Is Vigorous Exercise Training Superior to Moderate for CVD Risk after Menopause?

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ABSTRACT

Postmenopausal women have an increased risk for cardiovascular disease through many factors, such as a sedentary lifestyle and reduced heart rate variability (HRV). Endurance training improves coronary risk but the role of exercise intensity is unclear. The purpose of this observational study was to evaluate the effects of moderate versus vigorous exercise on cardiovascular disease risk in postmenopausal women. Thirty-six postmenopausal women who self-reported training at moderate (3–5.9 METS; n = 18; age 58.9 ± 4.4yr) or vigorous intensities (> 6 METS; n = 18; age 59.7 ± 5.2yr) participated. C-reactive protein (CRP), HRV, VO$_2$max, and stress (Perceived Stress Survey, Menopause Rating Scale) were measured. Groups were compared using independent samples t-tests, and associations of exercise intensities with CRP and HRV were assessed using multiple regression. CRP, HRV, and VO$_2$max were similar ($p > 0.05$). Vigorous exercise had lower stress subscale scores ($p < 0.01$) and higher counter-stress subscale scores compared to moderate ($p < 0.05$). There was a positive association between time spent in vigorous exercise and HRV ($p < 0.05$).Vigorous exercise may not confer additional benefits in CRP and HRV over moderate, except for stress reduction. However, more time spent in vigorous exercise was associated with higher HRV. Therefore, increased parasympathetic tone may provide cardioprotection after menopause.

Abbreviations

HRV	heart rate variability
METS	metabolic equivalents
CRP	C-reactive protein
MOD	moderate group
VIG	vigorous group
RR	time between QRS complexes in electrocardiography
MRS	Menopause Rating Scale
PSS	Perceived Stress Scale
HT	hormone therapy
SDNN	standard deviation of normal to normal RR intervals
rMSSD	root mean square of the successive differences

Introduction

Postmenopausal women are at an increased risk for cardiovascular disease (CVD) [23]. Multiple risk factors such as hypertension and sedentary lifestyle can lead to increases in proinflammatory cytokines and the development of atherosclerosis [28]. Two clinical measures of CVD are high plasma concentrations of C-reactive protein (CRP) [8], and heart rate variability (HRV), a noninvasive assessment of autonomic nervous system (ANS) dysfunction [27]. The inflammatory response in CVD has been shown to be initiated by CRP in its dissociated form [44]. Further, reduced HRV indicates inadequate ANS response to stimuli and may augment cardiovascular mortality [9]. In addition, HRV is a measure of the sympathetic imbalance reflected by psychological stress common during menopause [37].

Endurance exercise training increases parasympathetic tone and provides a dose-response decrease in CRP that may contribute to the anti-inflammatory effects of exercise [22]. While HRV declines with age, physically active women have higher HRV than sedentary women [7]. Reland et al. reported a vagal withdrawal in the highly active group compared to the low and moderate group, suggesting that exercise intensity may enhance the sensitivity of the sinus node and therefore, attenuate the effects of age on cardiovascular disease risk [35]. On the other hand, Sugawara et al. determined that moderate and vigorous physical activity exhibited equal effects on the clinical implications of central arterial stiffness in postmenopausal women [41].

While studies on the effects of endurance exercise training on younger athletes are prevalent [3], observational studies on the relationship between exercise intensity and coronary risk in older women are limited and equivocal [47]. Therefore, the purpose of this study was to evaluate the effects of exercise intensity (moderate versus vigorous) on cardiovascular disease risk in postmenopausal women. We hypothesized that older women who trained at a vigorous level will have increased HRV and lower CRP compared to those who trained at a moderate level, thus reducing their cardiovascular disease risk.

Methods

Study design and participants

Thirty-six female postmenopausal (no menstruation previous 12 months; surgical menopause allowed) volunteers were recruited. Participants self-reported their current exercise status as (1) Vigorous training ≥ 12 sessions/month with average training intensity ≥ 6 METS (VIG); age 59.7 ± 5.2yr; or (2) moderate intensity ≥ 12 sessions/month with average training intensity 3–5.9 METS (MOD); age 58.9 ± 4.4yr [24]. To be classified in the VIG group, women were required to be current competitive or masters swimmers, rowers, cyclists, or runners (5–7 mph). For MOD classification, women were recreational exercisers who participated in activities such as walking (3–4 mph), cycling (10–12 mph), or recreational swimming.

Assuming an effect size of.8 for group differences in the standard deviation of RR intervals (ms), with a power of 0.8 at a significance level of $p = 0.05$, we calculated a sample size of 15 participants in each group using G * Power 3 (Germany) [11].

Exclusion criteria

Exclusion criteria were chronic disease (i. e., CAD, hypertension, cardiomyopathy, diabetes, severe arthritis), smoking, β-blockers and antiarrhythmic drugs. Subjects with CRP values > 10 mg/L were excluded from the analysis due to the likelihood of infectious or inflammatory conditions [29]. All participants had one or fewer CAD risk factors as specified by ACSM [24]. As such, no physician supervision was required for maximal exercise testing.

Procedures

The participants made one visit to the Exercise Physiology Laboratory at the university at least 24 h following their last regular exercise bout. The participants refrained from ingesting food, alcohol, or caffeine within three hours of testing [45]. Prior to this visit, they completed a health history questionnaire by telephone or email to verify their eligibility for study inclusion. Qualified subjects were emailed copies of the Menopause Rating Scale (MRS) [18] and Perceived Stress Survey (PSS) [5] to be completed and brought to their laboratory visit. For the PSS, scores for "stress" (negative) and "counter-stress" (positive) were analyzed separately [2]. The MRS sums responses in three categories: somatic, psychological and urogenital.

The Institutional Review Board at the university approved the study protocol and it meets the ethical standards of the International Journal of Sports Medicine [15]. Written consent was obtained from all participants.

Resting measurements

Following the completion of informed consent, a heart rate monitor (Polar RS800cx, Finland) transmitter was placed on the participant's chest and a receiver (watch) attached to their wrist. Subjects lay supine on a mat for measurement of resting HRV. After heart rate stabilized (~5 min), RR intervals (time subsequent QRS peaks) were recorded for 5 min with participants breathing normally [40]. Data files were transferred via infrared interface and checked by the primary investigator for atypical beats using visual inspection and the algorithm within the Polar ProTrainer 5 Software (Polar Electro Oy, Kempele, Finland). Acceptable data files were transferred to HRV analysis software (Kubios HRV 2.1, Kuopio, Finland).

The HRV analysis included mean heart rate (HR), mean RR interval, the root mean square of sequential deviations (RMSSD), and the percentage of all sequential RR deviations exceeding 50 ms (pNN50) in the time domain, plus high- (HF) and low- frequency (LF) power in the frequency domain [40].

Immediately following the HRV procedure, resting blood pressure (supine, sitting) was measured. Waist circumferences were measured and body fatness (BF %) was estimated using the sum of 3 skinfolds (triceps, suprailiac, thigh) (Lange; Cambridge Scientific Products, Cambridge, MA, USA). Population-specific equations were used to convert body density to percent body fat [20]. Following these measurements, height and weight were measured.

Subjects were then seated for the hs-CRP measurement. A lancet was inserted into the subject's finger and 10 µL of whole blood was obtained using a blood collection capillary. The capillary was inserted into a tube and shaken in order to draw the blood into the tube. Two drops of a reagent were applied to the sample and inserted into the holder of an iCHROMA reader (BODITECH MED INC., Chuncheon, Republic of Korea). The hs-CRP value was automatically read and visible on the screen in three minutes. The iCHROMA reader has been shown to have significant correlations with both the immunoturbidimetry ($r = 0.988$) and immunonephelometry ($r = 0.989$) methods, as well as intra- and interassay CVs of < 3 % and < 5 %, respectively [32].

Aerobic capacity

Maximum oxygen consumption (VO_2max) was determined using the Bruce protocol. The speed and grade of the treadmill (Quinton TM55, Cardiac Science, Waukesha, WI, USA) were increased every three minutes until indications for terminating exercise testing as specified by the American College of Sports Medicine (ACSM) were present, e. g., subject's desire to stop, signs of poor perfusion, drop in systolic blood pressure > 10 mm Hg from baseline [45]. Expired gases were collected continuously using a calibrated metabolic cart (ParvoMedics True Max 2400, Sandy, UT, USA). Heart rate (Polar) was monitored throughout exercise testing, while exercise blood pressures and rating of perceived exertion were recorded every 3 min. Following the exercise test, subjects walked at a self-selected pace (2.0 mph) for five minutes. Recovery heart rate was recorded at minutes 1 and 2 and 5.

Exercise intensity measures and energy expenditure

To objectively quantify current exercise training intensity, subjects were lent a heart rate monitor (Polar RCX5) to wear during three typical workouts of their exercise routine. Participants were instructed not to change or modify their exercise program, only to exercise as normal. For consistency, participants were encouraged to complete the 3 workouts in the following 2 weeks. Three days of monitoring were selected based on previous research and subject convenience [16]. Watches were programmed based on maximal HR data from the VO_2max test. Classification of physical activity intensities were "light" (50–63 %), "moderate" (64–76 %), "vigorous/hard" (77–93 %), "vigorous/very hard" (94–99 %) and "maximal" (100 % HR_{max}) as specified by ACSM [45]. Participants were given instruction on HR monitor operation and practiced prior to leaving the laboratory. Heart rate monitors were returned by mail.

Heart rate data was transferred via Polar WebSync (v2.7) software for analysis. Caloric expenditures were calculated from the metabolic equivalents using the 2011 Compendium of Physical Activities [1]. The METS for each activity were converted to $kcal \cdot kg^{-1} \cdot hr^{-1}$ ($1 MET = 1 kcal \cdot kg^{-1} \cdot hr^{-1}$) and multiplied by each subject's body mass in kg. Caloric expenditure per minute was calculated by dividing this amount by 60 min [20].

Statistical analysis

Student's independent t-tests were used to compare the outcome variables between the two levels of exercise intensity. Associations between HRV or CRP as the dependent variable and exercise intensity as the independent variable were assessed using multiple regression (method: enter). Menopause years and BMI were controlled for due to their influence on HRV measurements [37]. There were five participants in the MOD group taking hormone therapy (HT) and one in VIG. Therefore, the CRP and HRV values were analyzed with and without the participants who were on HT. Previous research from Harvey et al. (2015) reported a lack of improvement in HRV following estrogen therapy [17]. Chi square was used to determine group differences for HT.

Normality was checked with the Shapiro-Wilk test. Variables with a skewed distribution were log-transformed prior to analysis. The level of significance was set a $p < 0.05$. Statistical analyses were performed using IBM SPSS Statistics 20.0.

Results

▶ **Table 1** shows the participant characteristics. Of the 18 women in the VIG group, there were 13 master swimmers, 2 competitive rowers, 2 cyclists and 1 runner. The MOD group had 14 recreational swimmers, 1 runner, and 3 women who worked out at the gym (elliptical, walking). The VIG group had significantly higher values for waist circumference (81.3 ± 9.6 cm vs. 74.1 ± 5.0 cm; $p < 0.01$), resting supine SBP (120.8 ± 11.8 mm Hg vs. 106.7 ± 9.7 mm Hg; $p < 0.001$), resting sitting SBP (119.1 ± 16.5 mm Hg vs. 105.0 ± 10.0 mm Hg, $p < 0.001$), as well as sitting DBP (72.5 ± 11.5 mmHg vs. 64.4 ± 7.3 mm Hg; $p < 0.05$). The menopausal age of the moderate and vigorous groups were 7.5 ± 3.8yr and 8.1 ± 5.9yr, respectively ($p > 0.05$).

▶ **Table 2** gives the group comparisons for the VO_2max testing. The VIG group performed longer during the treadmill test (11.6 ± 2.6 min vs. 10.5 ± 2.2 min; ES = 0.46) and had a slightly higher VO_2max (34.5 ± 5.1 ml/kg/min vs. 32.4 ± 5.7 ml/kg/min; ES = 0.39), but these measurements did not reach statistical significance ($p > 0.05$). ▶ **Table 3** shows the group comparisons for HRV at rest. Although VIG had higher values for most measurements, there were no significant differences between the two groups. When the data from the participants who were taking HT were removed, there also were no significant differences between the HRV values ($p > 0.05$).

For the stress variables, the PSS showed that VIG had significantly lower stress (6.11 ± 2.95 vs. 9.69 ± 4.36) and higher counter-stress (13.61 ± 1.88 vs. 11.72 ± 2.37) compared to MOD ($p < 0.05$). For the MRS values, VIG had a sum of 8.3 ± 6.1, whereas MOD had 10.9 ± 4.6 ($p > 0.05$).

For group comparisons of the workout data, the VIG group expended significantly higher average kcal (487.9 ± 163.9 kcal vs.

▶ **Table 1** Participant Characteristics.

	Moderate (MOD; n = 18)	Vigorous (VIG; n = 18)	P value
Age (yr)	58.9 ± 4.4	59.7 ± 5.2	0.60
BMI (kg/m^2)	23.0 ± 2.7	24.6 ± 3.0	0.13
SBP (supine; mm Hg)	106.7 ± 9.7	120.8 ± 11.8	0.001
DBP (supine; mm Hg)	68.1 ± 6.4	73.4 ± 11.5	0.1
SBP (seated; mm Hg)	105.0 ± 10.0	119.1 ± 16.5	0.004
DBP (seated; mm Hg)	64.4 ± 7.3	72.5 ± 11.5	0.017
WC (cm)	74.1 ± 5.0	81.3 ± 9.6	0.008
BF (%)	23.8 ± 4.7	24.5 ± 3.9	0.65
RHR	62.8 ± 5.9	59.9 ± 8.7	0.25
CRP (mg/L)	1.1 ± 2.0	0.43 ± 0.33	0.22
HT (%)	6	28	0.36

All values are mean ± SD; unadjusted values; MOD, trained at 3.0–5.9 METS; VIG, ≥ 6.0 METS; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; WC, waist circumference; BF, body fat; RHR, resting heart rate; CRP, C-reactive protein; HT, hormone therapy.

▶ **Table 2** Treadmill VO_2max Testing.

	Moderate (MOD; n = 18)	Vigorous (VIG; n = 18)	P value
VO_2max (ml/kg/min)	32.4 ± 5.7	34.5 ± 5.1	0.24
RPEmax	17.8 ± 1.6	18.0 ± 1.4	0.66
RERmax	1.23 ± 0.10	1.24 ± 0.11	0.75
Test duration (min)	10.5 ± 2.2	11.6 ± 2.6	0.15
HRmax (bpm)	163.9 ± 10.6	162.1 ± 10.9	0.60
HR recovery min 1 (bpm)	24.4 ± 9.3	22.7 ± 9.0	0.85

All values are mean ± SD; VO_2max, maximal uptake of oxygen, directly measured; RPE, rating of perceived exertion; RER, respiratory exchange ratio; HR, heart rate.

292.8 ± 157.6 kcal; $p < 0.01$) over the three workouts. There were no significant differences between the groups for average minutes spent exercising "hard" (22.7 ± 11.9 vs 22.17.7 ± 14.2 min) or moderately (22.3 ± 20.9 vs 20.0 ± 15.2 min) for VIG and MOD, respectively ($p > 0.05$).

Since there was no significant difference for total minutes exercising at each intensity, for the multiple regression analysis we pooled the data for overall minutes (collapsed data by group). Controlling for BMI and menopause years improved the fit of both of these models. For SDNN and rMSSD, the prediction models were statistically significant, ($p < 0.01$, $p < 0.05$, respectively), with total minutes of hard exercise (77–93 % HRmax) showing a positive (healthy) association with HRV indices (▶ **Table 4**).

Discussion

This observational study showed that vigorous exercise was similar to moderate exercise in terms of cardiovascular disease risk. We also demonstrated that more time spent performing vigorous exercise, regardless of group, resulted in higher select HRV indices. The women in the VIG group benefited however, from their intense training with improvements in stress management.

We found that more time spent exercising at a higher level improved both SDNN and rMSSD, both time domain measures of HRV. As women age, they are at increased risk for cardiovascular disease as the reduced HRV reflects an increased dependence on the sympathetic nervous system [26]. Accordingly, the risk of malignant arrhythmias increase as the protective effect of vagal activity has been compromised [39]. Recently, high-intensity interval training (85–95 % HRmax) for 12 weeks was found to be superior to moderate training for SDNN, representing enhanced vagal modulation [34].

▶ **Table 3** Resting HRV.

	Moderate (MOD; n = 18)	Vigorous (VIG; n = 18)
MEANRR	6.85 ± 0.09	6.90 ± 0.14
SDNN	3.41 ± 0.48	3.41 ± 0.38
RMSSD	3.20 ± 0.51	3.34 ± 0.43
pNN50	1.72 ± 1.06	1.94 ± 1.08
LF (ms^2)	6.06 ± 1.10	6.16 ± 1.01
HF (ms^2)	5.08 ± 0.93	5.47 ± 0.82
LF (nu)	4.16 ± 0.35	4.11 ± 0.28
HF (nu)	3.19 ± 0.88	3.42 ± 0.78
LFHF ratio	0.97 ± 1.19	0.68 ± 1.02

All values are mean ± SD and are log-transformed; $p > 0.05$ for all comparisons; Time domain: MEANRR, mean RR interval; SDNN, standard deviation of all normal RR intervals; RMSSD, root mean square of sequential deviations; pNN50, percentage of all sequential RR deviations exceeding 50 ms; Frequency domain: LF, low frequency; HF, high frequency; nu, normalized units; ms^2, absolute units.

It is important to mention that our participants' cardiovascular risk profiles reflected their training, with healthy values for CRP, body fat and blood pressure. Healthy CRP levels are essential through and beyond menopause due to their potential involvement in the transition to from subclinical to clinical disease [25]. It was not surprising in the present study to find that the VIG group had significantly higher (although healthy values) SBP, DBP and WC compared to MOD. The majority of the women in the VIG group were competitive and masters swimmers who raced in open water. Previous studies have shown that regular swimming can elevate blood pressure [6]. Additionally, swimming is not as effective in reducing body fat or weight, compared to running or walking [43].

Several studies have shown the importance of exercise in stress management. Gerber et al. reported that meeting ACSM's guidelines for vigorous activity resulted in lower amounts of stress, pain, depression and sleep disturbances [14]. Importantly, these benefits were superior to those reported in the moderately trained group. In a study on older adults (> 65yr) by Marcellini et al., those reporting reduced levels of PA had subsequently higher depression (Geriatric Depression Scale) and PSS scores [31]. Both moderate and vigorous exercise has been shown to improve major depressive disorder [38]. In the present study, although there was no significant difference in VO_2max between the groups, the VIG women had mean values (34.5 ml · kg^{-1} · min^{-1}) that were ranked in the "good" category for 50–59yr according to ACSM [24]. An increased level of cardiorespiratory fitness has been shown to offset the detrimental effects of the aging-psychological stress combination on the hypothalamic-pituitary-adrenal axis [46], thus further increasing susceptibility of inflammatory diseases in older adults [19].

Not all studies have shown a clear benefit of high-intensity exercise. Campbell et al. reported no decrease in CRP following 12 months of moderate-vigorous aerobic exercise training in men and women 40–75 years [4]. Manson et al. found an equal risk reduction of nearly 30 % in walkers and women who exercised at a high level [30]. Pavey et al. concluded that there was no additional benefit to adding vigorous exercise except at the > 2000

▶ **Table 4** Multiple regression models evaluating the association with HRV variables with exercise intensities.

Dependent variable	Predictor	Adjusted *R*^{2}	Unstandardized coefficient	Standardized coefficient	P value
lnSDNN	Hard PA	0.288	0.011	0.349	0.03
	Mod PA		− 0.002	− 0.102	0.50
lnCRP	Hard PA	0.182	0.023	0.308	0.066
	Mod PA		0.007	0.120	0.46
lnRMSSD	Hard PA	0.219	0.014	0.386	0.02
	Mod PA		− 0.002	− 0.080	0.62

SDNN, standard deviation of all normal RR intervals; CRP, C-reactive protein; RMSSD, root mean square of sequential deviations; ln, logarithmically transformed; Hard PA, physical activity at 77–93 % HRmax; Mod PA, physical activity at 64–76 % HRmax.

MET · min · wk^{-1} level [33]. Recently, Roxburgh et al. compared the cardiorespiratory fitness values following 12 weeks of moderate or moderate + high-intensity interval training [36]. Although the results were equivocal as to the added benefits of high intensity exercise, the combined group had a 1 MET increase in cardiorespiratory fitness following the training. Previous research has shown that this increase could reduce the likelihood of CVD by 8–17 % [42].

The current ACSM position stand for quantity and quality of exercise specifies adding vigorous exercise (≥ 20 min · d on ≥ 3 d · wk (≥ 75 min · wk) or a combination of moderate and vigorous exercise to one's training program [13]. Perhaps, as suggested by Sugawara et al., cardioprotection can result from an interaction of the two intensities [41]. It is also possible that the women in the present study achieved a "threshold" level in their arterial function through their lifetime commitment to physical activity and training [10]. The importance of exercise in chronic disease prevention throughout the lifespan cannot be overstated. In a recent large observational study using NHANES data, Fishman et al. reported that moderate-intensity exercise was associated with lower mortality but pointed out that there were considerable benefits even from moving from a sedentary lifestyle to a program of low-intensity exercise [12].

There are some limitations to our study. First, our sample size was small due to the strict inclusion and exclusion criteria. Our sample of participants is not reflective of the general population, which limited our ability to generalize our findings. As such, these results can be generalized only to women who were highly motivated to train and compete in settings that provided a network of teamwork and support, regardless of intensity level. Secondly, we also would have benefited from a sedentary control group. However, previous studies have reported improved cardiometabolic biomarkers with moderate and vigorous exercise over light [21]. Third, we found it important for our participants to maintain their current exercise routine during the objective measurements of intensity. Still, some women possibly overestimated their training efforts at the time of enrollment, whereas others underestimated. Using the 6 MET as a cut-off between moderate and vigorous intensity was specified by ACSM [45]. Many of our moderate level participants trained at the high end (i. e., 6 METS for "bay swimming"), whereas some of the vigorous level participants trained at the low end (i. e., 3.3 METS for "walking 2.5 mph"). Although 75 % of our participants were swimmers, it is a limitation that we included other exercise modes as well. It is important to note, however, that all women were endurance trained for a minimum of 6 months. We did not recruit strength-trained or racket athletes. Fourth, the women used self-ratings for the PSS and MRS, which only reflected their current psychological state and not an average.

Overall, our findings suggest that vigorous exercise may be beneficial for stress reduction and improved heart rate variability. Specifically, more time spent exercising at a vigorous level, with or without formal interval training, is associated with improved autonomic function. Although no significant differences were found between MOD and VIG, exercise guidelines as specified by ACSM state the importance of adding vigorous exercise (either alone or in combination with moderate exercise) to develop and maintain cardiorespiratory health throughout the aging process.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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