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# Lifestyle physical activity and rapid-rate non-sustained ventricular tachycardia in arrhythmogenic cardiomyopathy

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## ABSTRACT

**Objective** To investigate the association of accelerometer-measured lifestyle physical activity with rapid-rate non-sustained ventricular tachycardias (RR-NSVTs) in patients with arrhythmogenic cardiomyopathy (AC).

**Methods** This multicentre, observational study enrolled 72 patients with AC, including right, left and biventricular forms of the disease, with underlying desmosomal and non-desmosomal mutations. Lifestyle physical activity, objectively monitored with accelerometers (ie, movement sensors) and RR-NSVT, identified as >188 bpm and >18 beats from a textile Holter ECG for 30 days.

**Results** Sixty-three patients with AC (38±17.6 years, 57% men) were included. A total of 17 patients experienced ≥1 RR-NSVTs, and a total of 35 events were recorded. The odds of occurrence of ≥1 RR-NSVT during the recording did not increase as a function of either total physical activity (OR 0.95, 95% CI (CI<sub>95%</sub>) 0.68 to 1.30 for 60 min increase) or moderate-to-vigorous activities (OR 0.89, CI<sub>95%</sub> 0.71 to 1.08 for 5 min increase). Participants presenting RR-NSVTs during the recording (n=17) did not present greater odds of RR-NSVT in the days with more time either in total physical activity (OR 1.05, CI<sub>95%</sub> 0.84 to 1.29 for additional 60 min) or moderate-to-vigorous activities (OR 1.05, CI<sub>95%</sub> 0.97 to 1.12 for additional 5 min). Physical activity levels were neither different between the patients with and without RR-NSVTs during the recording period nor in the days of occurrence of RR-NSVT compared with the rest of the days. Finally, 4 of the 35 RR-NSVTs recorded in the 30 days occurred during physical activity (3 during moderate-to-vigorous intensity and 1 during light-intensity activities).

**Conclusions** These findings suggest that lifestyle physical activity is not associated with RR-NSVTs in patients with AC.

## INTRODUCTION

Arrhythmogenic cardiomyopathy (AC) is a genetic cardiac condition characterised by fibrofatty replacement of the ventricular myocardium in one or both ventricles.<sup>1</sup> This provides the anatomical substrate for ventricular tachycardias and sudden cardiac death (SCD).<sup>1</sup> The underlying genetic aetiology is expanding with the emerging evidence on non-desmosomal targets such as intermediate filaments,

## WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Arrhythmogenic cardiomyopathy (AC) is associated to sport-triggered sudden cardiac death.
- ⇒ Competitive sports and high-intensity exercise are contraindicated in patients with AC.
- ⇒ Rapid-rate non-sustained ventricular tachycardias (RR-NSVTs) are a surrogate of sudden cardiac death in this population.

## WHAT THIS STUDY ADDS

- ⇒ Conscious investigation on the association of lifestyle physical activity of different intensities with RR-NSVTs in patients with AC with non-desmosomal and left-dominant forms.
- ⇒ Accelerometer-measured lifestyle physical activity, mainly of light and moderate intensity, was not associated with the occurrence of RR-NSVTs.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ This study supports the notion that lifestyle physical activity of light and moderate intensity could be promoted among patients with AC to ensure they obtain the multiple benefits associated with physical activity.

ion channels and nuclear envelope proteins.<sup>1,2</sup> The presence of rapid-rate non-sustained ventricular tachycardia (RR-NSVT) predicts appropriate future implantable cardioverter-defibrillator (ICD) shocks, interpreted as a surrogate marker for SCD.<sup>3</sup> Thus, RR-NSVT is an important risk factor for SCD in patients with AC.<sup>4</sup>

Competitive sports are contraindicated in patients with AC since they increase the risk of SCD.<sup>5–7</sup> Less evidence is available about the role of lifestyle physical activities on SCD in patients with AC. Lifestyle physical activities may reach light (ie, 1.5–2.9 times the resting energy expenditure or metabolic equivalents (METs)), moderate (ie, ≥3 METs) or even vigorous (ie, ≥6 METs) intensities.<sup>8</sup> Patients with AC are exposed to these lifestyle activities in their daily life (eg, when commuting, working or in their leisure time),<sup>9</sup> and there are not evidence-based

**Table 1** Characteristics of patients (n=63)

Characteristic	Value
Sociodemographic	
Male sex, n (%)	36 (57)
Age (years)	48.0 (17.6)
Genetics	
Desmosomal mutations, n (%)	23 (36.5)
DSP	10 (15.9)
DSG2	5 (7.9)
PKP2	8 (12.7)
Non-desmosomom mutations, n (%)	29 (46)
FLNC	14 (22.2)
DES	8 (12.7)
TMEM43	5 (7.9)
LMNA	2 (3.2)
Gene elusive, n (%)	11 (17.5)
Phenotypic form	
ARVC, n (%)	24 (38.1)
ALVC, n (%)	32 (50.8)
Biventricular AC, n (%)	7 (11.1)
Clinical features	
Left ventricular ejection fraction, n (%)	
>52%	34 (54)
≤52%	29 (46)
VT/VF history	21 (33.3)
ICD, n (%)	36 (57)
Appropriate ICD shocks history	11 (17.5)
Medications at baseline	
Beta-blocker, n (%)	38 (60)
ACE inhibitor, n (%)	21 (33)
Sacubitril/valsartan, n (%)	16 (25)
Sotalol, n (%)	9 (14)
Amiodarone, n (%)	0 (0)
Physical activity	
Total physical activity (min/day)	290.2 (123.2)
Moderate-to-vigorous intensity (min/day)	20.9 (16.3)
Ventricular tachycardias, n	
Sustained VT	0
RR-NSVT	35

Mean (SD) unless otherwise stated.

AC, arrhythmogenic cardiomyopathy; ALVC, arrhythmogenic left ventricular cardiomyopathy; ARVC, arrhythmogenic right ventricular cardiomyopathy; DES, desmin; DSG2, desmoglein-2; DSP, desmoplakin; FLNC, filamin C; ICD, implantable cardioverter defibrillator; LMNA, lamin A/C; LVEF, left ventricular ejection fraction; PKP2, plakophilin-2; RR-NSVT, rapid-rate non-sustained ventricular tachycardia; TMEM43, transmembrane protein 43; VT/VF, ventricular tachycardia/ventricular fibrillation.

guidelines about whether lifestyle activities of any intensity should be discouraged. Activities of light-to-moderate intensity are recommended in this population based on previous observational studies.<sup>5-7 10</sup> However, these studies are limited by their retrospective designs and the use of self-reported exercise and sport participation measures, which are of questionable validity and reliability.<sup>11-13</sup>

Modern accelerometers (ie, movement sensors) allow for the long-term and objective monitoring of physical activity. This allows assessing the physical activity pattern at the exact moment a ventricular arrhythmia occurs and, consequently, the association of lifestyle physical activity with RR-NSVT in patients with AC, which has not been examined before. This study aimed to

evaluate the association of lifestyle physical activity with the occurrence of RR-NSVT in patients with AC. Our hypothesis was that more time accumulated in lifestyle physical activity is associated with higher odds of RR-NSVTs.

## METHODS

### Study design and population

AC probands and family members were enrolled from two Spanish centres (Virgen de las Nieves and Virgen de la Victoria University Hospitals Referral Inherited Heart Diseases Clinics) in this multicentre, observational study. The baseline assessments and a continuous recording of physical activity and ventricular arrhythmias for 30 days were conducted from May 2019 to March 2021. The study population comprised 72 patients with AC diagnosed as definite AC based on the 2020 international diagnostic Padua criteria, including either right, left or biventricular forms.<sup>14</sup> Patients aged less than 14 years and those who could not wear the accelerometers or the textile ECG were excluded. Of the 72 patients with AC initially recruited, patients wearing the accelerometers and the textile ECG for less than 14 days were excluded (n=9), resulting in an analytical sample of 63 patients.

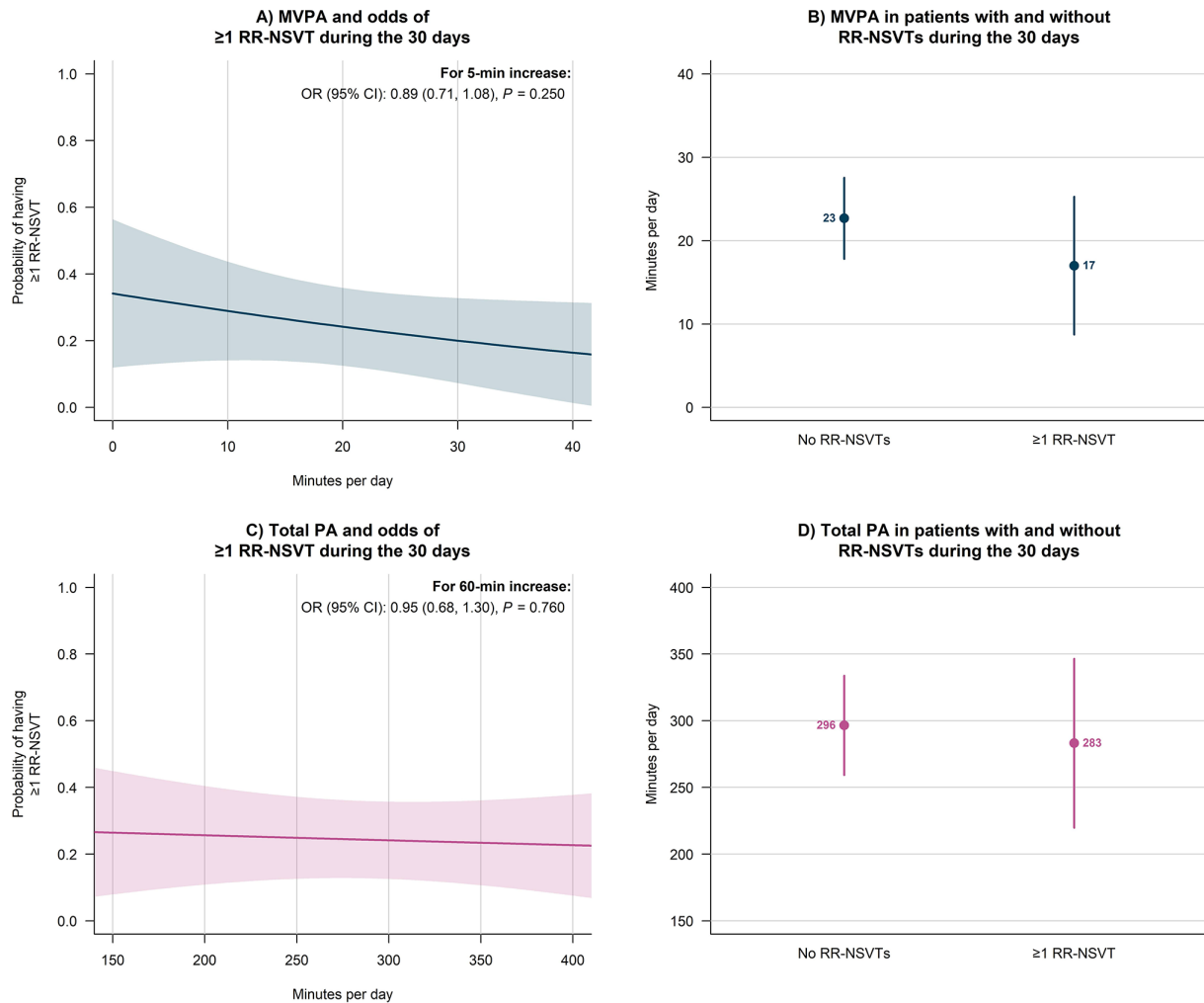
### Procedures

All patients were clinically and genetically characterised with ECG, advanced cardiac imaging and next-generation sequencing AC panels at baseline. Left and right ventricular volume and function was analysed according to standard guidelines, and AC was classified as left, right or biventricular. Those measurements were followed by a 30-day monitoring of the physical activity with accelerometers and ventricular arrhythmias with a textile ECG Holter. All participants had been required to avoid high-intensity exercise and competitive sports since the first diagnosis. Participants were asked to maintain their usual lifestyle during the recording and to wear the devices as much as possible (ie, except the ECG Holter for water-based activities). The accelerometers and ECG Holter data were then processed by staff members who were masked to the information provided by the other device.

## Measurements

### Physical activity

The lifestyle physical activity was continuously monitored for 30 days with an accelerometer worn on the non-dominant wrist (Axivity AX3, OmGui, Newcastle University). The accelerometer records accelerations in the x, y and z axes, and these are used to estimate the physical activity intensity. Participants wore the devices during the whole day and night. The accelerometers were set to record accelerations at 25 Hz to ensure the battery life and storage capacity during the whole period. Raw acceleration values were then downloaded in the OmGui open-source software (OmGui, Newcastle University) and saved in cwa format. These files were processed in the open-source software GGIR.<sup>15</sup> The data processing pipeline included the following: 1) autocalibration of the data according to the local gravity; 2) cleaning and aggregation of the acceleration values over 5 s epochs; 3) detection and imputation of the non-wear time based on an automated algorithm; 4) classification of waking and sleeping times based on the variability of the arm position<sup>16</sup>; 5) previously calibrated acceleration thresholds were used to define the physical activity intensity.<sup>17 18</sup> To smooth out spontaneous arm movements that are not related to physical activity, we determined the occurrence of physical activity when the intensities were reached



**Figure 1** Association of physical activity with RR-NSVT at person level ( $n=63$ ) (A, C), and comparison of physical activity between participants presenting at least one RR-NSVT during the 30-day recording period ( $n=17$ ) and their peers who did not present any event ( $n=46$ ) (B, D). Note: error bars represent 95% CIs. Note: models adjusted for age, sex, implanted ICD and left ventricular ejection fraction. ICD, implantable cardioverter-defibrillator; MVPA, moderate-to-vigorous physical activity; RR-NSVT, rapid-rate non-sustained ventricular tachycardia.

continuously for 1 min (with a tolerance of 20% of the time for not meeting the threshold criteria).

Activities of vigorous intensity were rarely performed by the patients with AC included in this study (ie, 80% of participants performed less than 1 min/day in vigorous intensity activities, and 5.7 min was the maximum value recorded in one day).<sup>9</sup> Thus, we merged the time in activities of moderate and vigorous intensity into one category (ie, moderate-to-vigorous physical activity) for person-level and day-level analyses. We also computed a variable for the total physical activity, which combined all activities of any intensity (ie, including light, moderate and vigorous intensity) for analyses. All days in which the participants wore the accelerometers for at least 16 hours were included in the day-level and person-level analyses. For epoch-level analyses, all the data were included as long as the devices were worn at the moment of occurrence of a RR-NSVT.

### Ventricular tachycardia

Ventricular tachycardias were recorded during a 30-day period with a textile ECG Holter (Nuubo ECG PLATFORM). A RR-NSVT was defined as self-terminated NSVTs of at least 18 beats in duration and at least 188 bpm. Episodes not fulfilling both criteria were not considered. An independent

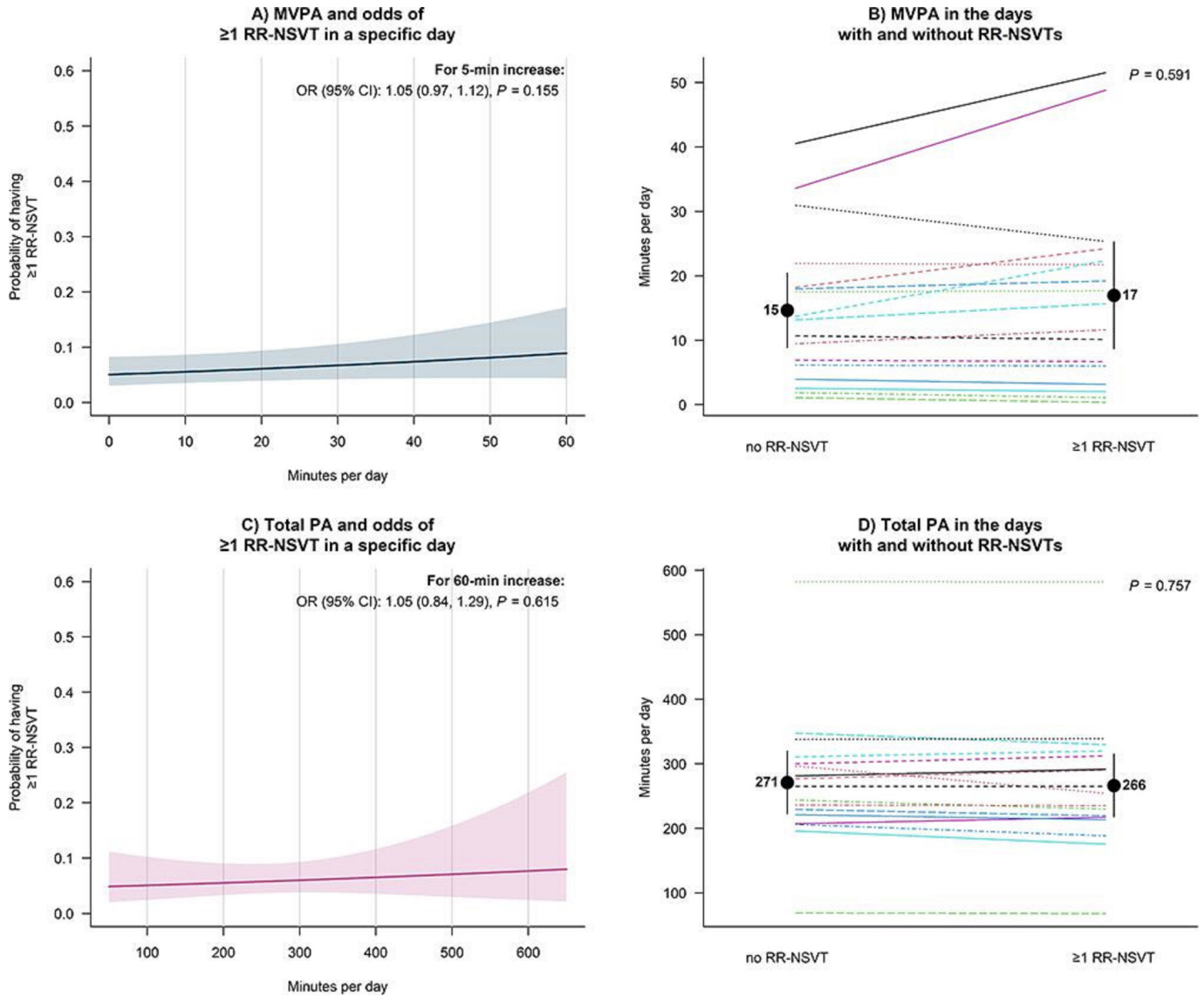
electrophysiologist blinded for the patients' medical history and exercise level reviewed the ECG Holter and registered the RR-NSVTs.

### Patient involvement

Patients were involved mainly in the execution and dissemination phases of the research. The burden of the data collection and assessments on the patients was carefully considered, and decisions were made to lower this burden (eg, selection of the accelerometer device and the body attachment site to ensure comfort during the data collection). Once the data were collected and processed, the results were presented to the participants in an effective manner to facilitate their understanding. We intend to disseminate the main results to the patients and will seek patient and public involvement in the development of an appropriate method of dissemination.

### Statistical analysis

The descriptive characteristics of the participants were summarised as mean and SD, or frequencies and percentages, as appropriate. First, in the person-level analysis, we used generalised linear models to investigate the association of physical



**Figure 2** Association of physical activity with RR-NSVT at day level in the patients presenting at least one RR-NSVT ( $n=17$ ) (A, C), and comparison of physical activity between the days with at least one RR-NSVT (ie, 30 days) and the days without (ie, 443 days). Note 1: error bars represent 95% CIs. Note 2: individual and group differences estimated from mixed models with the days in which the RR-NSVT occurred (yes or no) as fixed factor and the patient IDs as random factor. MVPA, moderate-to-vigorous physical activity; RR-NSVT, rapid-rate non-sustained ventricular tachycardia.

activity (ie, moderate-to-vigorous intensity and total) with the odds of having at least one RR-NSVT during the 30 days. In addition, we compared the average daily physical activity in those patients who experienced at least one RR-NSVT versus their peers who did not, using analysis of covariance. All models were adjusted for age, sex, implanted ICD and left-ventricular ejection fraction. As sensitivity analyses, we additionally adjusted the model for right-ventricular ejection fraction, and betablocker medication. Second, the day-level analysis was exclusively focused on those patients presenting at least one RR-NSVT. We used generalised linear mixed models to evaluate the odds of presenting at least one RR-NSVT (outcome) in a specific day as a function of the physical activity accumulated in that day (fixed factor) and considering the patient IDs as random factor. Furthermore, we compared the physical activity (ie, moderate-to-vigorous intensity or total physical activity) accumulated in days of RR-NSVT occurrence with the physical activity accumulated in the days of no RR-NSVT occurrence using a linear mixed model, considering the patients' IDs as random factor.

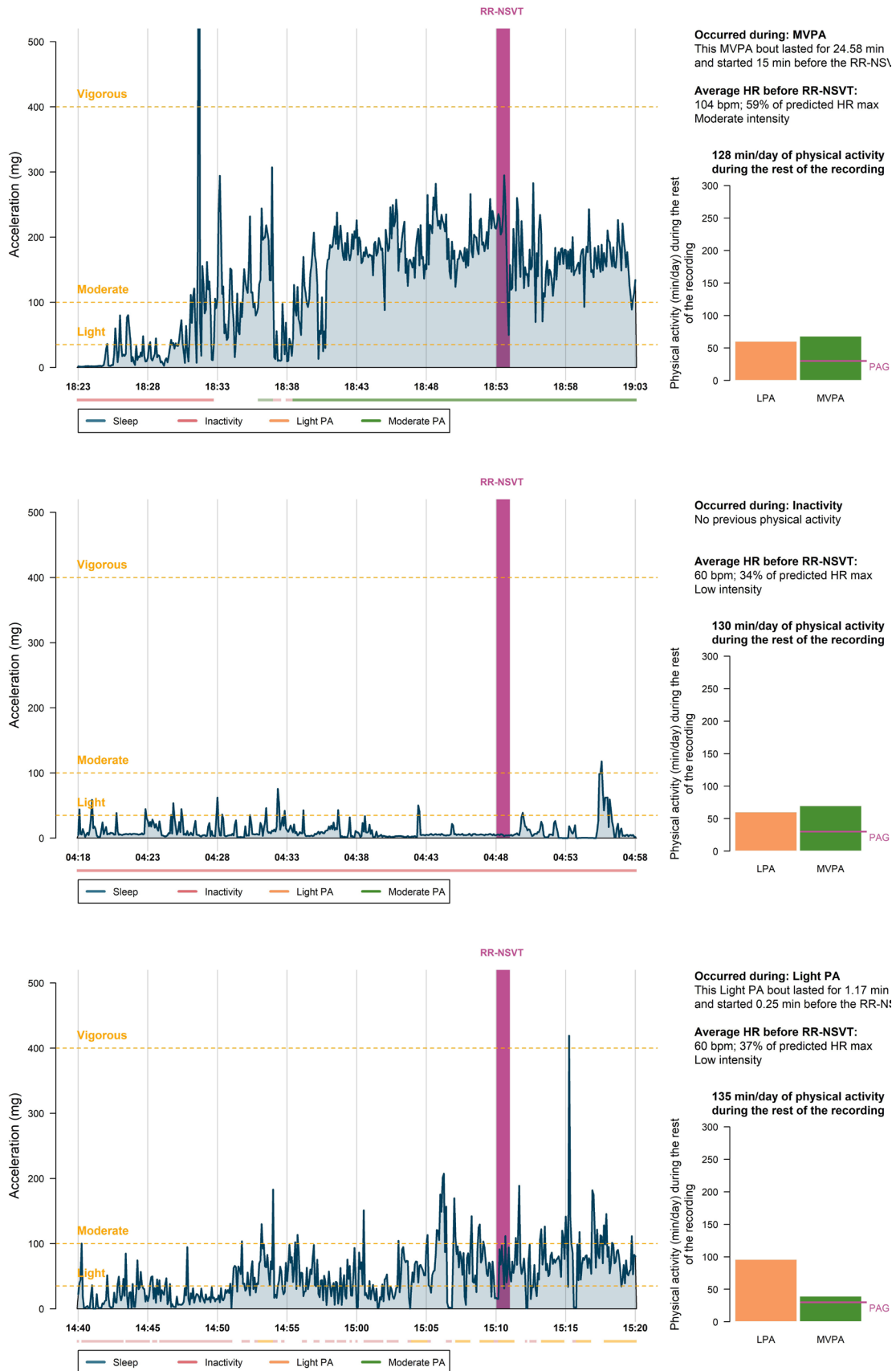
Random and fixed intercepts were defined to investigate the within-group (occurrence or not of RR-NSVT) and within-patient effect of physical activity. Finally, at epoch level, we determined the type of behaviour (ie, sleep, sedentary time, or light, moderate or vigorous physical activity) that was taking place 1) at the moment of every RR-NSVT and 2) during the preceding 30 min. In addition, we investigated the average heart rate in the 30 s preceding the RR-NSVT and classified this heart rate into low, moderate or high aerobic intensity following the classification proposed by the European Society of Cardiology.<sup>7</sup> All the analyses were performed in R V.4.2.0 and the statistical significance was set at  $p < 0.05$ .

## RESULTS

### Baseline characteristics

Table 1 presents the baseline characteristics of the patients included in the analyses ( $n=63$ ). Most of the patients presented with a left or biventricular form of AC due to a non-desmosomal





**Figure 3** Examples of the accelerations recorded during the occurrence of RR-NSVTs during moderate-to-vigorous physical activity (MVPA) (top), during inactivity (middle) and during light physical activity (LPA) (bottom) during the 30-day recording period. HR, heart rate; RR-NSVT, rapid-rate non-sustained ventricular tachycardia.

gene mutation, with a mean LVEF of  $50.39 \pm 11.92\%$ . There was a high prevalence of familial SCD and prior ventricular arrhythmias, so more than half of the patients carried an ICD for primary or secondary prevention of SCD. The most prevalent underlying mutated genes were desmin (DES), desmoplakin (DSP) and filamin (FLNC). The patients performed an average of 290 (SD=123) min/day of total lifestyle physical activity, of which 21 (SD=16,3) min/day were in activities of moderate-to-vigorous intensity. A total of 35 RR-NSVTs were recorded during the 30-day measurement, with 17 (27%) participants presenting at least one RR-NSVT. We observed that 9 of the RR-NSVTs occurred in participants with biventricular form of AC and the remaining 26 in patients with left-ventricular form of AC. However, no sustained ventricular tachycardias were observed during the recording.

### Person-level associations

At person level, the average time accumulated in physical activity was not associated with the odds of presenting at least one RR-NSVT (figure 1A,C); physical activity was not significantly different between patients experiencing RR-NSVTs and those who did not (figure 1B,D). Specifically, the patients presenting  $\geq 1$  RR-NSVTs performed 6 min per day less of activities of moderate-to-vigorous intensity (17 (CI<sub>95%</sub> 9 to 25) vs 23 (CI<sub>95%</sub> 18 to 28) min/day,  $p=0.245$ ) and 13 min per day less of total physical activity (283 (CI<sub>95%</sub> 220 to 346) vs 296 (CI<sub>95%</sub> 259 to 334) min/day,  $p=0.720$ ) than patients with no RR-NSVTs, after adjusting for age, sex, implanted ICD and left-ventricular ejection fraction. The results remained unchanged after additional adjustments for right-ventricular ejection fraction and beta-blocker medication.

### Day-level associations

At day level, those patients with AC with RR-NSVTs during the recording ( $n=17$ ) did not have greater odds of RR-NSVT as a function of the physical activity accumulated over the day (figure 2A, 2C). In this line, the patients did not show different levels of physical activity in the days of RR-NSVT occurrence compared with their days of no RR-NSVT occurrence (figure 2B, 2D). These patients performed 2 min per day more of moderate-to-vigorous intensity activities (17 (CI<sub>95%</sub> 9 to 25) vs 15 (CI<sub>95%</sub> 9 to 20) min/day,  $p=0.591$ ) and 5 min less of total physical activity (266 (CI<sub>95%</sub> 237 to 296) vs 271 (CI<sub>95%</sub> 223 to 320) min/day,  $p=0.757$ ) in the days of RR-NSVT occurrence. At individual level, most participants ( $n=14$ ) showed similar patterns of moderate-to-vigorous physical activity ( $\pm 6$  min/day), except for three patients who increased the time in activities of moderate-to-vigorous intensity (+9, +12 and +16 min/day). All patients showed similar levels of total physical activity in the days of RR-NSVT occurrence compared with the days of no RR-NSVT occurrence ( $\pm 20$  min/day), except for one patient who spent 44 min less per day in the days of RR-NSVT occurrence.

### Epoch-level associations

At epoch level, an example of the accelerometer-derived graphs representing examples of RR-NSVTs occurring during different types of behaviours is shown in figure 3 (the entire set of graphs displaying the accelerometer activity before, during and after the RR-NSVT are presented in online supplemental file 1). Of the 35 RR-NSVTs, 8 occurred during sleep, 20 during inactivity, 1 during physical activity of light intensity and 3 during moderate-to-vigorous physical activity, and 3 occurred during periods of time with many peaks in the acceleration data that could not

**Table 2** Physical activity and heart rate characteristics observed before the occurrence of the RR-NSVTs

Characteristic	When	Value
Physical activity		
Moderate-to-vigorous intensity (min/day)	30 min before	0 (0)
Light intensity (min/day)	30 min before	0 (1.4)
Heart rate		
Average heart rate (bpm)	30 s before	62 (20)
Percentage of maximum heart rate* (%)	30 s before	38 (9.5)
Estimated intensity from heart rate†		
Vigorous intensity (n)	30 s before	0
Moderate intensity (n)	30 s before	2
Low intensity (n)	30 s before	33
Data presented as median (IQR).		
*Maximum heart rate= $208-(0.7 \times \text{age})$ .		
†Intensity classified following the European Society of Cardiology standards. <sup>7</sup>		

be classified in a specific behaviour. None of the RR-NSVTs occurred after or during vigorous physical activity. All the RR-NSVTs occurred with preceding heart rates indicating low intensity activity, while only 2 RR-NSVTs occurred at moderate intensity (ECG signal examples can be found in online supplemental file 2). We observed a substantial amount of physical activity in most of these participants that were not surrounding any RR-NSVT (figure 3 and online supplemental file 1). Physical activity and heart rate characteristics preceding the RR-NSVTs are summarised in table 2.

### DISCUSSION

The main findings of this study suggest that lifestyle physical activity is not associated with the acute occurrence of RR-NSVTs in patients with AC during a 30-day measurement period. Interestingly, our data were gathered in a group of high-risk patients with AC predominantly with non-desmosomal and left dominant disease forms. These results support the notion that lifestyle physical activity of light and moderate intensity could be promoted among patients with AC.

In 2003, Corrado *et al* demonstrated that athletes 18–35 years old living with AC were at an increased risk of SCD compared with age-matched non-athletes with AC.<sup>19</sup> Several subsequent studies observed that self-reported regular exercise and athletic activity are associated with more electrical or structural progression of AC.<sup>20–23</sup> Furthermore, Ruwald *et al* found that those patients with AC who reported participating in competitive/professional sports before and after diagnosis were at increased risk of ventricular tachycardia and death than those reporting either participating in recreational sports or being inactive.<sup>10</sup> These authors, however, did not observe an increased risk in those patients participating in recreational sports compared with the inactive ones.<sup>10</sup> Thus, although it seems that exercise intensity is associated with arrhythmogenic risk in a dose-response fashion, this has only been confirmed in animal models.<sup>24</sup> The aforementioned studies have common limitations, such as the use of self-reported exercise and sports history, which is subject to recall bias, social desirability bias and inaccuracy.<sup>12 13</sup> In addition, the retrospective design of these studies might increase the recall bias in the assessment of exercise and sports participation in the past.

Regular exercise and sports are not the only source of physical activity; patients with AC may also perform physical activities of different intensities in their daily life (eg, for transportation, work related or in their leisure time). The association of the lifestyle physical activity with the occurrence of ventricular tachycardia has not been investigated to date. In this study, we observed that

lifestyle physical activity was not associated with the occurrence of RR-NSVTs in patients with AC. In addition, we observed that 1) patients with AC with RR-NSVTs did not show higher lifestyle physical activity levels than patients with AC without RR-NSVTs during our 30-day recording, 2) patients with AC with RR-NSVTs showed similar physical activity patterns in the days when the RR-NSVTs occurred compared with the days without RR-NSVT, and 3) the RR-NSVTs very rarely occurred when participants were doing physical activity, and we observed a substantial amount of physical activity in our participants that did not trigger any RR-NSVT. It is noteworthy that patients with AC did barely engage in activities of vigorous intensity, with an average of 3 min/day in this study sample and with 80% of the patients not reaching 1 min/day. Therefore, these findings mainly apply to activities of light and moderate intensity, which seem to be safe for patients with AC, in line with current guidelines for this population.<sup>7</sup> Future studies should investigate the risk of performing lifestyle physical activities of higher intensities.

This study contributes to the existing literature by 1) investigating the lifestyle physical activity in patients with AC in relation to the occurrence of arrhythmia, whereas previous literature had only focused on competitive sports and regular exercise; 2) including patients with AC presenting both desmosomal and non-desmosomal variants instead of only including desmosomal forms of AC as previous studies; 3) using objective tools to quantify the physical activity, while previous research relied on self-reported retrospective methods (eg, questionnaires, interviews) of questionable validity and reliability; 4) the measurement of physical activity of all intensities, including light, moderate and vigorous, instead of only relying on high-intensity regular exercise and sports participation; 5) the objective assessment of RR-NSVTs, which are considered a surrogate marker of SCD.

### Limitations

This study presents a number of limitations. First, the outcome was RR-NSVTs of at least 18 beats as the relatively short recording period did not allow registering sustained ventricular tachycardias or ventricular fibrillations, which would have been stronger outcomes. However, RR-NSVTs are recognised as a powerful and independent risk factor for SCD in patients with AC.<sup>4 25 26</sup> Second, the study participants rarely engaged in vigorous intensity activities and future studies should investigate whether lifestyle physical activities of vigorous intensity (ie,  $\geq 6$  METs) are associated with RR-NSVT and other ventricular arrhythmias. Finally, the cross-sectional design of this study precludes establishing causal relationships between physical activity and RR-NSVT.

### CONCLUSIONS

The findings of this study suggest that lifestyle physical activity is not associated with the occurrence of RR-NSVTs in patients with AC. This provides preliminary evidence for the active promotion of lifestyle physical activity among patients with AC to ensure they obtain the multiple benefits and risk reductions associated with physical activity. Future prospective studies with larger sample sizes and longer follow-up periods are needed to characterise the effects of lifestyle physical activity of moderate and vigorous intensity on the arrhythmic risk in patients with different forms and arrhythmic burden of AC.

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**Contributors** JR-M and JHM contributed equally to this study and share the first authorship. AS-M and JJ-J contributed equally and share the senior authorship. JR-M, JHM, AS-M and JJ-J conceived the study. JR-M, MM-J, EC-B, ARS, AS-M and JJ-J collected data for the study. JHM designed and conducted the analysis, and JR-M, AS-M and JJ-J commented on the analysis plan. JHM and JR-M wrote the initial manuscript. All coauthors contributed to the review of the results and extensive revision of the manuscript. JJJ is the guarantor responsible for the overall content of the article

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**Patient and public involvement** Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

**Patient consent for publication** Not applicable.

**Ethics approval** This study involves human participants and was approved by the Research Ethics Committee of Granada (ref: CEIM/CEI/3-19 [12/4/19]). All patients signed an informed consent to participate in the study before taking part.

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**Data availability statement** Data are available on reasonable request. Data are available on reasonable request to the corresponding author.

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