Full title: The association between cardiorespiratory fitness, cardiovascular disease risk factors, and quality of life in perimenopausal and postmenopausal women: a cross-sectional study

Running Title: CRF, CVD risk and QoL during menopause.

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Abstract

Objective

Cardiovascular disease risk increases for women during the menopause transition. While cardiorespiratory fitness is linked to lower cardiovascular disease risk, its predictive relationship with cardiovascular health and quality of life during menopause is unclear. This study investigated the relationships between cardiorespiratory fitness, cardiovascular health markers, and quality of life in peri- and post-menopausal women.

Methods

Fifty-eight participants underwent a graded exercise test to assess cardiorespiratory fitness, alongside measurements of vascular function, blood lipids, blood pressure, and anthropometrics. Questionnaires were used to evaluate physical activity (IPAQ) and quality of life (menopause-specific [MENQOL] and general health [EQ-5D]). Linear and ordinal regression analysis were conducted to assess associations.

Results

After adjusting for age and physical activity, regression models indicated that cardiorespiratory fitness was significantly associated with high-density lipoprotein cholesterol, waist-to-hip ratio, and triglycerides, explaining 11-15% of their variance. Higher cardiorespiratory fitness was also linked to a lower burden of self-reported menopause-related symptoms in the MENQOL physical domain (Odds Ratio = 0.91 per unit increase in cardiorespiratory fitness). However, no significant associations were found between cardiorespiratory fitness and vascular function measures.

Conclusions

These findings suggest that cardiorespiratory fitness is independently associated with a more favourable cardiometabolic risk profile and may be related to fewer menopause-related symptoms in midlife women. In our sample, we did not find an association with vascular function, which may indicate that other factors might play a more prominent role in vascular health during the menopause transition.

Keywords: aerobic capacity, menopause, quality of life, cardiovascular disease risk

Summary sentences: This cross-sectional study of 58 peri- and postmenopausal women found that higher cardiorespiratory fitness was associated with more favourable cardiovascular risk factors and better menopause-related quality of life. These findings indicate that fitness may be related to cardiometabolic risk and symptom burden during the menopausal transition.

1. Introduction

Menopause, caused by the natural decline in endogenous oestrogens and cessation of menses typically after age 45 [1], induces substantial physiological changes in women. Adverse changes in body composition, lipid metabolism, and vascular function [2] during the menopause transition collectively contribute to an accelerated rise in cardiovascular disease (CVD) risk. As CVD remains the leading cause of death among women, accounting for one-third of female mortality annually [3], the menopause transition represents a critical window for identification and attenuation of CVD risk [2].

Cardiorespiratory fitness (CRF) is a robust indicator of cardiovascular, respiratory, and skeletal muscle system function [4] and serves as a proxy for habitual physical activity (PA) [4]. Unlike self-reported PA, which presents issues with recall error and underestimates associations with health, CRF provides a more reliable assessment of PA-related risk [4]. Evidence from large cohort studies demonstrates that CRF is more strongly associated with all-cause mortality than self-reported PA [4], supporting its potential value in CVD risk assessment [5]. Accordingly, CRF may offer a clinically useful, objective tool for evaluating cardiometabolic health during and after the menopause transition.

Emerging research suggests that higher CRF is associated with more favourable CVD risk profiles in perimenopausal and postmenopausal women [6-8], including healthier lipoprotein particle distributions [9], body composition [10] and metabolic syndrome characteristics [11]. However, despite these promising findings, the predictive utility of CRF for established CVD risk factors in this population has not been well established [7]. Moreover, although vascular dysfunction, such as increased arterial stiffness, is a key early marker of CVD risk in women [12, 13], few studies have examined the relationship between CRF and vascular function specifically during the menopause transition [14]. Given that CRF is influenced by both age and PA [15], it remains unclear whether any observed associations between CRF and CVD are independent of these factors. This is essential for determining whether CRF could legitimately serve as a clinical stratification tool.

Beyond cardiometabolic health, menopause is also associated with reductions in health-related quality of life (HRQoL) [16]. Prior research indicates that higher CRF may predict better menopause-specific QoL [17], suggesting that CRF could have dual relevance for both physical and psychosocial health outcomes. Despite this, limited studies have explored these relationships across different QoL instruments or within diverse menopausal groups.

Given these gaps, a cross-sectional study offers an appropriate approach to characterise the relationship between CRF, CV health, and QoL in midlife women. Such evidence is a necessary first step toward evaluating the potential of CRF as a practical, clinical measure for CVD risk stratification and symptom-related QoL during the menopause transition. Therefore, the aims of this study were to: 1) examine the predictive relationship between CRF and cardiovascular health measures, including vascular function, in perimenopausal and postmenopausal women, while accounting for relevant covariates, and 2) assess whether CRF predicts menopause-specific and general QoL.

2. Methods

This was a single-site, single-visit cross-sectional study. Ethical approval (ETH2324-0059) was granted by York St John University School Ethics Committee in January 2024. All participants provided written informed consent prior to undergoing any procedures. This study is reported in accordance with the STROBE Statement checklist for cross-sectional studies [18].

2.1. Eligibility Criteria

Participants were recruited using convenience sampling. Inclusion criteria were females aged ≥45 years in either the late menopausal transition stage (STRAW+10 stage −1) or postmenopausal stage (STRAW+10 stage +1 and onward). Late menopausal transition was defined by increased cycle-length variability (interval of amenorrhea of >=60 days) and supported by the presence of vasomotor symptoms, when hormonal fluctuations accelerate alongside CVD risk [19]. Postmenopausal status (STRAW+10 stage +1 and onward) was determined by ≥12 months since the final menstrual period. No upper chronological age cut-off was applied as eligibility was based on reproductive staging.

The exclusion criteria were current, clinically defined CVD or a history of cardiac events, a recent injury causing cessation of PA (within the last six weeks), cigarette smokers, or a diagnosis of diabetes (type 1 and type 2). Hormonal contraceptives were excluded but hormone therapy (HT) was included, as it provides lower-dose systemic or localised hormones for symptom management. Intrauterine levonorgestrel devices (e.g., Mirena) were included when used as part of HT rather than for contraception.

2.2.Recruitment

Participants were recruited via internal callout for staff at York St John University, as well as notices (online via social media and email newsletters) at local menopause groups. A recruitment poster was circulated with a QR code leading to an expression of interest form. Potential participants were then contacted by the researchers to confirm eligibility. Participants were recruited between April-September 2024.

2.3.Outcomes and Procedures

Prior to their laboratory appointment, participants were asked to fast and avoid caffeine for four hours, refrain from strenuous exercise for 24 hours, and refrain from alcohol for 12 hours. Upon arrival, participants completed self-report questionnaires collecting demographic information and assessing PA and QoL, before measures of anthropometric and lipid outcomes were collected. Participants then completed a supine rest, followed by measures of blood pressure, and vascular function (common carotid artery stiffness and intima-media thickness, and brachial artery flow-mediated dilation). CRF was then assessed. The procedures are outlined, in order of testing, below.

2.3.1. Demographics

Participants self-reported demographic information including, age, menopausal status, time since last menses, and whether HT was in use, including which type.

2.3.2. Quality of Life

Menopause-specific QoL was measured using the menopause-specific quality of life questionnaire (MENQOL), a self-report questionnaire developed to measure changes in QoL during the menopause transition [20]. Participants were asked whether they experienced 29 symptoms over the past week, and if so, to rate how bothersome on a 7-point Likert scale (0 = not at all bothered to 6 = extremely bothered). The items are divided into four domains: vasomotor, psychosocial, physical, and sexual. Each item score was converted using a scale from 1-8; 1 = symptom not experienced, 2 = symptom experienced but not at all bothersome, up to 8 = symptom was extremely bothersome. For each domain, a mean summary score

(ranging between 1 to 8), and a total mean summary score were calculated [21]. Higher scores indicate a greater impact of QoL.

The EQ-5D-5L was administered to measure self-reported general health-related QoL. The EQ-5D-5L measures health across five domains (mobility, self-care, usual activities, pain/discomfort, and depression/anxiety) using five levels of severity (from 1 = no problems to 5 = extreme problems) [22]. The questionnaire also includes a visual analog scale (VAS) where participants were asked to rate their health on a scale from 0-100.

2.3.3. Physical Activity

Self-reported PA was assessed using the International Physical Activity Questionnaire (IPAQ) Short Form which measures the number of days and time spent walking, as well as moderate and vigorous activity over the last week. Data were cleaned and truncated according to IPAQ guidelines. A metabolic equivalent (MET) score per week for each category was calculated and each PA category was then summed to provide a total MET minute per week score [23].

2.3.4. Stature and Anthropometry

Mass was measured using an electronic scale (Tanita, Chicago, IL). Height was measured using a stadiometer (Seca, Hamburg, Germany). Body mass index (BMI) was subsequently calculated (mass/stature^2). Waist circumference (WC) was measured with the tape measure placed around the narrowest part of the torso, between the umbilicus and the xyphoid process [24]. Hip circumference (HC) was measured with the tape measure placed around the maximum circumference of the buttocks [24]. Waist-to-hip ratio (WHR) was calculated (WC/HC).

2.3.5. Blood Lipids

Blood lipids were measured using a Cobas b101 system that uses capillary blood samples and was calibrated before use according to manufacturer's instructions (Roche, Basel, Switzerland). Lipid measures included total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides, low-density lipoprotein cholesterol (LDL-C), non-HDL cholesterol, and TC-to- HDL ratio (TC: HDL). It should be noted that blood lipids were measured after only four hours of fasting to reduce participant burden given the maximal exercise testing protocol. Evidence indicates that TC, HDL-C, and LDL-C are minimally affected by fasting status, although triglycerides may show greater postprandial variability [25].

2.3.6. Resting Blood Pressure and Heart Rate

Systolic and diastolic blood pressure (SBP and DBP) and heart rate (HR) were measured using an automatic blood pressure monitor (Omron M3, Milton Keynes, UK) after at least 5 minutes of quiet, supine rest. Measures were collected in duplicate and averaged.

2.3.7. Vascular Function: Intima Media Thickness (IMT)

Prior to vascular testing, participants underwent 10 minutes of supine rest [26]. High-resolution B-mode ultrasound imaging was performed using a Terason ultrasound (T3300, Terason, Burlington, MA) with a 15L4 Smart Mark transducer (Terason). Longitudinal images of the common carotid artery (CCA) were measured approximately one to two cm inferior to the bifurcation to measure IMT of the posterior wall. IMT were analysed using the 'Carotid Studio' function of the Cardiovascular Suite software (Version 2.8.1, Quipu, Italy) for offline edge detection analysis. Mean IMT (mm) was measured over three consecutive cardiac cycles during diastole, as recommended by Selzer et al. [27], and averaged per participant.

2.3.8. Vascular Function: β-Stiffness Index

Short-axis images of the CCA were taken approximately one to two cm inferior to the bifurcation and at least three cardiac cycles were stored. Maximum and minimum diameters (cm) of the CCA was measured using the calliper function of the Terason software, where the calliper was placed at the lumen and tunica-intima interface.

β-stiffness index was calculated from the below equation, where "ln" refers to natural logarithm, "DiamSYS" refers to maximum diameter of the artery during systole, and "DiamDIAS" refers to maximum diameter of the artery during diastole.

$$\beta\text{-stiffness index } (cm^2/kPa) = \frac{In\,(SBP/DBP)}{(DiamSYS - DiamDIAS)/DiamDIAS}$$

2.3.9. Vascular Function: Flow-mediated Dilation (FMD)

Brachial artery FMD was assessed according to published guidelines [26]. A large diameter pneumatic cuff was placed distal to the elbow and the arm was abducted approximately 90 degrees. To record an image of the brachial artery, the same ultrasound machine and probe were used as described previously. The transducer was positioned longitudinally above the elbow on the upper arm to locate a straight and parallel segment of the brachial artery. To obtain the arterial diameters, the ultrasound parameters were adjusted to enhance the B-mode image of the lumen-arterial wall interface. Once a suitable image was detected, the transducer was held in this position. Additionally, blood flow was assessed via Doppler ultrasound using the same machine with an insonation angle of 60 degrees and the sample volume placed in middle of the lumen, aligned with the blood flow. Following a one-minute baseline, the cuff was rapidly inflated using an automatic rapid cuff inflator (Vascular Assessment Pressure Cuff Controller, Moor Instruments, Devon, UK) to supra-systolic pressure (220 mmHg) to occlude blood flow to the lower arm for five minutes. After cuff deflation, arterial diameter and blood flow recordings were continued for three minutes.

Data were analysed using Cardiovascular Suite, an automated edge-detection and wall-tracking software. The analysis process has been described in detail elsewhere [28]. Baseline arterial diameter and blood flow were determined as the mean of the data acquired 1-minute prior to cuff inflation. Following cuff deflation, peak arterial diameter was automatically calculated, and FMD (%) was calculated as the percentage change in arterial diameter from baseline diameter ([peak arterial diameter - baseline arterial diameter] / baseline arterial diameter) × 100%). Shear rate (SR) area under the curve (AUC) was automatically calculated from post cuff deflation until the point of peak arterial diameter. SR AUC was also used to normalise the FMD response (FMD % / SR AUC).

All FMD measurements and analyses were performed by a single experienced sonographer, and all IMT and carotid measurements and analyses were performed by a second experienced sonographer, in accordance with established guidelines [26, 27] to minimise inter-observer variability.

2.3.10. Cardiorespiratory Fitness

All participants completed a physical activity readiness questionnaire (PAR-Q) before the test and obtained clearance from their physicians if required. Due to the variable age range and CVD risk profile of the cohort and the absence of a physician on site, our laboratory safety

protocol stipulated that participants with persistent resting hypertension (≥140/90 mmHg) did not undergo maximal testing, consistent with conservative interpretations of American College of Sports Medicine/American Heart Association risk-stratification guidance [29]. Therefore, six participants completed a submaximal Ekblom-Bak cycle ergometer test which has demonstrated acceptable validity for estimating maximum oxygen uptake ($\dot{V}O_{2max}$) in an adult population [30]. The assessment was carried out as per the guidelines, reported elsewhere [30].

A step-based cycling protocol was used to directly determine $\dot{V}O_{2max}$ in the remaining participants. Participants cycled on an ergometer (Excalibur, Lode, Groningen, Netherlands) until volitional exhaustion or until they were no longer able to maintain a pedal cadence of >50 rpm. Breath-by-breath oxygen uptake ($\dot{V}O_2$) and carbon dioxide (CO_2) was measured via an online gas analysis system calibrated according to manufacturer's instructions (Metalyzer 3B, Cortex Medical, Leipzig, Germany). HR was monitored continuously using short-range telemetry (Polar, Kempele, Finland). Participants completed a five-minute warm up at a self-selected resistance. The test began with 50 W of resistance and increased by 30 W every two-minutes. During the final 20 seconds of each stage, participants rated their exertion using the Borg rating of perceived exertion (RPE) scale, and HR was recorded. Criteria for participants reaching their maximal capacity was achieving a respiratory exchange ratio >1.15, attainment of ≥90% of age-predicted maximal HR, and/or a Borg RPE of 20. All participants reached the criteria for $\dot{V}O_{2max}$. $\dot{V}O_{2max}$ was calculated via MetaSoft Studio (Cortex Medical, Leipzig, Germany).

2.4.Data analysis and handling

Analyses were conducted using Jamovi version 2.6.13 and IBM SPSS Statistics version 29.0.2.0. Descriptive statistics were generated to characterise the population according to demographics, CVD risk factors, and QoL. There were two missing observations each for TC: HDL, LDL-C, and non-HDL-C, and one missing observation for HDL-C due to the measurements being out of range of the lipid analyser. There were two missing observations for IMT and one for FMD due to inadequate image quality.

Continuous data were tested for normal distributions using the Shapiro-Wilk test. Pearson's product moment or Spearman's rank correlation coefficients (depending on normality) were used to assess bivariate relationships between $\dot{V}O_{2max}$ and markers of cardiovascular health. For ordinal data, Spearman's rank was used to investigate the relationship between CRF and QoL domains. CVD risk factors were added individually to a simple linear regression model (model 1) to analyse the independent, predictive relationship between CRF (as the predictor variable) and CVD risk factors, or CRF and QoL domains (using ordinal logistic regression). Covariates (PA and age) were added to regression models as continuous variables (model 2). Covariates were chosen based on established relationships with CVD risk factors [31, 32], and previous research on CRF and QoL in this population [17]. There were no significant correlations between CRF and age or PA in this sample. To avoid multicollinearity, BMI, which was significantly correlated with CRF, was not added as a covariate because relative $\dot{V}O_{2max}$, used as the predictor variable, is already adjusted for body mass. All linear regression models were reviewed to ensure the assumptions were met. Ordinal logistic regression models were also reviewed against assumptions, including proportional odds using the test of parallel lines. Significance was accepted at $p<0.05$.

2.5. Sample Size

Sample size was determined to detect the incremental effect of CRF on CVD risk factors while adjusting for age and PA as covariates. Using G*Power 3.1, a linear multiple regression

(fixed model, R^2 increase) was specified, with the number of tested predictors = 1 (CRF) and total predictors = 3 (CRF, PA, Age). We assumed a medium effect size ($f^2 = 0.15$), $\alpha = 0.05$, and power ($1 - \beta$) = 0.8. The required sample size was N=55. To account for potential missing data, we recruited 58 participants to ensure adequate power to detect the effect of CRF beyond covariates. In addition, our sample size is based on similar studies examining associations between CRF and CVD risk factors/QoL in menopausal women [9, 17, 33].

3. Results

Figure 1 details the flow of participants through the study. Fifty-eight participants attended the laboratory and underwent all tests. Table 1 presents descriptive statistics for demographic data.

3.1. Descriptive statistics

Participants were predominantly postmenopausal with a mean age of 54.5 ± 6.5 years, and 37.9% were using some form of HT, with use more common among perimenopausal participants (Table 1). Information on the type and delivery route of HT is provided in Supplemental Digital Content 1 (table, Supplemental Digital Content 1, additional statistics). Overall, participants had a generally healthy CVD risk profile although mean BMI (26.7 ± 4.9 kg/m²) and total cholesterol were elevated (5.4 ± 1.0 mmol/L) above recommended thresholds [34] (Table 2). Scoring of self-reported PA was high, with participants averaging over 3000 MET minutes/week, though variability was considerable (SD ± 2782 MET minutes/week). In the context of cycle ergometer reference standards from the FRIEND Registry, the 90th percentile $\dot{V}O_{2peak}$ for women aged 50–59 years is approximately 21.4 mL·kg^{-1}·min^{-1}, indicating that the mean $\dot{V}O_{2max}$ of 30.4 mL·kg^{-1}·min^{-1} in our sample is considerably higher than typical age-matched peers [35]. For vascular function, FMD (5.1 ± 3.1%) fell between the 25th and 50th percentiles [36], while IMT (0.63 ± 0.10 mm) fell between the 50th and 75th percentiles for females aged 55 years [37](Table 3). QoL measures suggested that menopausal symptoms were, on average, at least minimally bothersome across all MENQOL domains (Table 4), while participants predominantly reported 'no problems' on the EQ-5D-5L in mobility, self-care, and usual activities. Scores were more variable across both pain/discomfort and anxiety/depression domains (Table 5).

3.2. Bivariate analysis

In bivariate correlation analyses of continuous variables, there was a significant correlation between CRF and triglycerides (r= -0.3, p= 0.02), BMI (r = -0.47, p <0.001), WHR (r =-0.42, p <0.001), and EQ-5D VAS (ρ = 0.32, p= 0.02), showing inverse associations. In correlation analyses of ordinal variables, there was a significant correlation between CRF and MENQOL Physical (ρ = -0.31, p= 0.02), MENQOL Sexual (ρ = -0.22, p= 0.02), and MENQOL Total Score (ρ = -0.31, p= 0.02). No other significant correlations between CRF and other variables were observed. Tables 6 and 7 show Pearson's r, Spearman's ρ, and p values for all variables.

3.3. Linear Regression

Variables that violated normality assumptions were transformed prior to analysis. Normality was assessed using visual inspection of Q-Q plots and Shapiro-Wilk tests. Non-HDL-C, triglycerides, TC:HDL ratio, WHR, SBP, and DBP were log-transformed (ln), EQ-5D VAS and β-stiffness index were transformed using Box-Cox transformation, and MET minutes/week and FMD SR/AUC were transformed using square root transformation. Normality was confirmed following transformation. Model statistics presented in the tables

reflect transformed data. Table 8 presents key statistics for each regression analysis where there was a significant association with CRF, including Model 1 (simple regression) and Model 2 (multiple regression with the addition of covariates age and PA). Supplemental Digital Content 2 provides full model statistics for each variable (table, Supplemental Digital Content 2, full regression model statistics).

CRF remained a significant independent variable for HDL (adjusted $R^2 = 0.12$, $p = 0.02$), triglycerides (adjusted $R^2 = 0.14$, $p = 0.009$), and WHR (adjusted $R^2 = 0.16$, $p = 0.007$), even after adjusting for age and PA. However, the influence of CRF was less consistent for other markers; for EQ-5D-VAS, the addition of the covariates significantly improved model fit (adjusted $R^2 = 0.19$, $p = 0.003$), though CRF was no longer a significant contributor, while for TC:HDL, CRF remained significant despite the overall model losing significance (adjusted $R^2 = 0.05$, $p = 0.14$). Notably, while Model 2 was significant for SBP (adjusted $R^2 = 0.13$, $p = 0.01$), β-stiffness index (adjusted $R^2 = 0.1$, $p = 0.03$), and Petersons Elastic Modulus (adjusted $R^2 = 0.16$, $p < 0.01$) these vascular outcomes were driven exclusively by Age ($p < 0.01$). Similarly, the variance explained in the IMT model (adjusted $R^2 = 0.22$, $p < 0.01$) was attributed solely to PA ($p < 0.01$).

Collectively, these findings indicate that CRF explains a proportion of the variance in HDL (11%), triglycerides (10%), and WHR (15%) with only minimal to low increases in adjusted R^2 following adjustment for age and PA. Conversely, PA and age, rather than CRF, were statistically significant covariates for EQ-5D-VAS, IMT, SBP and measures of arterial stiffness. All models were powered to detect effects of CRF and thus findings for other covariates should be interpreted as exploratory.

3.4. **Ordinal Regression**

Table 9 presents key statistics from the ordinal regression models where there was a significant association. Full model statistics are available in Supplemental Digital Content 2 (table, Supplemental Digital Content 2, full regression model statistics).

CRF remained a significant independent variable when controlling for PA and age for both MENQOL Physical ($\chi^2 = 9.29$, $p = 0.03$) and MENQOL Total ($\chi^2 = 10.35$, $p = 0.02$). The odds ratios suggest that for every one-unit increase in CRF, the odds of reporting a higher physical symptom burden and a higher total domain score on the MENQOL decreases by 8%. With the addition of covariates, this decreases by only 1% further.

3.5.Exploratory Hormone Therapy Analysis

While the initial sample size was powered for two covariates (age and PA), due to the proportion of participants using HT, we conducted a post-hoc sensitivity analysis to incorporate HT status (Model 3). In most cases, inclusion of HT did not significantly alter the direction or magnitude of associations between CRF and CVD factors, nor was HT an independent predictor.

However, Model 3 reached statistical significance for TC:HDL (adjusted $R^2 = 0.10$, $p = 0.05$) and SBP (adjusted $R^2 = 0.24$, $p < 0.01$). In these models, HT was a significant independent variable alongside CRF for TC:HDL and alongside age for SBP. Furthermore, out of all three models, Model 3 was the only significant model for DBP (adjusted $R^2 = 0.14$, $p = 0.04$), with significance driven solely by HT status ($p < 0.01$). It is important to reiterate that the study was not a priori powered to include HT. Detailed model statistics are provided in Supplemental Digital Content 2 (table, Supplemental Digital Content 2, full regression model statistics).

4. Discussion

4.1. Summary of main findings

In this study, we found that CRF was significantly associated with menopause-specific QoL, specifically the physical domain, as well as total QoL scores, independent of age and self-reported PA. Cardiorespiratory fitness was also a significant predictor of several CVD risk factors incuding TC:HDL, HDL-C, triglycerides, and WHR. These results suggest that CRF may be associated with physiological and psychosocial health during the menopause transition.

4.2.Cardiorespiratory fitness and quality of life

Our findings indicate that higher CRF is associated with better menopause-specific QoL, specifically in the physical domain, whereas CRF was not associated with general, subjective health as measured by the EQ-5D-VAS. This suggests that CRF may be more strongly related to symptom-specific impacts of menopause, such as difficulty sleeping, decreases in physical strength and stamina, and lack of energy, rather than overall perceived wellness. This builds on previous research which has reported a predictive relationship between CRF and QoL using the Utian QOL (UQOL) questionnaire which measures QoL in menopause [17].

Several physiological and psychological mechanisms may explain these associations. Higher CRF is associated with greater energy efficiency and functional capacity, increasing tolerance for daily physical demands and potentially affecting the perceived impact of symptoms such as fatigue or muscle weakness [38]. In addition, regular exercise, which may equate to higher CRF, is also linked to better sleep quality [39] which has been associated with reduced severity of self-reported menopausal symptoms [40]. Moreover, both higher, objectively-measured CRF and greater PA levels have been associated with greater self-efficacy in older adults [41], which in turn are also associated with self-esteem and resilience [41]. High resilience has been shown to buffer the perception of menopausal symptoms [42], and this may be associated with the lower perceived psychological impact of physical menopause symptoms in our cohort. Together, these pathways suggests that improving CRF may have both physiological and psychological benefits for women during the menopause transition.

These results build on prior research in which CRF was indirectly measured in PA interventions for menopausal women, and QoL outcomes were reported using generic HRQoL instruments such as the SF-36 scale and the Nottingham Health Profile [43, 44]. These studies reported improvements in overall HRQoL, but did not specifically investigate menopause-specific QoL or directly measure CRF. By using objectively measured CRF and the MENQOL questionnaire, our study directly links CRF to menopause-specific QoL, highlighting CRF as a potential marker associated with physical symptom burdon during the menopause transition.

4.3.Cardiorespiratory fitness and cardiovascular disease risk factors

Cardiorespiratory fitness was significantly associated with lipid measures (HDL-C, triglycerides) and WHR, independent of PA and age, suggesting that CRF may be associated with CVD risk through mechanisms related to lipid metabolism and central adiposity [6-11]. Higher CRF is associated generally with greater habitual PA [45] which increases skeletal muscle mitochondrial content, enhances insulin sensitivity, and improves whole-body metabolic health [46]. Conversely, lower CRF may reflect lower PA and poorer insulin sensitivity, leading to dyslipidemia via an increased mobilisation of free-fatty acids, very low-density lipoprotein production, and lower HDL-C concentrations [47, 48]. Central adiposity may further contribute via endocrine signalling, with visceral adipose tissue producing

inflammatory mediators such as interleukin-6 and tumour necrosis factor that interfere with energy metabolism, insulin sensitivity, and vessel health [49].

Despite this, no associations were observed between CRF and SBP, DBP, or FMD. This may partly reflect the relatively healthy profile of the study population, leading to reduced variability in vascular outcomes and thus limiting the ability to detect associations between CRF and vascular function. Insulin stimulates endothelial nitric oxide synthase (eNOS) and its cofactor, enhancing nitric oxide production which mediates endothelial-dependent vasodilation [50]. In states of insulin resistance, eNOS and its cofactor are downregulated, leading to impaired endothelial function and hypertension [50]. If insulin metabolism were the primary mechanism linking CRF to lipids and central adiposity, we might also expect to relationships between CRF and vascular function; the absence of such associations suggests that additional factors are involved. The lack of association between CRF and FMD in our study aligns with previous studies showing that higher CRF or device-measured moderate-to-vigorous PA is not consistently associated with FMD in peri- and postmenopausal women [14, 51, 52]. Hormonal changes during the menopause transition, including fluctuations in follicle stimulating hormone and oestradiol may also influence vascular function independently of CRF [14 52].

Consistent with prior research, lipid profiles were more favourable in women with higher CRF [9, 33], and aerobic exercise interventions in postmenopausal women improve both CRF and lipid profile, such as decreased LDL-C and increased HDL-C [53, 54]. Dyslipidemia is an established CVD risk factor, and improving lipid profiles is associated with reduced risks in midlife women; for example, a cohort study of 6,147 women aged 50-59 years reported a 16% increase in myocardial infarction risk for each unit increase in TC:HDL even after adjustment for age, smoking, and blood pressure [55].

Moreover, adverse blood lipid profiles contribute to arterial stiffness via oxidative stress and inflammation [56], while elevated cyclic pressures from persistent hypertension promote structural adaptations in the arterial wall, including collagen crosslinking and elastin degradation[57]. Higher CRF is associated with a reduced risk of hypertension, with every 1-MET increment in $\dot{V}O_{2max}$ corresponding to an 8% reduction in hypertension risk[58]. In our study, however, CRF was not associated with blood pressure, and no association with carotid stiffness was observed. Instead, age was a statistically significant covariate for SBP and carotid stiffness. Our findings align with Campbell et al. [59], who report no relationship between CRF and β-stiffness index in middle-aged women, although they did find associations with carotid compliance using more sensitive ultrasound speckle tracking techniques [60]. Therefore, limited sensitivity of β-stiffness index may have contributed to the lack of observed associations in the study, and future research using more sensitive vascular imaging is warranted.

Previous studies have also shown that higher CRF is linked to lower carotid IMT, with each 1 ml/kg/min increase in $\dot{V}O_{2max}$ associated with a 0.026 mm reduction in IMT [61]. Based on the variation in CRF in our cohort (SD ± 6.92 ml/kg/min), this could correspond to 0.18 mm difference in IMT between individuals with low and high CRF [62]. However, we observed no significant association between CRF and IMT. While lipids were associated with CRF in our cohort, previous research suggests that blood pressure has a stronger relationship on IMT than blood lipid levels [63, 64]. This may be relevant in interpreting the lack of association observed in the present study, alongside the observed association between age and SBP in our cohort. Instead, self-reported PA was a statistically significant covariate for IMT. Additional

menopause-related factors that were not assessed in this study, including inflammation and oxidative stress, are also known to influence both CRF and vascular structure [65-67]. Collectively, these findings suggest that while CRF may be a robust independent predictor of metabolic and anthropometric risk factors, other mechanisms such as hormonal, inflammatory, or oxidative factors, chronological aging, and habitual PA may contribute to vascular changes during menopause. This is supported by our exploratory sensitivity analyses in which HT was significantly associated with SBP and DBP. These findings should be interpreted cautiously given that the study was not powered to examine HT. Nonetheless, they provide a foundation for future work.

4.4.Strengths and Limitations

The primary strength of this study is the use of an objective measure of CRF rather than relying on self-reported levels of PA, which was related to few variables in our study. However, six participants did undergo an estimated submaximal test due to hypertension. We also used regression analysis to examine whether changes in CRF were associated with changes in other CVD and QoL variables, which provides a basis for future research to explore potential mechanisms, and bolsters justification for the use of CRF as a screening tool in menopause. Another strength includes the examination of markers of vascular health which are seldom studied in this population, such as CCA stiffness.

The limitations of our study include its cross-sectional design which cannot demonstrate causation or the direction of any causal effect, nor explore mechanisms. An additional limitation of the vascular outcome analysis is that relevant hormone concentrations, such as oestrogen and FSH, were not assessed. Menopausal stage may also influence CV and vascular outcomes independently of chronological age. However, it was not included as an independent variable in the regression models. This was due to its close relationship with chronological age, which may introduce multicollinearity, in addition to the study not being specifically powered to detect its independent effects. Future studies designed to identify the independent effects of chronological age and menopause status are warranted.

Self-reported QoL data is a limitation. The use of self-reported PA using the IPAQ is also a limitation, and the lack of association between self-reported PA and most other variables may reflect this. However, this demonstrates why objective indicators of habitual PA, such as CRF, may be more appropriate in PA studies. Additionally, blood lipids were measured after only 4 hours of fasting to reduce participant burden, which may have introduced variability in triglycerides. Finally, the sample size was calculated for linear regression models, but QoL outcomes were analysed using ordinal regression, which may have reduced statistical power. These factors should be considered when interpreting the respective outcomes.

5. Conclusion

Our study identified associations between CRF and CVD risk factors (triglycerides, HDL-C, WHR) and QoL (MENQOL Physical and Total domains) in perimenopausal and postmenopausal women. In line with previous research, these findings suggest that higher CRF may be associated with a more favourable cardiometabolic risk profile and better quality of life during and after the menopausal transition. CRF may therefore represent a useful marker in the context of CVD risk stratification in this population. However, given the cross-sectional design, causal inferences cannot be made. Future studies should explore the longitudinal association of CRF and CVD risk in menopause to identify causal relationships and elucidate other important covariates, including use of HT.

6. Statements and Declarations

6.1.Acknowledgements

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6.2.Ethics approval

Approval was obtained from the ethics committee of York St John University. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

6.3.Consent to participate

Informed consent was obtained from all individual participants in the study.

6.4.Funding

No funding supported this study.

6.5.Competing Interests

The authors have no competing interests to declare.

6.6.Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

6.7.Author contributions

All authors contributed to the conception and design of the study, undertaking data collection and analysis, writing and reviewing the report.

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List of Supplemental Digital Content

Supplemental Digital Content 1: SDC 1.docx

Supplemental Digital Content 2: SDC 2.docx

Figure titles

Fig 1. Flow of participants through the study. TC: HDL= total cholesterol to high-density lipoprotein cholesterol ratio, LDL-C = low-density lipoprotein cholesterol, IMT= intima media thickness, FMD= flow-mediated dilation