory myocarditis-like episodes:

1) In recent years, P/LP *DSP* variants have been well-described in patients presenting with clinical myocarditis, *i.e.,* the presence of symptoms, an elevated troponin, and CMR findings meeting Lake Louise criteria.[8,28]
2) The case definition used in the current cohort of young individuals would have excluded most cases of ischemia, as it required the presence of symptoms such as chest pain and dyspnea, an elevated troponin, and an imaging study that excluded the presence of coronary artery disease.
3) The majority of individuals in this study with myocardial injury had evidence of LGE in a subepicardial/midmyocardial pattern consistent with a nonischemic etiology.

Exercise is known to impart both acute and chronic effects on the immune system, and transient dysfunction of both innate and adaptive immunity is well described following heavy exertion.[29] Furthermore, classical autopsy studies attributed a fifth of episodes of sudden cardiac death among young individuals to myocarditis, with many of these episodes occurring during exercise.[30,31] As a result, current guideline documents recommend that individuals with clinical myocarditis not engage in moderate to vigorous intensity exercise for 3-6 months and until inflammation has resolved.[23,32] Consistent with this increased risk of sudden death during a traditional episode of myocarditis, we found substantially increased immediate risk of VA during

435 the index episode of myocardial injury. In contrast, clinical HF followed with a latency of
436 months to years after the index episode of myocardial injury.
437
438 *Clinical Implications*
439 Although not directly comparable, it is illustrative to contrast the current findings with
440 the results of prior studies demonstrating the impact of exercise in classical ARVC. In our
441 original study showing the risk of exercise on penetrance and outcomes in 87 genotype positive
442 individuals, most had P/LP *PKP2* variants. That study showed that over 8.4 years of clinical
443 follow-up, there was a dose-dependent increase in likelihood of ARVC penetrance with
444 increasing endurance exercise, that athletes had more than twice the lifetime risk of VA, and that
445 clinical HF only developed in athletes.[10] Similarly, in a cohort with 43 individuals who had gene-
446 elusive ARVC, participants with the greatest exercise dose presented at a younger ages and had
447 shorter survival free from VA.[33] Thus, in *PKP2*-ARVC and gene elusive ARVC, endurance
448 exercise directly increases likelihood of disease onset as well as increasing risk of arrhythmias,
449 while in *DSP*-cardiomyopathy, exercise appears to worsen clinical trajectory by potentiating
450 myocardial injury events with the impact on penetrance uncertain.
451 Current recommendations for exercise among individuals with a P/LP *DSP* variant are
452 either non-specific for *DSP* or are based predominately on expert opinion. The 2019 Heart
453 Rhythm Society (HRS) expert consensus statement on ACM recommends counseling for
454 individuals with P/LP variants in ARVC-associated genes – including *DSP* – that competitive or
455 frequent high-intensity endurance exercise is associated with increased likelihood of developing
456 ARVC and ventricular arrhythmias.[24] The 2020 European Society of Cardiology (ESC)
457 Guidelines on sports cardiology and exercise in patients with cardiovascular disease recommends

that individuals with ACM not participate in high-intensity recreational exercise/sports or any competitive sports, and notes *DSP* to be a particularly high-risk genotype that may benefit from more frequent 6 monthly follow-up among those who exercise.[23] Similarly, the 2024 HRS expert consensus statement on arrhythmias in the athlete highlights *DSP* as a higher risk genotype and indicates that vigorous endurance exercise is associated with arrhythmias.[34] The findings of this study are in line with these recommendations as we showed that endurance exercise is associated with worse clinical outcomes in *DSP*-cardiomyopathy, albeit with a likely lower effect size than for gene-elusive or *PKP2*-ARVC.

Contemporary guidelines for sports and exercise among patients with cardiovascular disease also increasingly strongly recommend a shared decision-making (SDM) model.[23,34] Our results do not challenge these recommendations. Importantly, we have previously shown that the use of SDM is associated with lower decisional conflict and decisional regret following a diagnosis of ARVC; and with no difference in post-diagnosis exercise.[35] Given that *DSP*-cardiomyopathy is a diagnosis that carries substantial risk of arrhythmia, heart failure and symptomatic myocardial injury regardless of exercise exposure, we expect most individuals with a P/LP *DSP* variant will decrease their overall endurance exercise. Indeed, that is what was shown in this cohort, just 38% of participants who developed symptoms or were identified through family screening engaged in any moderate or high intensity exercise after baseline evaluation. However, a small proportion of individuals with particular preferences and a higher risk tolerance, may opt to continue engaging in endurance exercise at moderate and vigorous levels. For these individuals, close follow-up with specific counseling regarding attention to cardiac symptoms, guidance for when and how to seek care, and implementation of a comprehensive emergency action plan are recommended.

Limitations

The study included a limited sample size and was underpowered to detect more subtle relationships between exercise and adverse, disease-specific clinical outcomes. This limitation was particularly evident when assessing the effect of post baseline evaluation exercise. Nearly all participants substantially reduced their endurance exercise after diagnosis, in line with guidelines, which limited our ability to robustly assess the impact of post-diagnosis endurance exercise on clinical outcomes and markers of subclinical disease. Additionally, most participants already had clinical signs and symptoms of *DSP*-cardiomyopathy at baseline evaluation which limited our ability to assess the impact of exercise on penetrance. Nonetheless, our study includes both a larger sample size and a more thorough dose-response assessment than in the landmark classical ARVC paper upon which current ACM exercise guidelines are based.[10] Finally, the study predominantly assessed the effect of dynamic exercise on *DSP*-cardiomyopathy which limits conclusions regarding the effects of static exercise.

Conclusions

In contrast to PKP2-ARVC, exercise was not an independent predictor of incident VA or clinical HF events in patients with P/LP *DSP* variants, but it was associated with the development of clinically relevant symptomatic myocardial injury events. Participants with *DSP*-cardiomyopathy who experienced myocardial injury were at increased risk of subsequent VA and HF events. This risk will steer shared decision-making discussions between the patient and clinician regarding moderate to vigorous intensity endurance exercise. Further extensive and multi-center studies are required to further evaluate the effects of exercise on ventricular arrhythmias and clinical heart failure.

504 Table 1. Baseline clinical and demographic data between endurance athletes and non-athletes

	Total	**Non-athletes METhr/wk ≤24 (N=40)**	**Endurance athletes METhr/wk >24 (N=60)**	**P-value**
Demographics				
Age at baseline evaluation (years), mean (SD)	36.0 (15)	39.3 (15)	33.8 (14)	0.07
Female, N (%)	66 (66)	30 (75)	36 (60)	0.12
Probands, N (%)	47 (47)	19 (47.5)	28 (46.7)	0.93
White, N (%)	97 (97)	38 (95)	59 (100)	0.22
Genetic Variant				0.38
Missense variant, N (%)	15 (15)	7 (17.5)	8 (13.3)	
Truncating variant, N (%)	78 (78)	30 (75)	48 (80)	
Splice site variant	7 (7)	3 (7.5)	4 (6.7)	
Presentation				
Symptomatic with sustained VA, N (%)	13 (13)	4 (4)	9 (9)	0.51
Symptomatic without sustained VA, N (%)	48 (49)	17 (42.5)	31 (52.7)	0.36
Asymptomatic family screening, N (%)	29 (29)	13 (32.5)	16 (26.7)	0.53
Medication use at baseline evaluation				
Beta-blocker, N (%)	62 (62)	20 (50)	42 (70)	0.07
ARB/ACE-I, N (%)	37 (37)	13 (32.5)	24 (40)	0.45

Aldosterone Receptor Antagonist, N (%)	12 (12)	4 (10)	8 (13.3)	0.76
Anti-Arrhythmic Drug, N (%)	10 (10)	6 (15)	4 (6.7)	0.19
Clinically affected at baseline evaluation				
Overall, N (%)	77 (77)	32 (80)	45 (75)	0.56
Sustained VA, N (%)	13 (13)	4 (4)	9 (9)	0.51
Clinical HF, N (%)	5 (5)	1 (3)	4 (7)	0.35
Myocardial injury, N (%)	25 (25)	7 (18)	18 (30)	0.16
PVC count >500/24 hours, N (%)	4 (4)	3 (3)	1 (1)	0.30
ECG parameters				
ECG with TWI in ≥ 3 precordial leads, N (%)	28 (28)	9 (23)	19 (32)	0.33
ECG with TWI in V1-V3, N (%)	11 (11)	5 (13)	6 (10)	0.68
ECG with TWI in ≥2 inferior leads, N (%)	15 (15)	5 (13)	10 (17)	0.58
ECG with TWI in V4-V6, N (%)	24 (24)	9 (23)	15 (25)	0.79
Cardiac Magnetic Resonance parameters, N (%)	85/100 (85%)	30/40 (75%)	55/60 (92%)	
RVEDVi, median (IQR)	86 (74-102)	79 (67-100)	87 (80-102)	0.11
RV EF, median (IQR)	50 (46-54)	50 (45-54)	50 (46-55)	0.75
RV RWMA, N (%)	23 (23)	5 (17)	18 (33)	0.11
LVEDVi, median (IQR)	87 (72-98)	87 (72-99)	86 (73-96)	0.79
LV EF, median (IQR)	55 (49-60)	55 (48-60)	54 (49-60)	0.81

LV RWMA, N (%)	16/85 (19)	8/30 (27)	8/55 (15)	0.17
Late gadolinium enhancement present, N (%)	47/85 (47)	15/30 (50)	32/55 (58)	0.82

METhr/wk=Metabolic-equivalent hours per week, ARB/ACE-I/ARNI = Angiotensin receptor blocker/Angiotensin converting enzyme inhibitor/Angiotensin receptor-neprilysin inhibitor, VA=Ventricular arrhythmia, TWI= T-wave inversion, PVC=Premature ventricular complex, RV= Right ventricle, RVEDVi=Indexed right ventricular end diastolic volume, EF=Ejection fraction, RWMA= Regional wall motion abnormality, LV= Left ventricle, LVEDVi=Indexed left ventricular end diastolic volume, Symptomatic=presence of cardiac symptoms such as chest pain, shortness of breath, palpitations or syncope.

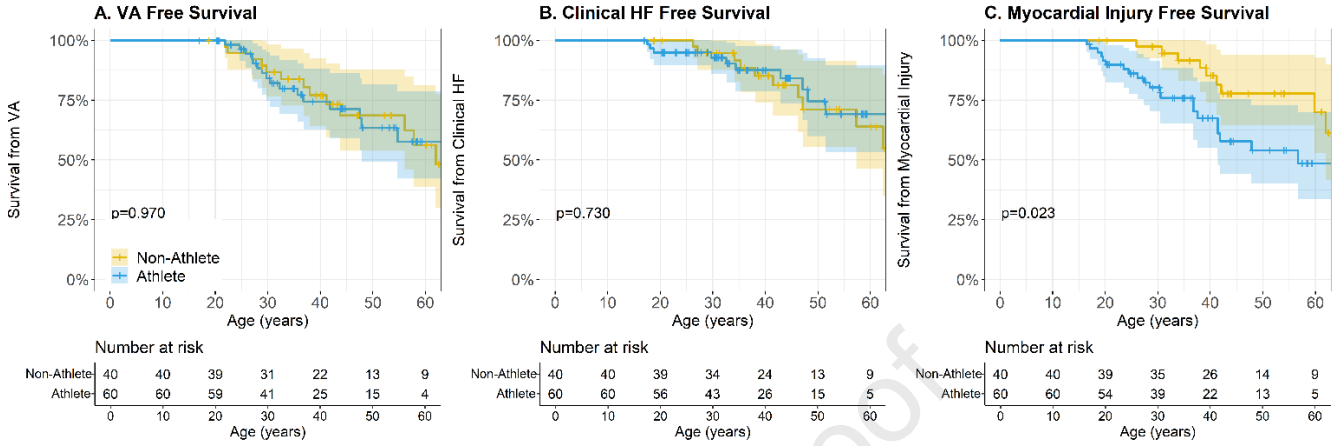
Table 2. Cox proportional hazards regression for athlete status and clinical outcomes, adjusting for female sex and accounting for intrafamilial clustering.

Covariate	Hazard Ratio	95% Confidence Interval	P-value
Ventricular arrhythmia			
Endurance athlete	1.00	0.50-1.98	0.993
Female sex	0.74	0.34-1.56	0.431
Clinical heart failure			
Endurance athlete	0.86	0.36-2.05	0.729
Female sex	0.85	0.38-1.96	0.711
Myocardial injury			
Endurance athlete	2.37	1.11-5.05	0.025
Female sex	0.77	0.40-1.49	0.442

Table 3. Time-varying Cox proportional hazard analysis for clinical outcomes adjusting for athlete status and episode of myocardial injury.

Covariate	Hazard Ratio	95% Confidence Interval	P-value
Ventricular arrhythmia			
Endurance athlete	0.91	0.44-1.92	0.812
Myocardial Injury	7.86	3.56-17.33	<0.001
Clinical heart failure			
Endurance athlete	0.68	0.28-2.11	0.501
Myocardial Injury	10.28	2.95-35.83	<0.001

Figure 1. Kaplan-Meier Analysis for survival free from clinical outcomes comparing participants exercising at an endurance athlete level exercise dose, with those exercising less than athlete level, prior to baseline evaluation.



VA=Sustained ventricular arrhythmia, HF=Heart failure

Figure 2. Kaplan-Meier Analysis for survival free from myocardial injury comparing participant exercise dose prior to baseline evaluation, divided by tertile.

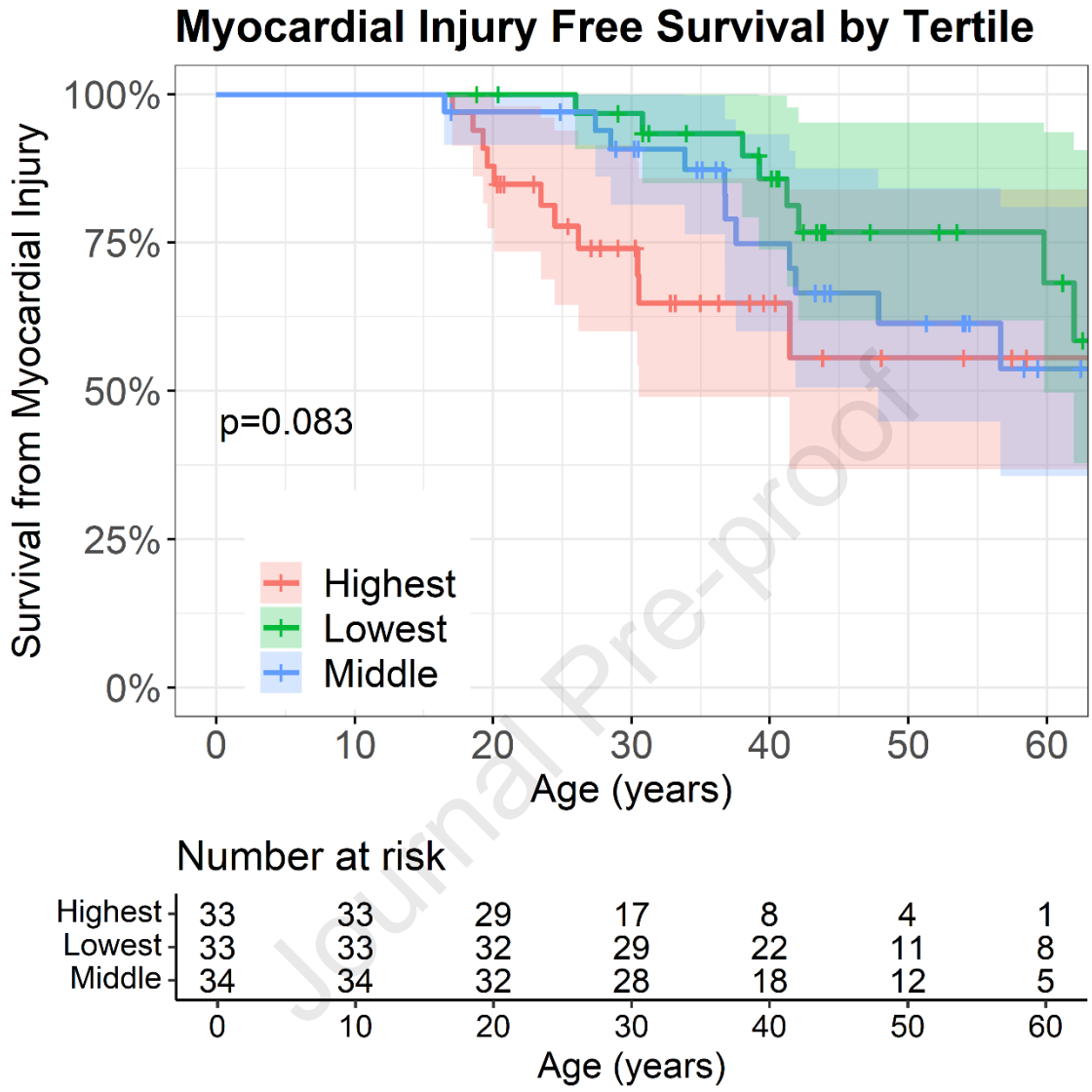
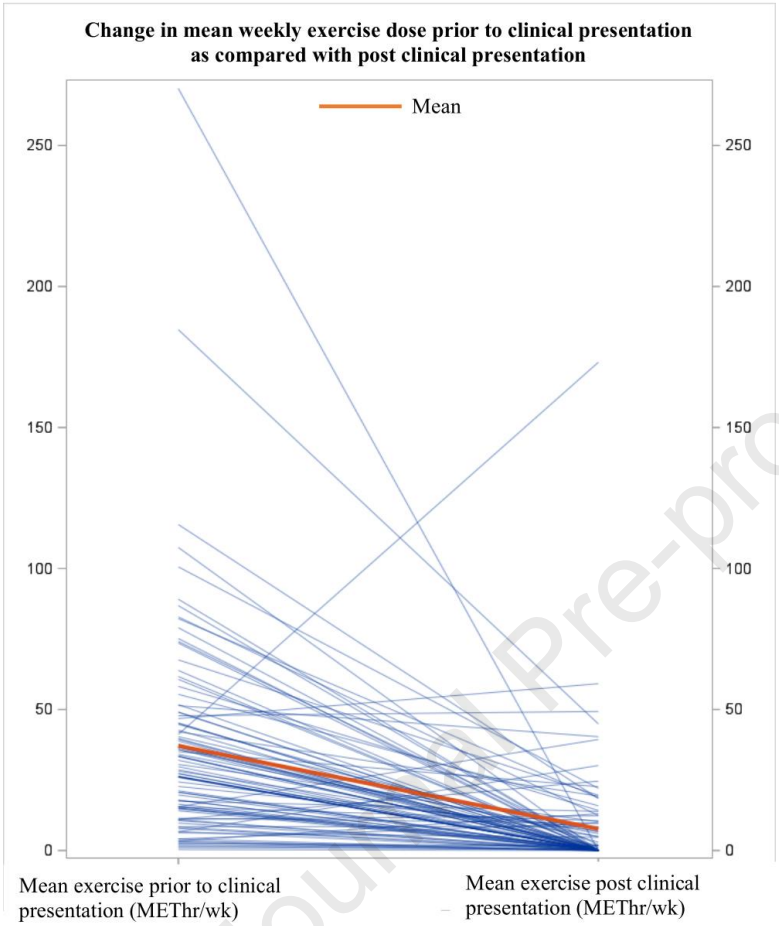


Figure 3. Change in mean weekly exercise dose prior to baseline evaluation as compared with post baseline evaluation



References:

1. Smith ED, Lakdawala NK, Papoutsidakis N, et al. Desmoplakin Cardiomyopathy, a Fibrotic and Inflammatory Form of Cardiomyopathy Distinct From Typical Dilated or Arrhythmogenic Right Ventricular Cardiomyopathy. *Circulation*. Jun 09 2020;141(23):1872-1884. doi:10.1161/CIRCULATIONAHA.119.044934
2. Gasperetti A, Carrick RT, Protonotarios A, et al. Clinical features and outcomes in carriers of pathogenic desmoplakin variants. *Eur Heart J*. Sep 17 2024;doi:10.1093/eurheartj/ehae571
3. Scheel PJ, Murray B, Tichnell C, et al. Arrhythmogenic Right Ventricular Cardiomyopathy Presenting as Clinical Myocarditis in Women. *Am J Cardiol*. Apr 15 2021;145:128-134. doi:10.1016/j.amjcard.2020.12.090
4. Wang W, Murray B, Tichnell C, et al. Clinical characteristics and risk stratification of desmoplakin cardiomyopathy. *Europace*. Feb 02 2022;24(2):268-277. doi:10.1093/europace/euab183
5. Gasperetti A, Carrick R, Protonotarios A, et al. Long-Term Arrhythmic Follow-Up and Risk Stratification of Patients With Desmoplakin-Associated Arrhythmogenic Right Ventricular Cardiomyopathy. *JACC Adv*. Mar 2024;3(3):100832. doi:10.1016/j.jacadv.2024.100832
6. Carrick RT, Gasperetti A, Protonotarios A, et al. A novel tool for arrhythmic risk stratification in desmoplakin gene variant carriers. *Eur Heart J*. Jul 16 2024;doi:10.1093/eurheartj/ehae409
7. Kissopoulou A, Fernlund E, Holmgren C, et al. Monozygotic twins with myocarditis and a novel likely pathogenic desmoplakin gene variant. *ESC Heart Fail*. Jun 2020;7(3):1210-1216. doi:10.1002/ehf2.12658
8. Ammirati E, Raimondi F, Piriou N, et al. Acute Myocarditis Associated With Desmosomal Gene Variants. *JACC Heart Fail*. Oct 2022;10(10):714-727. doi:10.1016/j.jchf.2022.06.013
9. Poller W, Haas J, Klingel K, et al. Familial Recurrent Myocarditis Triggered by Exercise in Patients With a Truncating Variant of the Desmoplakin Gene. *J Am Heart Assoc*. May 18 2020;9(10):e015289. doi:10.1161/JAHA.119.015289
10. James CA, Bhonsale A, Tichnell C, et al. Exercise increases age-related penetrance and arrhythmic risk in arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated desmosomal mutation carriers. *J Am Coll Cardiol*. Oct 1 2013;62(14):1290-1297. doi:10.1016/j.jacc.2013.06.033
11. Bosman LP, Wang W, Lie Ø, et al. Integrating Exercise Into Personalized Ventricular Arrhythmia Risk Prediction in Arrhythmogenic Right Ventricular Cardiomyopathy. *Circ Arrhythm Electrophysiol*. Feb 2022;15(2):e010221. doi:10.1161/CIRCEP.121.010221
12. Lie Ø, Dejgaard LA, Saberniak J, et al. Harmful Effects of Exercise Intensity and Exercise Duration in Patients With Arrhythmogenic Cardiomyopathy. *JACC Clin Electrophysiol*. Jun 2018;4(6):744-753. doi:10.1016/j.jacep.2018.01.010
13. Ruwald AC, Marcus F, Estes NA, et al. Association of competitive and recreational sport participation with cardiac events in patients with arrhythmogenic right ventricular cardiomyopathy: results from the North American multidisciplinary study of arrhythmogenic right ventricular cardiomyopathy. *Eur Heart J*. Jul 14 2015;36(27):1735-43. doi:10.1093/eurheartj/ehv110

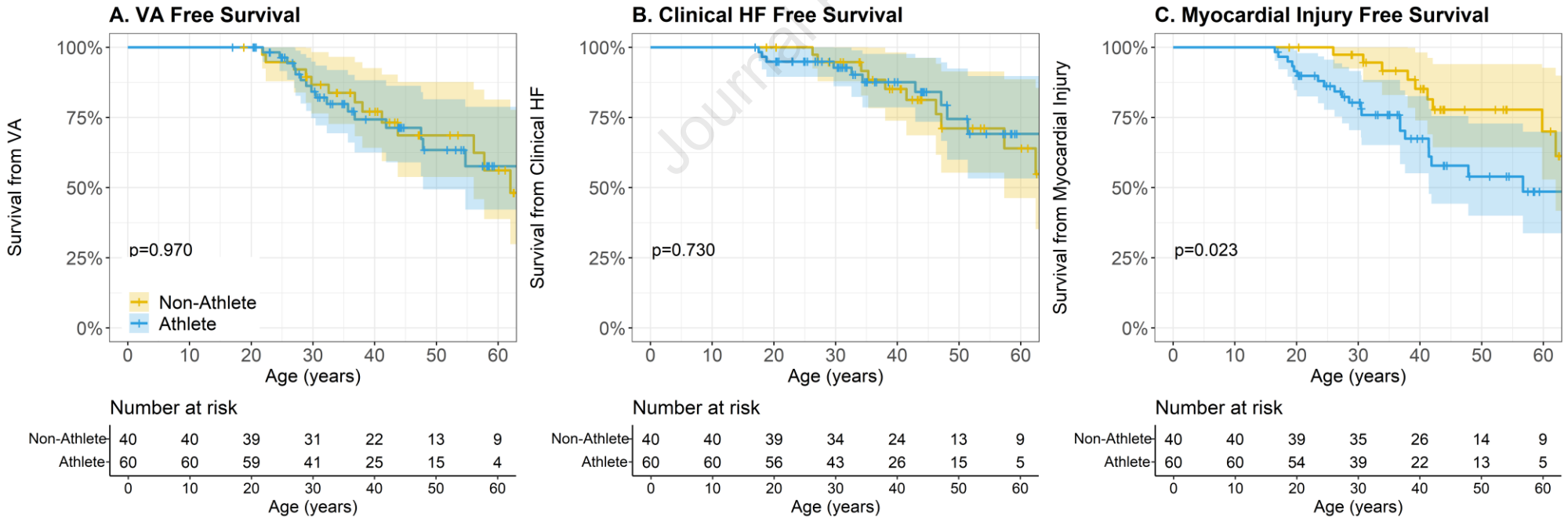
14. Saberniak J, Hasselberg NE, Borgquist R, et al. Vigorous physical activity impairs myocardial function in patients with arrhythmogenic right ventricular cardiomyopathy and in mutation positive family members. *Eur J Heart Fail*. Dec 2014;16(12):1337-44. doi:10.1002/ejhf.181
15. Paulin FL, Hodgkinson KA, MacLaughlan S, et al. Exercise and arrhythmic risk in TMEM43 p.S358L arrhythmogenic right ventricular cardiomyopathy. *Heart Rhythm*. Jul 2020;17(7):1159-1166. doi:10.1016/j.hrthm.2020.02.028
16. Skjølsvik ET, Hasselberg NE, Dejgaard LA, et al. Exercise is Associated With Impaired Left Ventricular Systolic Function in Patients With Lamin A/C Genotype. *J Am Heart Assoc*. Jan 21 2020;9(2):e012937. doi:10.1161/JAHA.119.012937
17. van Lint FHM, Hassanzada F, Verstraelen TE, et al. Exercise does not influence development of phenotype in PLN p.(Arg14del) cardiomyopathy. *Neth Heart J*. Aug 2023;31(7-8):291-299. doi:10.1007/s12471-023-01800-4
18. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. May 2015;17(5):405-24. doi:10.1038/gim.2015.30
19. Cadrin-Tourigny J, Bosman LP, Nozza A, et al. A new prediction model for ventricular arrhythmias in arrhythmogenic right ventricular cardiomyopathy. *Eur Heart J*. Aug 21 2022;43(32):e1-e9. doi:10.1093/eurheartj/ehac180
20. Muller SA, Gasperetti A, Bosman LP, et al. Individualized Family Screening for Arrhythmogenic Right Ventricular Cardiomyopathy. *J Am Coll Cardiol*. Jul 18 2023;82(3):214-225. doi:10.1016/j.jacc.2023.05.005
21. Arbelo E, Protonotarios A, Gimeno JR, et al. 2023 ESC Guidelines for the management of cardiomyopathies. *Eur Heart J*. Oct 01 2023;44(37):3503-3626. doi:10.1093/eurheartj/ehad194
22. Ainsworth BE, Haskell WL, Herrmann SD, et al. 2011 Compendium of Physical Activities: a second update of codes and MET values. *Med Sci Sports Exerc*. Aug 2011;43(8):1575-81. doi:10.1249/MSS.0b013e31821ece12
23. Pelliccia A, Sharma S, Gati S, et al. 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease. *Eur Heart J*. 01 01 2021;42(1):17-96. doi:10.1093/eurheartj/ehaa605
24. Towbin JA, McKenna WJ, Abrams DJ, et al. 2019 HRS expert consensus statement on evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy. *Heart Rhythm*. Nov 2019;16(11):e301-e372. doi:10.1016/j.hrthm.2019.05.007
25. McKinney J, Velghe J, Fee J, Isserow S, Drezner JA. Defining Athletes and Exercisers. *Am J Cardiol*. Feb 01 2019;123(3):532-535. doi:10.1016/j.amjcard.2018.11.001
26. Cadrin-Tourigny J, Bosman LP, Wang W, et al. Sudden Cardiac Death Prediction in Arrhythmogenic Right Ventricular Cardiomyopathy: A Multinational Collaboration. *Circ Arrhythm Electrophysiol*. Jan 2021;14(1):e008509. doi:10.1161/CIRCEP.120.008509
27. Piercy KL, Troiano RP, Ballard RM, et al. The Physical Activity Guidelines for Americans. *JAMA*. Nov 20 2018;320(19):2020-2028. doi:10.1001/jama.2018.14854
28. Lota AS, Hazebroek MR, Theotokis P, et al. Genetic Architecture of Acute Myocarditis and the Overlap With Inherited Cardiomyopathy. *Circulation*. Oct 11 2022;146(15):1123-1134. doi:10.1161/CIRCULATIONAHA.121.058457

29. Nieman DC, Wentz LM. The compelling link between physical activity and the body's defense system. *J Sport Health Sci*. May 2019;8(3):201-217. doi:10.1016/j.jshs.2018.09.009
30. Eckart RE, Scoville SL, Campbell CL, et al. Sudden death in young adults: a 25-year review of autopsies in military recruits. *Ann Intern Med*. Dec 2004;141(11):829-34.
31. Drory Y, Turetz Y, Hiss Y, et al. Sudden unexpected death in persons less than 40 years of age. *Am J Cardiol*. Nov 15 1991;68(13):1388-92. doi:10.1016/0002-9149(91)90251-f
32. Maron BJ, Udelson JE, Bonow RO, et al. Eligibility and Disqualification Recommendations for Competitive Athletes With Cardiovascular Abnormalities: Task Force 3: Hypertrophic Cardiomyopathy, Arrhythmogenic Right Ventricular Cardiomyopathy and Other Cardiomyopathies, and Myocarditis: A Scientific Statement From the American Heart Association and American College of Cardiology. *J Am Coll Cardiol*. Dec 01 2015;66(21):2362-2371. doi:10.1016/j.jacc.2015.09.035
33. Sawant AC, Bhonsale A, te Riele AS, et al. Exercise has a disproportionate role in the pathogenesis of arrhythmogenic right ventricular dysplasia/cardiomyopathy in patients without desmosomal mutations. *J Am Heart Assoc*. Dec 2014;3(6):e001471. doi:10.1161/jaha.114.001471
34. Lampert R, Chung EH, Ackerman MJ, et al. 2024 HRS expert consensus statement on arrhythmias in the athlete: Evaluation, treatment, and return to play. *Heart Rhythm*. May 15 2024;doi:10.1016/j.hrthm.2024.05.018
35. Sweeney J, Tichnell C, Christian S, et al. Characterizing Decision-Making Surrounding Exercise in ARVC: Analysis of Decisional Conflict, Decisional Regret, and Shared Decision-Making. *Circ Genom Precis Med*. Dec 2023;16(6):e004133. doi:10.1161/CIRCGEN.123.004133

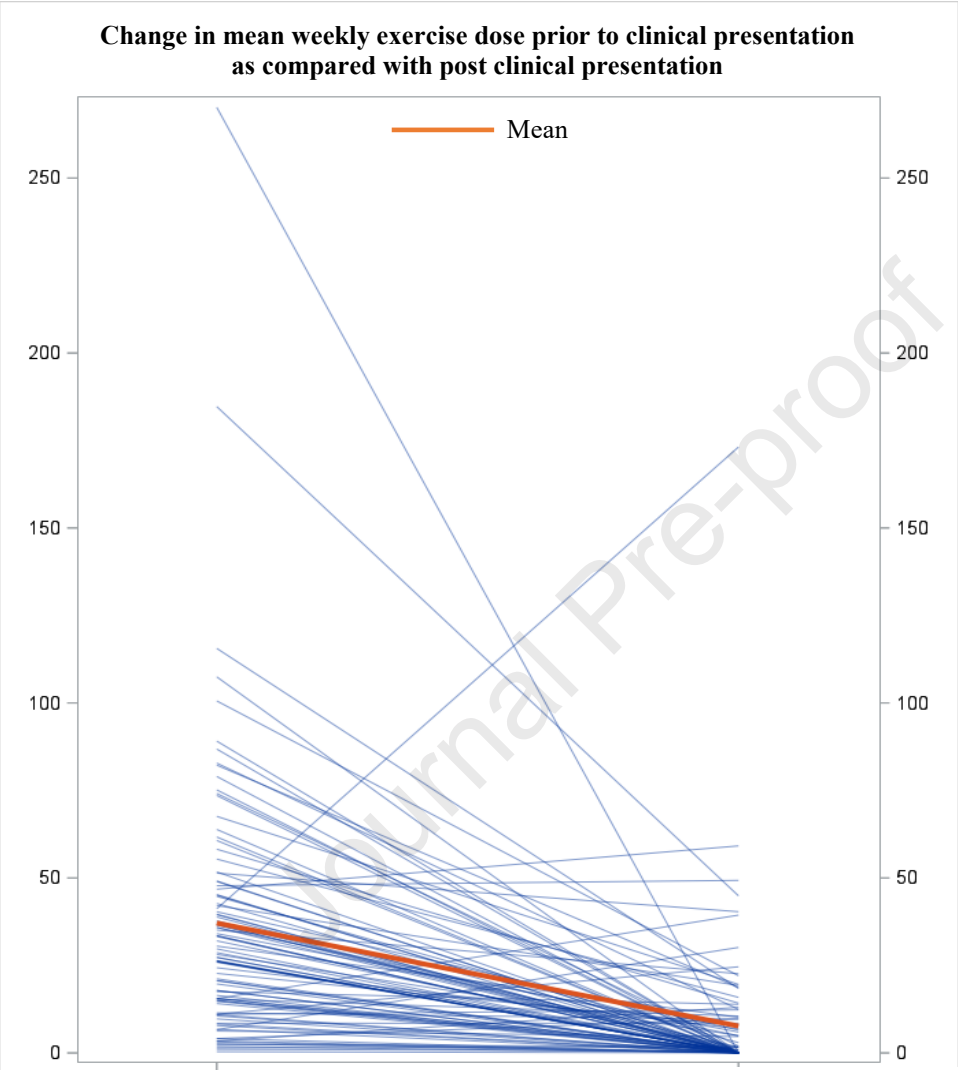
Endurance Exercise P[illegible] in Individuals with a Pathogenic Desmoplakin (DSP) Variant

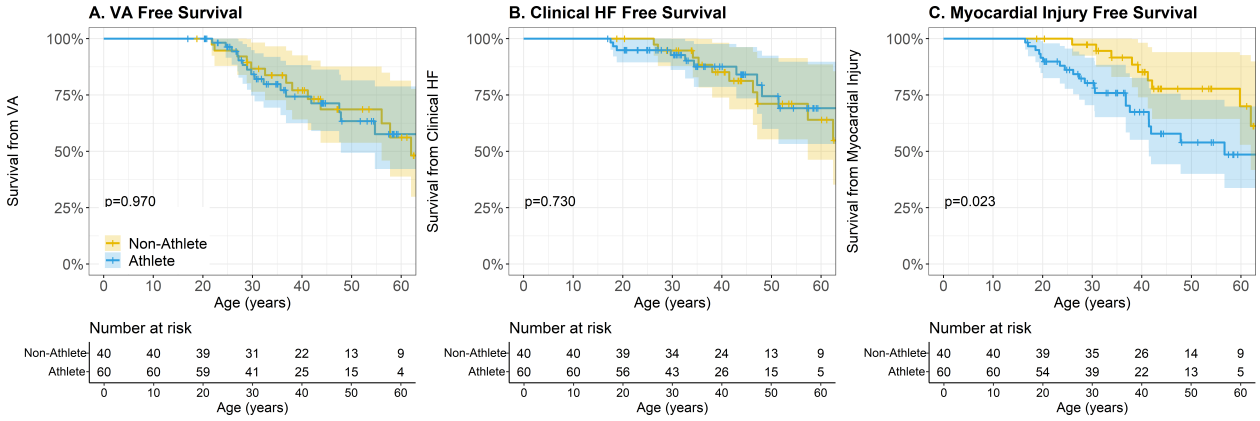
- Participants with a pathogenic or likely pathogenic desmoplakin variant
- N=100, 66% female, average age 36 ± 15 years
- 73% with phenotypic expression at presentation

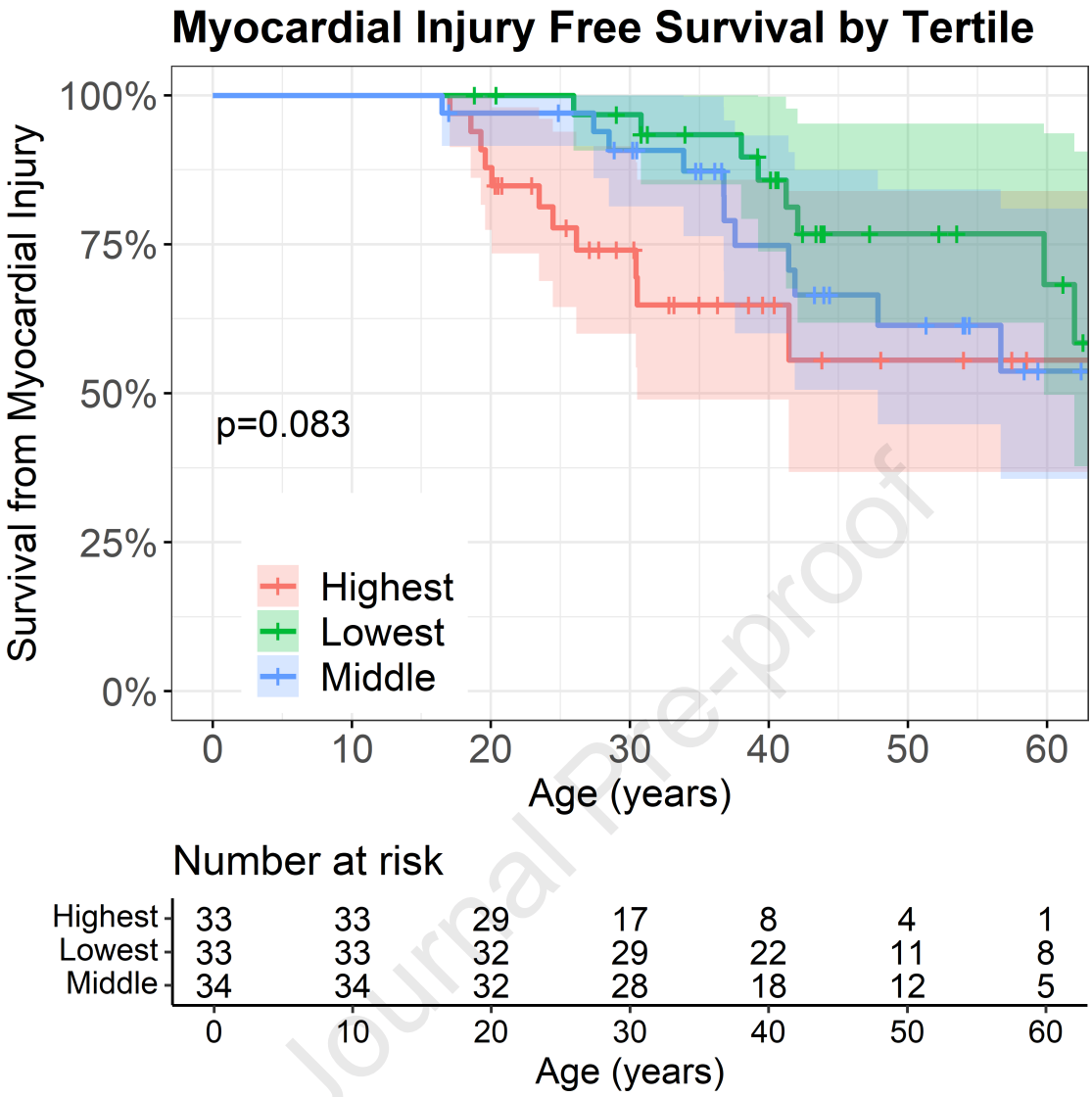
- Physical exercise data were collected by telephone interview from age 10
- Exercise dose was quantified in metabolic equivalent hours per week (METhr/wk)
- Participants were classified as athletes or non-athletes based on an exercise dose >24 METhr/wk



VA=Sustained ventricular arrhythmia, HF=Heart failure







Supplemental Material

Supplemental Table 1. Participant activities at the time of a sustained ventricular arrhythmia event at baseline evaluation and during follow up.

	Activities during presenting sustained VA episode	**Activity during first sustained VA episode in follow up**
Exercise	4	5
Within 1 hour of exercise	0	3
Sleeping	1	0
Emotional distress	1	0
Activities of daily living	4	10
Other	3	4
Unknown	0	2

VA=Sustained ventricular arrhythmia

Supplemental Table 2. Time-varying Cox proportional hazards regression for athlete status and clinical outcomes, adjusting for female sex and accounting for intrafamilial clustering.

Covariate	Hazard Ratio	95% Confidence Interval	P-value
Ventricular arrhythmia			
Endurance athlete	0.81	0.40-1.63	0.553
Female sex	0.82	0.37-1.79	0.617
Clinical heart failure			
Endurance athlete	0.49	0.17-1.41	0.187
Female sex	0.91	0.40-2.08	0.821
Myocardial injury			
Endurance athlete	2.61	1.23-5.50	0.012
Female sex	0.70	0.36-1.33	0.280

Supplemental Table 3. Time-varying Cox proportional hazards regression for Ln (METhr/wk) and clinical outcomes, adjusting for female sex and accounting for intrafamilial clustering.

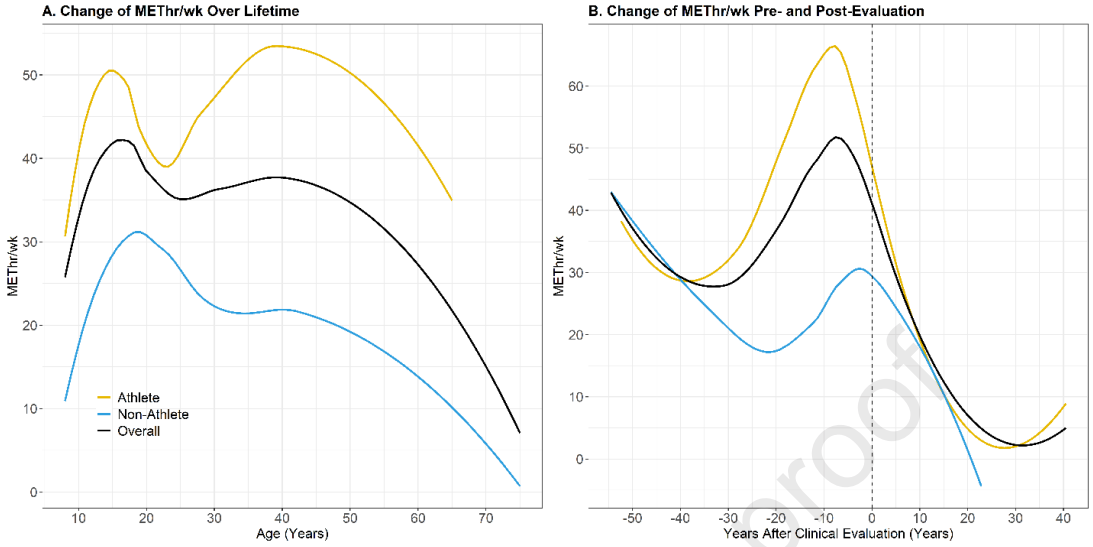
Covariate	Hazard Ratio	95% Confidence Interval	P-value
Ventricular arrhythmia			
Ln(METhr/wk)	0.93	0.75-1.15	0.507
Female sex	0.8	0.36-1.79	0.586
Clinical heart failure			
Ln(METhr/wk)	0.76	0.57-1.04	0.087
Female sex	0.85	0.37-1.92	0.699
Myocardial injury			
Ln(METhr/wk)	1.20	0.90-1.59	0.217
Female sex	0.74	0.39-1.39	0.342

Supplemental Table 4. Clinical outcomes among clinically affected participants who continued exercising at moderate and high intensity as compared with those who did not engage in any moderate or high intensity exercise following baseline evaluation.

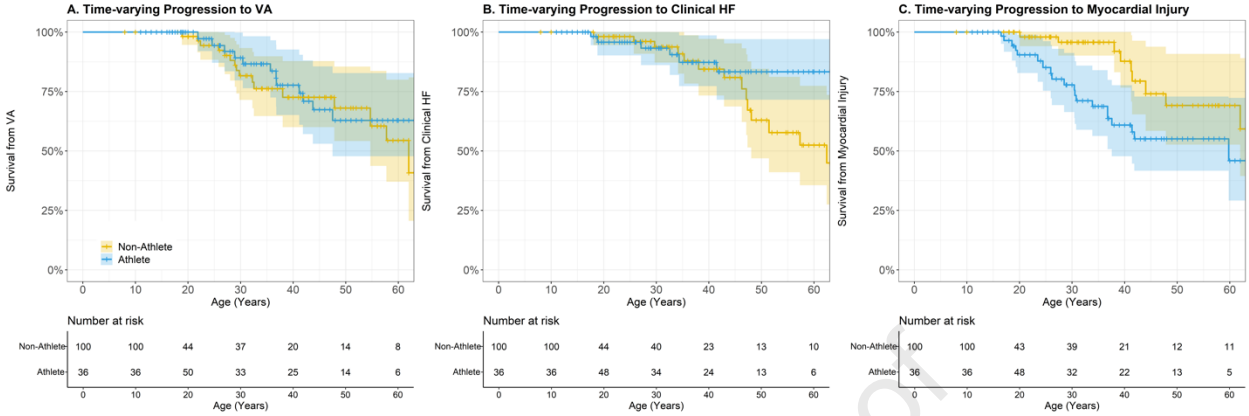
	No moderate or vigorous exercise post clinical presentation (N=46)	**Any moderate or vigorous exercise post clinical presentation (N=27)**	**P-value (Fisher's exact)**
VA, N (%)	17 (37)	7 (26)	0.44
Clinical HF, N (%)	13 (28)	3 (11)	0.14
Myocardial injury, N (%)	5 (12)	2 (7)	0.69

VA=Sustained ventricular arrhythmia, HF=Heart failure

Supplemental Figure 1A. Change in time-varying exercise dose over lifetime.
Supplemental Figure 1B. Change in time-varying exercise dose pre- and post-baseline evaluation.



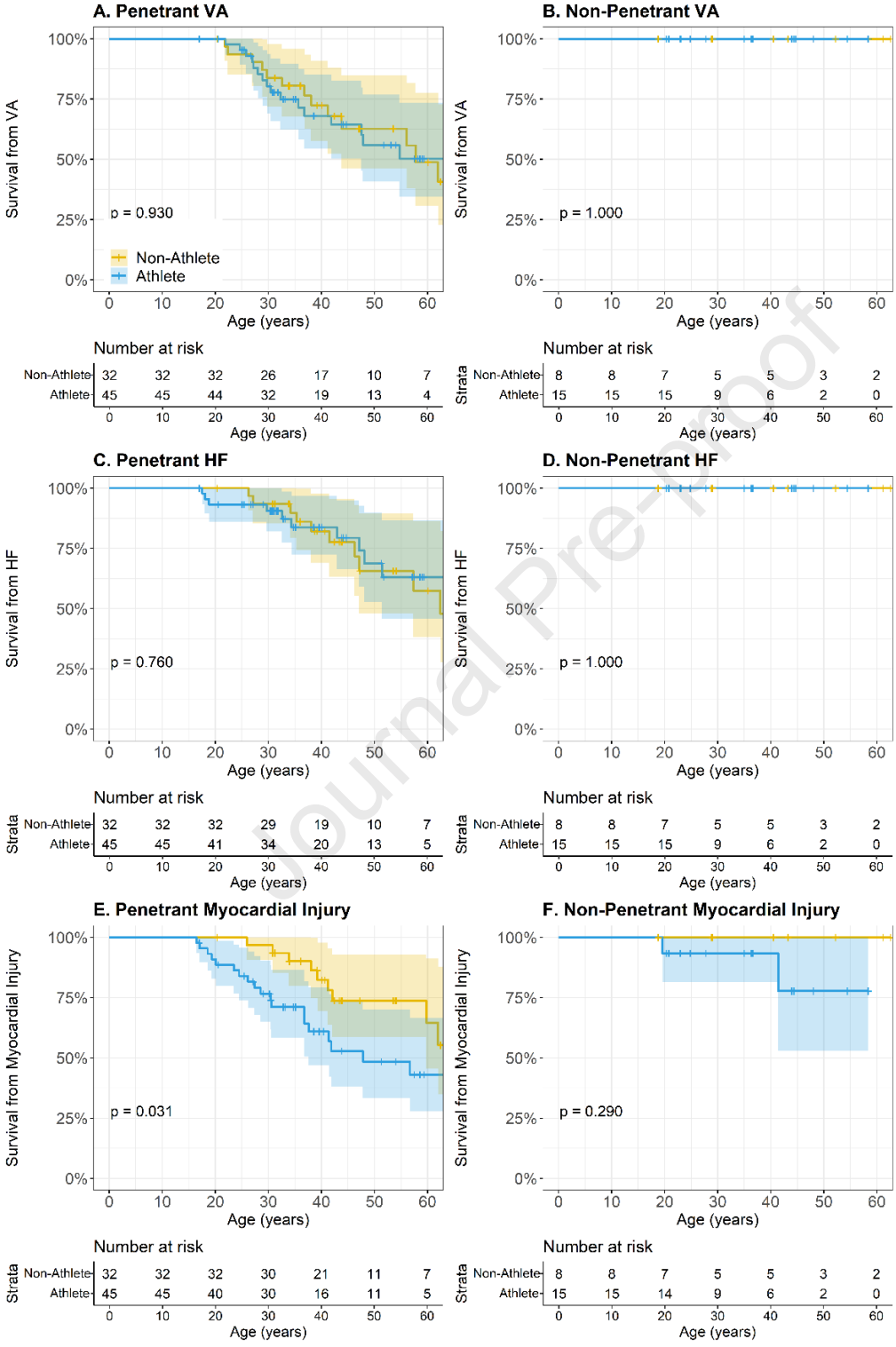
Supplemental Figure 2. Time-varying Kaplan-Meier analysis for survival free from clinical outcomes comparing participants exercising at an endurance athlete level exercise dose, with those exercising less than athlete level, prior to baseline evaluation.



VA=Sustained ventricular arrhythmia, HF=Heart failure

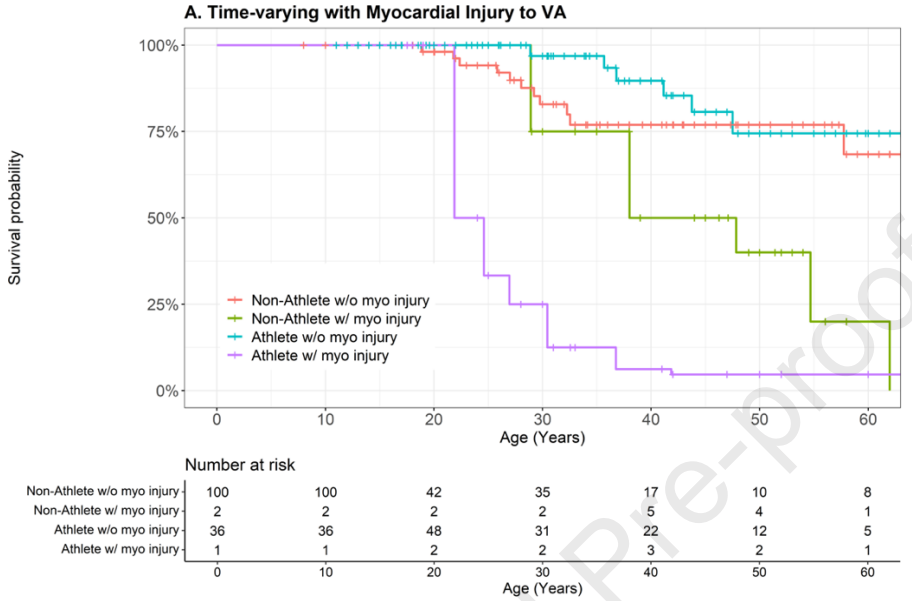
Note- The total number at risk may be greater than the total number of participants in the study due to the time-varying nature of the analysis.

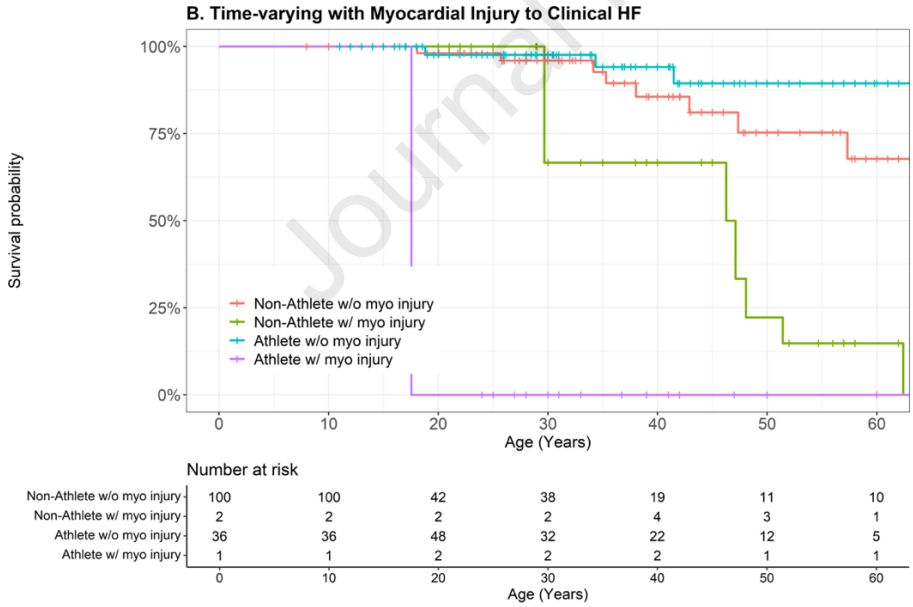
Supplemental Figure 3. Kaplan-Meier Analysis for survival free from clinical outcomes stratified by whether clinically affected or not, comparing participants exercising at an endurance athlete level exercise dose, with those exercising less than athlete level, prior to baseline evaluation.



VA=Sustained ventricular arrhythmia, HF=Heart failure

Supplemental Figure 4. Time-dependent Kaplan Meier analyses of the combined influence of exercise as defined by athlete status and myocardial injury events on survival free from sustained ventricular arrhythmias (panel A) and clinical heart failure (panel B). Following myocardial injury events (purple and green lines) risk of both VA and HF were elevated. While underpowered, this risk appeared particularly significant in participants who exercised >24 METhr/wk following the myocardial injury event (purple line).





VA=Sustained ventricular arrhythmia, HF=Heart failure

Note- The total number at risk may be greater than the total number of participants in the study due to the time-varying nature of the analysis.

Activity survey guide

INTRODUCTION

Hi. This is XXX from the Johns Hopkins ARVD program. You have been in touch with our program about setting up this interview about exercise and ARVD. I want to confirm that this is still a good time for you.

If no: Reschedule for: _____

If yes:

This interview is part of your participation in our ARVD Registry. Thank you for being part of this important research effort. During the interview we will ask you details about the exercise you have done since you were 10 years-old. We will focus on exercise you have done for recreation or sports. We will also ask about exercise you did as part of your job or for other reasons. All the information we collect is confidential and used for research only. It will not be possible to identify any particular individual in the results. The interview will take up to 30 minutes. Do you have any questions before we start?

LEISURE /RECREATIONAL ACTIVITY

First, I would like to ask about all your Leisure-time exercise. This includes exercise for conditioning/working-out, hobbies, and competitive and recreational sports. Think about the types of activities you participated in. Which one have you done most over the years? (Record activity)

I am going to read the definitions of light, moderate, and vigorous exercise. Please think about how you would categorize your participation in _____? I understand your intensity level may have changed over the years.

Light intensity are activities that require little effort and are easy to do.

Moderate intensity refers to effort that is harder than light intensity but not all out effort. These activities cause small increases in breathing or heart rate and are done for at least 10 minutes continuously.

Vigorous intensity is a very hard activity that requires close to all-out effort. Vigorous activity causes large increases in breathing or heart rate and is done for at least 10 minutes continuously unless the sport precludes this duration (eg football, sprinting).

Did you ever regularly do _____ at vigorous intensity? (If yes go to question 1 on next page. If no ask:

Did you ever regularly do _____ at moderate intensity? (If yes go to question 1 on next)

(Record intensity level)
NOTE – You will now go through each individual exercise with the subject and obtain and record details of age and duration at each applicable intensity level.

1. Between what ages did you participate in _____ at this intensity level?

Note down age started to age stopped in duration column

2. On average how many months of the year did you do this activity?

Write down in M/Y column

3. On average how many days of the months did you do this activity?

Write down in D/M column

4. On average how many hours of the day did you do this activity?

Write down in H/D column

We were discussing your activity at a _____ intensity. Did you ever do it at a different intensity level?
If yes, repeat 1-4 at alternate intensity.

Add clarifying details in the notes section if more information regarding a particular activity is needed to sort intensity or duration better. For all activities perceived as light –obtain details only if participation is in excess of at least 1 hr a day on a regular basis (2-3 times a week).

Weights - Light (<50% of max perceived effort), moderate (50-70%) and (>70%). Dance – Only formal organized dance considered
Walking/cycling/swimming – probe for speed.

Thank you for telling me about _____. Are there any other activities you have done on a regular basis? REPEAT 1-4 AS NEEDED

COMPETITIVE SPORTS

I am going to define competitive athlete and competitive organized sports. Please think about whether you were a competitive athlete in any of the activities we just discussed.

A competitive athlete is a person who participates in an organized team or individual sport that requires systematic training and regular competition against others that places a high premium on athletic excellence and achievement. Characteristics of competitive athletics is a situation in which

the athlete has a strong inclination to extend themselves to extremely high levels of exertion, often stretching their native physical limits sometimes for prolonged periods of time, regardless of other considerations.

For comparison I'm also going to define recreational sports. Recreational sports are those in which individuals engage in a range of exercise levels from modest to vigorous on either a regular or an inconsistent basis which do not require systematic ongoing training or the pursuit of excellence and are without the same pressure to excel against others.

1. Based on these definitions have you ever been a competitive athlete or participated in competitive organized sports?

   If yes: Which sports did you participate in as a competitive athlete? (review sports listed iteratively with subject)

   For each sport: For how many years did you do competitive _____? (note number of years as a competitive athlete on chart and repeat for each sport)

2. For any of these would you have been categorized as an elite, semi-professional or professional athlete

   If yes: Which sport

   For each sport: How many years

OCCUPATIONAL ACTIVITY

Next I'm going to ask you about physical activity you did for work. Has your work ever involved regular moderate or vigorous physical activity? Remember Moderate intensity refers to effort that is harder than light intensity but not all out effort. These activities cause small increases in breathing or heart rate and are done for at least 10 minutes continuously. Vigorous intensity is a very hard activity that requires close to all-out effort. Vigorous activity causes large increases in breathing or heart rate and is done for at least 10 minutes continuously unless the sport precludes this duration.

If no continue to TRANSPORTATION
If yes: Did you do this activity at least 2-3 times a week for an hour a day? If no continue to TRANSPORTATION
IF YES:

1. Between what ages did you participate in this activity at this level? Note down age started to age stopped in duration column
2. On average how many months of the year did you do this activity?

   Write down in M/Y column

3. On average how many days of the months did you do this activity?

Write down in D/M column

4. On average how many hours of the day did you do this activity?

Write down in H/D column

TRANSPORTATION

Next I'm going to ask you about physical activity you did to get somewhere. Has getting from place to place ever involved regular moderate to vigorous activity? Remember, Moderate intensity refers to effort that is harder than light intensity but not all out effort. These activities cause small increases in breathing or heart rate and are done for at least 10 minutes continuously.

If no continue to REVIEW
If yes: Did you do this activity at least 2-3 times a week for an hour a day? If no continue to REVIEW
IF YES:

1. Between what ages did you participate in this activity at this level? Note down age started to age stopped in duration column
2. On average how many months of the year did you do this activity?

Write down in M/Y column

3. On average how many days of the months did you do this activity?

Write down in D/M column

4. On average how many hours of the day did you do this activity?

Write down in H/D column

Repeat 1-4 as needed

REVIEW

Confirm and review the activity list. Add additional activities if any are missing.

DIAGNOSIS AND CHANGE OF ACTIVITY

When were you diagnosed

Any change in exercise since you were diagnosed? If so what changes?

THANK YOU

Thanks so much for answering these questions. We hope that be adding your answers with others that we can better understand the role of exercise in ARVD and be better able to provide sound advice about exercise to people with ARVD and their families. Do you have any questions about the study?

Get other phenotypic/ investigation information missing in database or get consent /hospital information so that it can be tracked down

Please feel free to contact us any time you have a question about the ARVD Registry, this interview, or really and question about ARVD. You can always contact us through our website arvd.com or you can contact me at _____.