

ORIGINAL INVESTIGATIONS

Association Between Left Ventricular Noncompaction and Vigorous Physical Activity



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ABSTRACT

BACKGROUND Left ventricular (LV) hypertrabeculation fulfilling noncompaction cardiomyopathy criteria has been detected in athletes. However, the association between LV noncompaction (LVNC) phenotype and vigorous physical activity (VPA) in the general population is disputed.

OBJECTIVES The aim of this study was to assess the relationship between LVNC phenotype on cardiac magnetic resonance (CMR) imaging and accelerometer-measured physical activity (PA) in a cohort of middle-aged nonathlete participants in the PESA (Progression of Early Subclinical Atherosclerosis) study.

METHODS In PESA participants (n = 4,184 subjects free of cardiovascular disease), PA was measured by waist-secured accelerometers. CMR was performed in 705 subjects (mean age 48 ± 4 years, 16% women). VPA was recorded as total minutes per week. The study population was divided into 6 groups: no VPA and 5 sex-specific quintiles of VPA rate (Q1 to Q5). The Petersen criterion for LVNC was evaluated in all subjects undergoing CMR. For participants meeting this criterion (non-compacted-to-compacted ratio ≥2.3), 3 more restrictive LVNC criteria were also evaluated (Jacquier, Grothoff, and Stacey).

RESULTS LVNC phenotype prevalence according to the Petersen criterion was significantly higher among participants in the highest VPA quintile (Q5 = 30.5%) than in participants with no VPA (14.2%). The Jacquier and Grothoff criteria were also more frequently fulfilled in participants in the highest VPA quintile (Jacquier Q5 = 27.4% vs. no VPA = 12.8% and Grothoff Q5 = 15.8% vs. no VPA = 7.1%). The prevalence of the systolic Stacey LVNC criterion was low (3.6%) and did not differ significantly between no VPA and Q5.

CONCLUSIONS In a community-based study, VPA was associated with a higher prevalence of CMR-detected LVNC phenotype according to diverse established criteria. The association between VPA and LVNC phenotype was independent of LV volumes. According to these data, vigorous recreational PA should be considered as a possible but not uncommon determinant of LV hypertrabeculation in asymptomatic subjects. (J Am Coll Cardiol 2020;76:1723-33)
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ABBREVIATIONS AND ACRONYMS

CI = confidence interval

CMR = cardiac magnetic resonance

IQR = interquartile range

LAX = long-axis

LV = left ventricular

LVEF = left ventricular ejection fraction

LVNC = left ventricular noncompaction

NC/C = noncompacted-to-compacted

PA = physical activity

RV = right ventricular

VPA = vigorous physical activity

Left ventricular noncompaction (LVNC) is defined as a primary genetic cardiomyopathy by the American Heart Association and as an unclassified cardiomyopathy by the European Society of Cardiology (1,2). Several studies have demonstrated the presence of genetic mutations showing a strong familial association with the LVNC phenotype, and the disease may be more generally related to as yet undetected mutations (3,4). In the absence of a generalized understanding of the genetic basis of LVNC, diagnosis is currently based on noninvasive imaging. However, imaging criteria are not highly specific to LVNC cardiomyopathy, and LVNC manifestations overlap with other entities, such as hypertrophic and dilated cardiomyopathies (3–5).

Moreover, some physiological conditions, such as pregnancy, can be associated with an LVNC phenotype (left ventricular [LV] hypertrabeculation). For these reasons, some investigators have argued that LVNC is an epiphenomenon of a diverse range of pathological and physiological entities (3,4).

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Although there are echocardiographic LVNC criteria, cardiac magnetic resonance (CMR) imaging has higher spatial resolution, and CMR-based criteria are the most extensively used to diagnose an LVNC phenotype. The most widely used CMR-based LVNC indicator in clinical and research studies is a noncompacted-to-compacted (NC/C) ratio >2.3 , according to criteria established by Petersen et al. (6); however, of all the available CMR measures, this has the highest sensitivity and the lowest specificity. Consequently, this LVNC diagnostic criterion is frequently fulfilled as an incidental finding, presenting a challenge for clinical management. In 2 population cohort studies (MESA [Multi-Ethnic Study of Atherosclerosis] and TASCFORCE [Tayside Screening for Risk of Cardiac Events]) enrolling asymptomatic participants with no known histories of

cardiovascular disease, LVNC prevalence according to the Petersen criterion was 25% and 15%, respectively (7,8). In response to this situation, other, more specific, CMR-based LVNC criteria have been proposed (9–13).

Vigorous training in athletes is associated with a high prevalence of fulfilled LVNC criteria in echocardiographic and CMR studies (14–16). It remains unclear whether vigorous physical activity (VPA) is associated with increased prevalence of LVNC criteria in the general population (nonathletes). A recent report from the UK Biobank study found no association in the general population between extremes of physical activity (PA) and LV trabeculation extent measured as the NC/C ratio in CMR long-axis (LAX) views (Petersen criterion), suggesting that trabeculation extent is not influenced by PA (17). These data conflict with the previously reported higher prevalence of LVNC phenotype in highly trained athletes (18).

In light of these controversial findings, we evaluated the association between PA and the presence of an LVNC phenotype according to 4 CMR-based LVNC criteria in the general population. The study population was taken from the ongoing PESA (Progression of Early Subclinical Atherosclerosis) cohort study, in which overtly healthy middle-aged participants undergo serial objective PA assessments using a triaxial accelerometer. A subset of 705 PESA participants underwent CMR, allowing us to relate PA to LVNC phenotype according to several criteria.

METHODS

POPULATION AND STUDY DESIGN. PESA is an observational prospective cohort study involving 4,184 asymptomatic middle-aged (40 to 55 years at enrollment) employees of Banco Santander with no histories of cardiovascular disease. The main objective of PESA is to study the prevalence and progression of subclinical atherosclerosis using serial noninvasive advanced imaging (2-dimensional and 3-dimensional multiterritorial vascular ultrasound and coronary artery calcium score) (19). PESA

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TABLE 1 Baseline Characteristics According to Quintiles of VPA

	Overall (n = 705)	No VPA (n = 226)	VPA Quintiles					p Value
			Q1 (n = 97)	Q2 (n = 96)	Q3 (n = 95)	Q4 (n = 96)	Q5 (n = 95)	
Age, yrs	47.8 ± 4.3	48.4 ± 4.2	48.2 ± 4	47.6 ± 4.1	47.5 ± 4.7	46.7 ± 4.3	47.8 ± 4.3	0.382
Female	115 (16.3)	51 (22.6)	13 (13.4)	13 (13.5)	13 (13.7)	13 (13.5)	12 (12.6)	0.002
BMI, kg/m ²	26.9 ± 3.6	27.5 ± 3.8	27.5 ± 3.9	27.3 ± 3.4	26.6 ± 3.2	26.0 ± 3.0	26.0 ± 3.1	<0.001
Obesity	124 (17.6)	54 (23.9)	22 (22.7)	19 (19.8)	13 (13.7)	7 (7.3)	9 (9.6)	<0.001
HTN	162 (23.0)	66 (29.2)	27 (27.8)	23 (24.0)	16 (16.8)	16 (16.7)	14 (14.9)	0.007
DL	410 (58.2)	137 (60.6)	64 (66.0)	61 (63.5)	55 (57.9)	48 (50.0)	45 (47.4)	0.001
DM	38 (5.4)	22 (9.7)	6 (6.2)	4 (4.2)	3 (3.2)	1 (1.0)	2 (2.1)	0.028
Smoking	154 (21.8)	87 (38.5)	22 (22.7)	13 (13.5)	9 (9.5)	15 (15.6)	8 (8.4)	<0.001
Physical activity, min/week								
Sedentary	4,443 ± 395	4,501 ± 372	4,505 ± 460	4,410 ± 420	4,430 ± 351	4,361 ± 394	4,368 ± 366	0.004
Light	2,002 ± 383	2,004 ± 387	2,019 ± 395	2,046 ± 407	2,007 ± 359	1,998 ± 374	1,934 ± 370	0.057
Moderate	267 ± 123	207 ± 106	256 ± 110	297 ± 122	282 ± 104	308 ± 118	331 ± 137	<0.001
Vigorous	5.2 (0-35)	0 (0-0)	1.2 (0.6-1.9)	7.0 (4.7-10.3)	19.8 (15.7-25.3)	44.6 (36.5-59.5)	110.2 (87.5-166.2)	<0.001
MVPA	271 (186-382)	181 (132-255)	233 (178-315)	292 (213-366)	289 (219-370)	344 (277-437)	428 (369-542)	<0.001

Values are mean ± SD, n (%), or median (interquartile range). Quintiles of PA are sex specific (i.e., the group of women in the study are distributed among the quintiles according to VPA as is done for men in order to have equal representation of women in each quintile).
BMI = body mass index; DL = dyslipidemia; DM = diabetes mellitus; HTN = hypertension; MVPA = moderate + vigorous physical activity; PA = physical activity; Q = quintiles; VPA = vigorous physical activity.

participants undergo vascular imaging every 3 years. To date, the first, second, and third rounds of imaging have been completed. A subset of participants (n = 705) underwent CMR at visit 2. Selection criteria for CMR have been published before (20). In brief, the selection of the subpopulation was based on the presence of subclinical atherosclerosis on arterial ultrasound and/or coronary calcium scoring at baseline (i.e., visit 1).

PA ASSESSMENT. At each visit, participants were provided with a waist-secured ActiTrainer activity monitor (ActiGraph, Pensacola, Florida) to provide an objective measure of the intensity of PA over 7 consecutive days (24 h × 7 days). Participants were instructed to remove the accelerometer during water-based activities (e.g., showering and swimming). The ActiTrainer device records movement acceleration as counts. Accelerometry data were processed using ActiLife software version 6.13. Wear time was validated according to the definitions of Troiano (21): a minimum threshold of 4 days with at least 600 min/day of valid data. On the basis of 60-s epoch files, cutoff points defined by Troiano et al. (22) were used to categorize PA intensities as sedentary (0 to 99), light (100 to 2,019), moderate (2,020 to 5,998), and vigorous (≥5,999) (22). Two sets of PA data were processed per subject, corresponding to the first and second follow-up visits, separated by 3 years. VPA reported in this study in each subject is the average VPA (minutes per week) from the 2 measurements

obtained at the first and second follow-up visits 3 years apart. Thus, mean PA intensities were derived as an estimate of mean PA over time.

The study population was divided into 6 groups according to the mean number of minutes spent in VPA per week: no time in the VPA range (0 min) and 5 quintiles of total time spent in VPA. Quintiles of VPA are sex specific (i.e., the group of women in the study are distributed among the quintiles according to VPA as is done for men in order to have equal representation of women in each quintile). Two additional divisions of the population were made on the basis of fixed time in each VPA range (0, 1 to 25, 25 to 50, 50 to 75, and >75 min) and on the basis of the recommendations of the 2018 PA guidelines for Americans for a healthy lifestyle (<150 min of moderate PA and ≤75 min of VPA, 150 to 300 min of moderate PA and ≤75 min of VPA, >300 min of moderate PA and ≤75 min of VPA, and >75 min of VPA).

CARDIAC MAGNETIC RESONANCE. The PESA protocol was designed to select a subpopulation of participants to undergo vascular positron emission tomography/magnetic resonance at recruitment (visit 1) and at 6-year follow-up. The selection process is detailed elsewhere (20). As per protocol, this subgroup underwent CMR at PESA visit 2 (3-year follow-up), which is the focus of the present study. The institutional ethics committee approved the study protocol, and all participants provided written informed consent.

TABLE 2 Cardiac Magnetic Resonance Imaging Parameters According to Quintiles of VPA

	Overall (n = 705)	No VPA (n = 226)	VPA Quintiles					p Value
			Q1 (n = 97)	Q2 (n = 96)	Q3 (n = 95)	Q4 (n = 96)	Q5 (n = 95)	
LVEDVi, ml/m ²	83.0 ± 13.7	78.6 ± 12.6	80.2 ± 12.9	82.0 ± 10.8	84.9 ± 13.7	87.7 ± 14.4	90.4 ± 14.4	<0.001
LVESVi, ml/m ²	32.9 ± 7.9	30.8 ± 7.5	31.7 ± 7.4	32.4 ± 6.2	33.5 ± 7.6	35.2 ± 8.2	36.6 ± 8.9	<0.001
LV stroke volume, ml	97.6 ± 18.3	92.8 ± 18.3	95.6 ± 17.9	96.9 ± 15.8	101.2 ± 17.8	102.1 ± 19.0	103.3 ± 17.9	<0.001
LVEF, %	60.6 ± 4.9	61.0 ± 5.4	60.6 ± 5.2	60.8 ± 4.1	60.8 ± 4.5	60.2 ± 4.4	59.7 ± 4.9	0.060
LV cardiac index, l/min/m ²	3.0 ± 0.5	3.0 ± 0.5	3.0 ± 0.5	3.0 ± 0.5	3.0 ± 0.5	3.0 ± 0.5	3.1 ± 0.4	0.563
LV myocardial mass, g/m ²	49.4 ± 9.7	47.1 ± 8.9	48.3 ± 9.3	48.9 ± 9.5	50.5 ± 9.1	51.9 ± 11.0	52.9 ± 9.5	<0.001
RVEDVi, ml/m ²	84.3 ± 14.8	78.3 ± 13.0	81.2 ± 13.1	83.0 ± 11.5	87.7 ± 14.0	90.1 ± 15.6	93.6 ± 15.8	<0.001
RVESVi, ml/m ²	34.2 ± 8.2	31.2 ± 6.9	33.0 ± 7.7	33.6 ± 6.9	35.7 ± 7.9	37.2 ± 9.0	38.5 ± 9.1	<0.001
RV stroke volume, ml	97.4 ± 18.6	90.7 ± 17.5	95.3 ± 18.0	96.5 ± 16.3	102.5 ± 18.4	103.0 ± 18.2	105.8 ± 18.9	<0.001
RV ejection fraction, %	59.6 ± 4.7	60.1 ± 4.7	59.6 ± 5.5	59.7 ± 4.7	59.5 ± 4.4	59.0 ± 4.6	59.1 ± 4.5	0.183
RV cardiac index, l/min/m ²	3.0 ± 0.5	3.0 ± 0.5	3.0 ± 0.5	3.0 ± 0.5	3.0 ± 0.5	3.1 ± 0.5	3.1 ± 0.5	0.034
Heart rate, beats/min (n = 510)	63.3 ± 10.4	67.0 ± 10.5	64.2 ± 10.6	63.1 ± 9.9	61.2 ± 9.2	60.2 ± 10.1	59.4 ± 9.1	<0.001

Values are mean ± SD. Quintiles of physical activity are sex specific.

LV = left ventricular; LVEF = left ventricular ejection fraction; LVEDVi = indexed left ventricular end-diastolic volume; LVESVi = indexed left ventricular end-systolic volumes; RV = right ventricular; RVEDVi = indexed right ventricular end-diastolic volume; RVESVi = right ventricular end-systolic volume; VPA = vigorous physical activity.

CMR ACQUISITION PROTOCOL. All studies were performed using a 3.0-T Philips Ingenuity magnetic resonance imaging scanner (Philips Healthcare, Best, the Netherlands) using dedicated surface coils for cardiac studies and retrospective electrocardiographic gating. Steady-state free precession cine sequences were acquired in 10 to 15 contiguous short-axis slices covering both ventricles from base to apex; these sequences were reconstructed into 25 cardiac phases each for the evaluation of biventricular volumes and function.

CMR ANALYSIS. Cine sequences were analyzed using specialized software (Philips Healthcare) by experienced researchers blinded to any clinical variable, including accelerometer data. On cine images, biventricular endocardial contours of the compacted myocardium were manually traced at end-diastole and end-systole in all short-axis slices excluding the papillary muscles. The Simpson method was applied to calculate biventricular volumes and ejection fractions. LV and right ventricular (RV) volumes were indexed to body surface area calculated using Brody's formula. Cardiac index was calculated as: [(end-diastolic volume – end-systolic volume) × heart rate]/1,000 and indexed to body surface area.

TRABECULATION ANALYSIS AND LVNC CRITERIA. The Petersen criterion is widely accepted as the most sensitive and least specific measure of LVNC phenotype (6,18) and was used to screen all 705 PESA CMR studies. Following this methodology, the NC/C ratio was calculated in the most prominent hypertrabeculated myocardial segments, excluding the most apical one in order to avoid an overestimation of prevalence, which reached 43% in MESA (7). Our first

analysis of the entire PESA CMR population thus included all 3 LAX views. The highest NC/C ratio was determined for each participant, and those with NC/C ratios ≥2.3 were further screened for 3 additional CMR LVNC criteria (Jacquier, Grothoff, and Stacey) with higher specificity (9–11).

The Jacquier criterion is estimated from the non-compacted myocardial mass as a percentage of total LV mass; a noncompacted mass ≥20% is considered to indicate an LVNC phenotype (9). For this analysis, the compacted layer was calculated at end-diastole by redrawing the endocardial contours including this time the papillary muscles. For the Grothoff criterion, the NC/C ratio is measured in diastolic short-axis views instead of LAX views, and the cutoff for LVNC is ≥3 (10). The Stacey criterion is calculated from end-systolic short-axis views, with NC/C ≥2 considered positive for an LVNC phenotype (11).

STATISTICAL ANALYSIS. The distribution of continuous variables was analyzed using graphical methods. For normally distributed variables, results are expressed as mean ± SD. Variables not normally distributed are presented as median (interquartile range [IQR]). Categorical variables are expressed as absolute frequency (percentage). For descriptive analyses, participants were grouped in the no-VPA category or in sex-specific VPA quintiles. Trend tests among VPA quintiles were performed by linear or logistic regression as appropriate, introducing VPA (minutes) as a continuous independent variable adjusted for sex. Comparisons between hypertrabeculation groups were made by parametric methods (nonpaired Student's *t*-test) or nonparametric methods (Mann-Whitney *U* and chi-square

TABLE 3 Prevalence of Left Ventricular Noncompaction According to 4 Cardiac Magnetic Resonance Criteria Across Quintiles of VPA

	Overall (n = 705)	No VPA (n = 226)	VPA Quintiles					p Value
			Q1 (n = 97)	Q2 (n = 96)	Q3 (n = 95)	Q4 (n = 96)	Q5 (n = 95)	
Petersen+	123 (17.4)	32 (14.2)	13 (13.4)	16 (16.7)	18 (18.9)	15 (15.6)	29 (30.5)	0.002
Jacquier+	109 (15.5)	29 (12.8)	10 (10.3)	15 (15.6)	16 (16.8)	13 (13.5)	26 (27.4)	0.002
Grothoff+	54 (7.7)	16 (7.1)	5 (5.2)	2 (2.1)	10 (10.5)	6 (6.3)	15 (15.8)	0.003
Stacey+	25 (3.6)	8 (3.5)	2 (2.1)	0 (0.0)	6 (6.3)	3 (3.1)	6 (6.3)	0.031

Values are n (%). Quintiles of physical activity are sex specific.
VPA = vigorous physical activity.

tests) as appropriate. The association between hypertrabeculation and VPA quintiles was estimated as prevalence odds ratios by sex- and risk factor-adjusted logistic regression.

RESULTS

BASELINE CHARACTERISTICS AND PA. A total of 705 PESA participants underwent CMR, and accelerometer-based PA data were available for all of them. Baseline characteristics of the entire population and the 6 VPA category groups are shown in [Table 1](#). The mean age of the population was 48 ± 4 years, and 16% were women. There was no difference in age across VPA quintiles. There were significantly fewer women in the highest VPA quintile (Q5). Participants in Q5 had significantly fewer classic cardiovascular risk factors (hypertension, hypercholesterolemia, diabetes, obesity, and smoking). Baseline characteristics between the PESA subpopulation included in this study and the rest of the PESA cohort are presented in [Supplemental Table 1](#).

In the entire population, median time in the VPA range was 5.25 min/week (0 to 35 min/week). Participants in Q5 spent the least time in the sedentary PA and light PA ranges, whereas they spent the most time in the moderate PA and VPA ranges. Time in the VPA range differed markedly between participants in Q4 (45 min/week; IQR: 37 to 60 min/week) and Q5 (110 min/week; IQR: 88 to 166 min/week) ($p < 0.05$) ([Table 1](#)).

CMR IMAGING DATA. LV and RV volumes, ejection fractions, stroke volumes, cardiac output, and myocardial mass in the entire population as well as in the 6 VPA category groups are presented in [Table 2](#). In the VPA groups (from no VPA time to Q5), there were progressive increases in LV and RV size (larger diastolic and systolic LV and RV volumes), stroke volumes, and LV mass. LV ejection fraction (LVEF) and heart rate decreased progressively from the no-VPA group to Q5.

LVNC PHENOTYPE IN DIFFERENT VPA QUINTILES. A total of 123 of the 705 participants (17.4%) had diastolic NC/C ratios ≥ 2.3 in any of the 3 LAX views, thus fulfilling the Petersen LVNC criterion. Of these participants, 109 (15.5% of the entire population) also fulfilled the Jacquier LVNC criterion, and 54 (7.7%) fulfilled the Grothoff LVNC criterion. Only 25 participants (3.6%) fulfilled the Stacey LVNC criterion ([Table 3](#)), and all of these participants also fulfilled the criteria for the diastolic measures. LVNC (Petersen criterion) was more frequent in men (19.5%) than in women (7%).

LVNC prevalence according to the Petersen criterion was significantly higher in participants in VPA Q5 than in the other quintiles: 30.5% in Q5 versus 15.6% in Q4, 18.9% in Q3, 16.7% in Q2, and 13.4% in Q1 ([Table 3](#)). The Petersen criterion was fulfilled in 14% of participants with no time in the VPA range ($p < 0.001$). LVNC phenotype prevalence was also significantly higher in VPA Q5 participants according to more specific diastolic criteria (Jacquier and Grothoff). However, LVNC prevalence according to the most restrictive (systolic) criterion (Stacey) was low (3.6%) overall and showed no significant differences across VPA quintiles ([Table 3](#)).

LVNC prevalence according to the 3 LVNC diastolic criteria among VPA Q5 participants was more than double than that among participants with no VPA. LVNC was also twice as prevalent in Q5 versus no VPA according to the systolic Stacey criterion; however, statistical significance could not be calculated for this difference, because of the low overall prevalence of this criterion ([Table 3](#)). When the population was divided on the basis of 5 groups of fixed time in the VPA range ([Supplemental Table 2](#)) or on the basis of the recommendations of the 2018 PA guidelines for Americans for a healthy lifestyle ([Supplemental Table 3](#)), similar results were found: subjects in the highest category had a higher prevalence of LVNC phenotype according to different criteria.

TABLE 4 Clinical and Cardiac Magnetic Resonance Imaging Characteristics Between Participants With and Without Petersen Criterion

	Petersen+ (n = 123)	Petersen- (n = 582)	p Value
Age, yrs	48.5 ± 4.4	47.7 ± 4.2	0.058
Female	8 (6.5)	107 (18.4)	0.001
BMI, kg/m ²	27.3 ± 3.3	26.8 ± 3.6	0.184
Obesity	25 (20.3)	99 (17.0)	0.385
HTN	27 (22.0)	135 (23.2)	0.758
DL	74 (60.2)	336 (57.7)	0.620
DM	5 (4.1)	33 (5.7)	0.474
Smoking	22 (17.9)	132 (22.7)	0.242
Physical activity, min/week			
Sedentary	4,409 ± 412	4,450 ± 391	0.306
Light	2,001 ± 385	2,002 ± 383	0.962
Moderate	294 ± 142	261 ± 118	0.006
Vigorous	14 (0-65)	4 (0-31)	0.016
LVEDVi, ml/m ²	87.4 ± 13.9	82 ± 13.5	<0.001
LVESVi, ml/m ²	35.9 ± 9.1	32.2 ± 7.4	<0.001
LV stroke volume, ml	102 ± 17.2	96.5 ± 18.4	0.001
LVEF	59.4 ± 5.5	60.9 ± 4.7	0.003
LV cardiac index, l/min/m ²	3.1 ± 0.5	3.0 ± 0.5	0.177
LV myocardial mass, g/m ²	51 ± 8.5	49 ± 9.9	0.040
RVEDVi, ml/m ²	88.9 ± 13.5	83.3 ± 14.9	<0.001
RVESVi, ml/m ²	36.5 ± 7.5	33.7 ± 8.3	<0.001
RV stroke volume, ml	104 ± 17.2	96 ± 18.7	<0.001
RV ejection fraction	59 ± 4.7	59.8 ± 4.7	0.097
RV cardiac index, l/min/m ²	3.1 ± 0.5	3.0 ± 0.5	0.017
Heart rate, beats/min (n = 510)	61.8 ± 9.1	63.6 ± 10.6	0.152

Values are mean ± SD, n (%), or median (interquartile range). Quintiles of physical activity are sex specific. Abbreviations as in [Tables 1 and 2](#).

INTERPLAY AMONG LV SIZE, LVNC CRITERIA, AND EXERCISE. Clinical characteristics, PA, and CMR parameters of the Petersen+ and Petersen- subpopulations are compared in [Table 4](#). Clinical characteristics, PA, and CMR parameters for the groups of subjects fulfilling none, 1, 2, 3, or 4 LVNC criteria are presented in [Table 5](#).

The subpopulation fulfilling the Petersen LVNC criterion included significantly fewer women and spent more time per week on moderate PA and VPA. Indeed, moderate PA and VPA are the only demographic parameters that differed between the Petersen+ and Petersen- subpopulations. CMR data also revealed that the Petersen+ subpopulation had larger LV and RV systolic and diastolic volumes, lower LVEFs, larger LV mass, and higher biventricular stroke volumes.

Because subjects in the highest quintile of VPA had larger LV sizes, we wanted to explore whether the association between the LVNC phenotype and VPA was driven by them. Adding the indexed LV end-diastolic volume to the model, compared with the reference (subjects without VPA at all), the odds

ratios for the LVNC phenotype were 0.84 (95% confidence interval [CI]: 0.42 to 1.70; $p = 0.629$) for Q1; 1.08 (95% CI: 0.56 to 2.10; $p = 0.820$) for Q2; 1.17 (95% CI: 0.61 to 2.24; $p = 0.633$) for Q3; 0.90 (95% CI: 0.45 to 1.78; $p = 0.754$) for Q4; and 2.01 (95% CI: 1.10 to 3.69; $p = 0.023$) for Q5.

DISCUSSION

In our study, we evaluated the association between objectively measured (accelerometer) VPA and the prevalence of LV hypertrabeculation fulfilling currently accepted CMR-based LVNC criteria in a population of 705 middle-aged nonathlete participants. The population was divided into 6 groups according to the time spent on VPA: no VPA and quintiles from lowest to highest time in the VPA range.

The main results are as follows. 1) Overall LVNC prevalence was 17%, 16%, 8%, and 4% according to the Petersen, Jacquier, Grothoff, and Stacey criteria, respectively, and LVNC prevalence was higher in men. 2) Participants in the highest VPA quintile had a much higher LVNC prevalence (31%, 27%, 16%, and 6% according to the different criteria), whereas prevalence among sedentary subjects was lower (14%, 13%, 7%, and 4%). 3) An interplay was observed between LVNC imaging criteria and ventricular size and systolic function, with subjects fulfilling LVNC imaging criteria having larger biventricular volumes and lower LVEFs and RV ejection fractions, albeit within the normal ranges ([Central Illustration](#)). In agreement with previous studies, we found an association between exercise and LV volumes; however, ours is the first study demonstrating that the association between VPA and LVNC phenotype is independent of LV volumes.

Although an embryological origin is not universally accepted, LVNC was originally described as a congenital disease secondary to failure of myocardial compaction during heart development ([23,24](#)). LVNC cardiomyopathy is associated with increased risk for malignant arrhythmias and thromboembolic events, as well as with progressive deterioration of LV systolic function ([25-29](#)). It is now accepted that isolated LVNC imaging criteria in the absence of familial antecedents or a personal history of arrhythmias or syncope is an insufficient basis for a definite diagnosis of LVNC. Nevertheless, the presence of LV hypertrabeculation fulfilling LVNC criteria presents a clinical challenge in some environments, such as sport participation and disqualification ([30,31](#)).

Some myocardial pathologies, such as dilated and hypertrophic cardiomyopathies, are associated with

TABLE 5 Clinical and Cardiac Magnetic Resonance Imaging Characteristics According to Left Ventricular Noncompaction Criteria Fulfilment

	Petersen– (n = 582)	Petersen+ (n = 123)	Jacquier+ (n = 109)	Grothoff+ (n = 54)	Stacey+ (n = 25)
Age, yrs	47.7 ± 4.2	48.5 ± 4.4	48.6 ± 4.3	48.1 ± 4.7	47.6 ± 5.2
Female	107 (18.4)	8 (6.5)	7 (6.4)	3 (5.6)	2 (8.0)
BMI, kg/m ²	26.8 ± 3.6	27.3 ± 3.3	27.3 ± 3.4	27.7 ± 3.3	26.9 ± 4.0
Obesity	99 (17.0)	25 (20.3)	25 (22.9)	16 (29.6)	6 (24.0)
HTA	135 (23.2)	27 (22.0)	24 (22.0)	12 (22.2)	6 (24.0)
DL	336 (57.7)	74 (60.2)	67 (61.5)	32 (59.3)	16 (64.0)
DM	33 (5.7)	5 (4.1)	5 (4.6)	3 (5.6)	2 (8.0)
Smoking	132 (22.7)	22 (17.9)	22 (20.2)	6 (11.1)	3 (12.0)
10-yr risk	7.9 (5.3–11.1)	8.4 (5.6–11.2)	8.5 (5.6–11.5)	7.9 (4.9–10.7)	7.3 (4.9–9.8)
Physical activity, min/week					
Sedentary	4,450 ± 391	4,409 ± 412	4,404 ± 415	4,409 ± 410	4,471 ± 287
Light	2,002 ± 383	2,001 ± 385	2,009 ± 385	1,948 ± 355	1,861 ± 239
Moderate	261 ± 118	294 ± 142	291 ± 144	287 ± 143	277 ± 150
Vigorous	4.1 (0–30.9)	14.0 (0–65.3)	14.0 (0–60.7)	15.7 (0–91.0)	16.9 (0–50.4)
LVEDVi, ml/m ²	82.0 ± 13.5	87.4 ± 13.9	88.0 ± 14.1	88.5 ± 15.4	91.6 ± 17.7
LVESVi, ml/m ²	32.2 ± 7.4	35.9 ± 9.1	36.0 ± 9.4	37.5 ± 10.3	40.2 ± 12.8
LV stroke volume, ml	96.5 ± 18.4	102.0 ± 17.2	103.0 ± 16.7	101.0 ± 15.6	102.0 ± 16.5
LVEF	60.9 ± 4.7	59.4 ± 5.5	59.4 ± 5.7	58.2 ± 5.5	56.8 ± 6.6
LV cardiac index, l/min/m ²	3.0 ± 0.5	3.1 ± 0.5	3.1 ± 0.5	3.0 ± 0.4	3.1 ± 0.5
LV myocardial mass, g/m ²	49.1 ± 9.9	51.0 ± 8.5	51.1 ± 8.3	50.4 ± 7.4	50.0 ± 7.3
RVEDVi, ml/m ²	83.3 ± 14.9	88.9 ± 13.5	89.1 ± 13.3	90.7 ± 13.7	90.5 ± 11.4
RVESVi, ml/m ²	33.7 ± 8.3	36.5 ± 7.5	36.6 ± 7.3	38.0 ± 7.5	38.3 ± 6.5
RV stroke volume, ml	96.0 ± 18.7	104.0 ± 17.2	105.0 ± 17.2	104.0 ± 17.0	104.0 ± 16.2
RV ejection fraction	59.8 ± 4.7	59.0 ± 4.7	59.0 ± 4.6	58.2 ± 4.7	57.7 ± 4.5
RV cardiac index, l/min/m ²	3.0 ± 0.5	3.1 ± 0.5	3.1 ± 0.5	3.1 ± 0.4	3.1 ± 0.4
Heart rate, beats/min (n = 510)	63.6 ± 10.6	61.8 ± 9.1	61.0 ± 8.5	60.6 ± 9.3	61.9 ± 9.7

Values are n, mean ± SD, n (%), or median (interquartile range). Quintiles of physical activity are sex specific.
Abbreviations as in Tables 1 and 2.

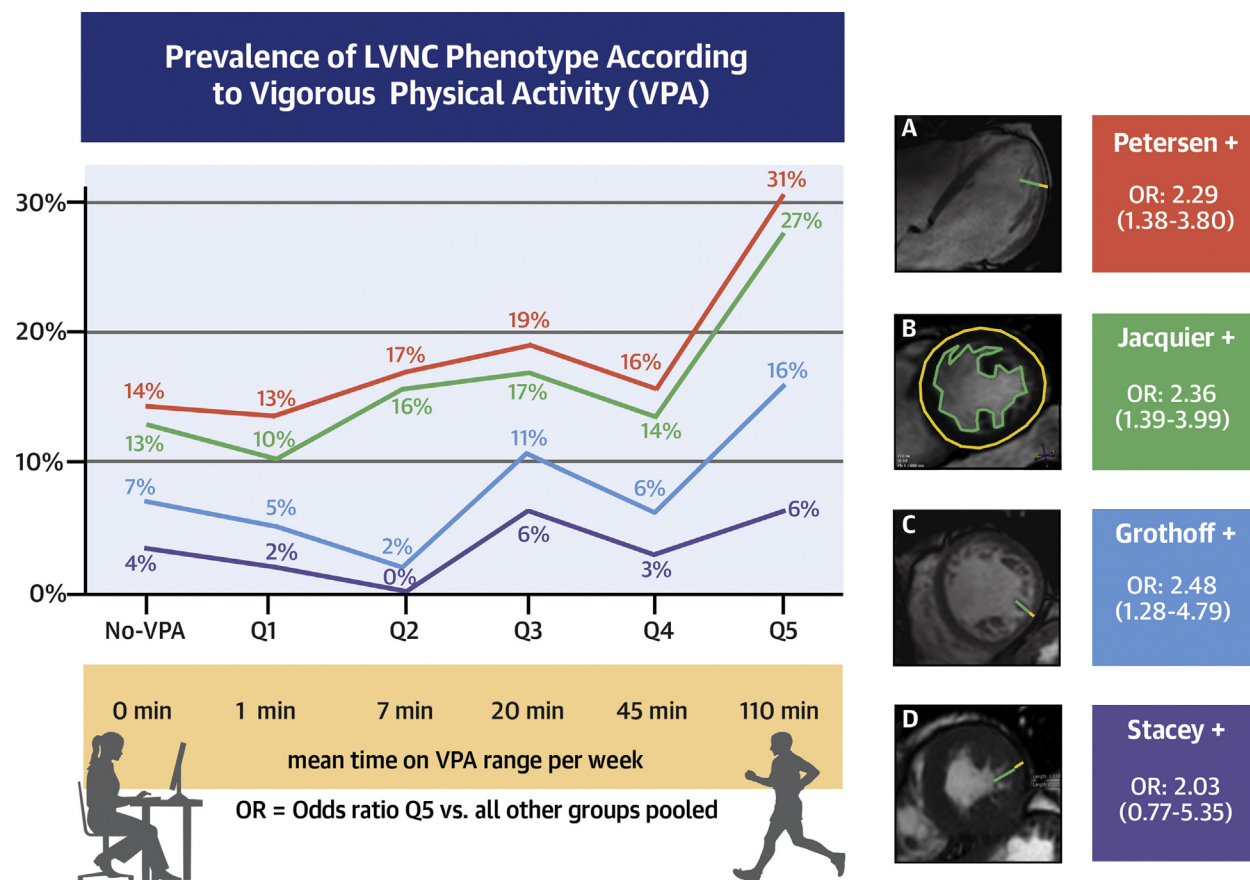
LV hypertrabeculation fulfilling CMR-based LVNC criteria. The prevalence of the Petersen criterion in patients with dilated cardiomyopathy has been reported to be twice as high as in healthy control subjects (36% vs. 17%), but the degree of hypertrabeculation had no impact on subsequent clinical events (32). A lack of association between LVNC phenotype and adverse prognosis has also been shown in studies of healthy subjects, such as MESA (7).

Some physiological stresses, such as pregnancy and athletic endurance training, can produce an LVNC phenotype meeting echocardiographic criteria. Gati et al. (33) showed that an LVNC imaging phenotype is present during pregnancy and regresses after delivery. These findings have led to the suggestion that LV hypertrabeculation might be a compensatory mechanism to reduce myocardial wall stress, especially in the apex, and thus prevent apical aneurysm formation under overload conditions (34,35). An alternative explanation could be that when the heart enlarges, existing LVNC just becomes more apparent.

Several studies have assessed the prevalence of echocardiography-measured hypertrabeculation in athletes. Gati et al. (14) were the first to report an increased prevalence of LVNC phenotype in a cohort of young elite athletes (mean age 21 years). In contrast, Caselli et al. (36) reported a much lower prevalence of a “pattern of prominent trabeculations” in a similar athlete population. Because exercise was not objectively quantified in these studies, it is not possible to establish a “dose-response” effect of exercise on LV hypertrabeculation.

The prevalence of LVNC criteria in the general population (i.e., nonathletes), as well as their association with exercise, has not been studied properly until recently. In MESA, 2,742 asymptomatic participants (mean age at enrollment 69 years) underwent 2 CMR studies 10 years apart; 25% of the population was positive for the Petersen LVNC criterion. However, the association between LV hypertrabeculation and exercise was not reported in this study (7). In the TASCFORCE cohort study, 1,480 asymptomatic subjects (mean age 54 years) underwent CMR. The

CENTRAL ILLUSTRATION Percentage of Affected Progression of Early Subclinical Atherosclerosis (PESA) Participants According to 4 Cardiac Magnetic Resonance Imaging-Based Left Ventricular Noncompaction Criteria



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Odds ratios (OR) were calculated comparing quintile 5 of vigorous physical activity (VPA) with the other groups pooled, adjusted for sex and risk factors. (A to D) Trabeculation analysis according to the 4 different cardiac magnetic resonance criteria. (A) End-diastolic noncompacted-to-compacted (NC/C) ratio in long-axis view for Petersen criterion (green line for the NC layer, yellow line for the C layer). (B) End-diastolic epicardial contour (yellow line) and endocardial contour including the papillary muscles (green line) for calculation of the Jacquier criterion. (C) End-diastolic NC/C ratio in short-axis view for Grothoff criterion (green line for the NC layer, yellow line for the C layer). (D) End-systolic NC/C ratio in short-axis view for Stacey criterion (green line for the NC layer, yellow line for the C layer).

prevalence of LVNC phenotype, meeting at least 1 CMR criterion, was 15%, and this study also did not report the association between LV hypertrabeculation and exercise (8). In the present study, LVNC prevalence among asymptomatic subjects was 17% according to the Petersen criterion in the overall cohort; this is in line with the values reported in the TASC-FORCE (8) and Amzulescu et al. (32) studies and lower than that reported in MESA (7). According to a recent meta-analysis, 15% of the general population likely has LV hypertrabeculation fulfilling the Petersen criterion for LVNC (18). This figure is similar to that reported here, suggesting that our data can be extended to the general population.

The first study evaluating the association between LVNC phenotype and exercise in the general population was published recently, in a report from the UK Biobank community-based cohort (17). This study assessed 1,030 participants using CMR and quantified their level of PA with a 7-day accelerometer, similar to our study. LVNC phenotype was evaluated only from the “maximal NC/C ratio” in LAX CMR images. No relationship was found between extremes of PA and the extent of LV trabeculation, suggesting that the latter is not influenced by PA, which directly contradicts our findings reported here. However, the 2 studies differ in 3 important respects. First, the studies used different instruments to measure PA: the

wrist-secured Axivity AX3 device in the UK Biobank study cohort versus the waist-secured ActiGraph device in PESA. These devices do not produce fully equivalent results; moreover, the measurement units are different (milligravity in the UK Biobank study vs. minutes of sedentary, light, moderate, and vigorous PA in our study). It is therefore not possible to directly compare absolute PA values between the 2 studies. Second, the UK Biobank study objectively assessed exercise at a single time point, whereas PESA includes 2 objective measurements per participant separated by 3 years; this may provide a better estimate of long-term PA. Third, there are differences in the population profiles between the 2 studies, with PESA participants younger than those included in the UK Biobank report. The younger age in the PESA population likely underlies the presence of a clear “athlete’s heart” phenotype in the highest VPA quintile (Q5), characterized by high ventricular volumes, a relatively low heart rate, and concomitant high stroke volume. Participants in VPA Q5 in our study spent close to 2 h a week in this activity range (in addition to more than 5 h of moderate PA); in contrast, participants in the fifth quintile of the UK Biobank cohort formed a very heterogeneous group, with a total PA range of 5,193 to 24,318 MET-min/week. It is thus plausible that even participants in the highest PA quintile in the UK Biobank study did not pass the threshold to be considered highly trained, and this might explain the lack of association with LV hypertrabeculation.

A number of different imaging criteria have been suggested for LVNC phenotype identification. Several echocardiographic criteria have been proposed, the most widely used and accepted being those of Chin et al. (37), Jenni et al. (38), and Stollberger et al. (39). CMR is considered the gold-standard technique for defining cardiac anatomy and is thus considered better suited for LVNC screening. Although more CMR-based LVNC criteria for LVNC diagnosis have been proposed, we monitored the 4 more widely available measures, which are based on different diastolic and systolic ratios in all 3 LAX and short-axis views. Given that some studies have used echocardiography and others CMR, and that CMR-based studies have used different criteria, it is difficult to make direct comparisons between studies. The most widely used CMR-based LVNC criterion is Petersen’s, despite its low specificity (18). As noted earlier, about 15% to 17% of the general population fulfills this criterion.

Our data suggest that isolated CMR-based LVNC criteria should not be used to establish a diagnosis of LVNC cardiomyopathy. For secure diagnosis, it is crucial to include genetic testing and to integrate

other clinical parameters, such as a family history of sudden cardiac death or syncope antecedents, or reduced LVEF. According to our findings, VPA is an important parameter that should be included in the clinical evaluation of these patients. In this regard, the European Society of Cardiology recommends against prohibiting sporting competition for asymptomatic athletes fulfilling LVNC imaging criteria unless this is accompanied by electrocardiographic abnormalities, a family background of cardiomyopathy, or abnormal LVEF (Class IIa, Level of Evidence: B) (31). A similar recommendation (albeit Class IIb, Level of Evidence: C rather than Class IIa, Level of Evidence: B) was proposed by the American College of Cardiology (30). Both guidelines highlight the need for additional studies to assess the interaction between endurance training, LVNC imaging phenotype and eventual clinical events. Our study partially meets these demands by showing a clear association between VPA and LV hypertrabeculation (LVNC phenotype according to 4 CMR criteria) in the general (nonathlete) population.

STUDY LIMITATIONS. Women were under-represented in the study population, accounting for only 16% of the PESA CMR cohort. The placement of the accelerometer on the participant’s waist may lead to underestimation of the total amount of VPA, because in this configuration the device does not correctly capture time spent on exercises such as cycling or weightlifting, likely misclassifying them as sedentary or light PA. Furthermore, the device must be removed for aquatic sports, and thus swimming cannot be considered. PA in our study was based on ActiGraph accelerometers and analyzed using ActiLife software. These tools do not provide METs per minute as output. The Petersen CMR criterion was the only one measured in the whole cohort, whereas the Jacquier, Grothoff, and Stacey criteria were assessed only in the Petersen+ subpopulation. This approach would therefore miss any Petersen– participants fulfilling the Jacquier, Grothoff, or Stacey criterion. However, we considered this possibility very unlikely because the Petersen criterion is widely accepted as the most sensitive and least specific of the 4 criteria evaluated here. In fact, the Petersen criterion was described in a very small sample of 7 cases in 2005. All the other proposed criteria have been developed in an effort to improve its specificity, given the remarkable overdiagnosis derived from its application (18).

The PESA cohort consists of a middle-aged, physically active population. Even the least active subjects (no VPA) reached mean moderate activity of >200 min/week, thus meeting the World Health Organization’s recommendation for PA in the general

adult population. Finally, longitudinal follow-up of participants would be desirable to compare the evolution of CMR and clinical parameters between subjects fulfilling and those not fulfilling LVNC criteria. It would be also interesting to determine whether the LVNC phenotype in highly physically active subjects reversed in response to reduced training intensity. The scheduled very long-term follow-up in PESA places this study in a strong position to address these relevant questions.

CONCLUSIONS

In a community-based study of middle-aged, asymptomatic subjects, there was a high prevalence (17%) of LVNC according to the most widely used CMR-based criterion (Petersen). LVNC phenotype prevalence in PESA participants was also high according to more restrictive criteria. The prevalence of positive LVNC criteria was highest (31%) in subjects in the fifth VPA quintile. Our study confirms the association between exercise and LV hypertrabeculation and is the first to demonstrate that the association between vigorous exercise and LVNC phenotype is independent of LV volumes. These results make a case for the inclusion of exercise status in the overall assessment of subjects with LV hypertrabeculation.

The mechanism of how such remodeling of the myocardial mass occurs in response to VPA is unclear, and it may result from the interplay between exercise

and genetics. Human genetics and model systems studies will aid in understanding this issue.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND

PROCEDURAL SKILLS: A history of intensive physical activity is associated with left ventricular hypertrabeculation fulfilling imaging criteria for noncompaction, and this association is independent of ventricular volume.

TRANSLATIONAL OUTLOOK: Further research is needed to develop more specific criteria for assessment of left ventricular noncompaction and elucidate the mechanisms responsible for the link between exercise and myocardial hypertrabeculation.

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KEY WORDS exercise, LVNC, magnetic resonance imaging, MRI, noncompaction

APPENDIX For supplemental tables, please see the online version of this paper.